Protocol

SALTS: Salt ALTernatives Study

SALTS: A randomised controlled trial to determine the effects of a 12-week dietary salt reduction intervention (SaltSwitch app + dietary salt substitute) on urinary sodium excretion in adults with high blood pressure

Trial Registration Number: ACTRN12619000352101
Universal Trial Number: **U1111-1225-4471**
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Project Sponsor

The SALTS trial is funded by a Health Research Council of New Zealand programme grant [HRC ID: 18/672]. The design, conduct, analyses and interpretation of trial results are all independent of the trial sponsor.

Source of Study Treatment

Participants in the intervention group will receive the SaltSwitch smartphone application (app) and supply of a high potassium, low sodium dietary salt substitute. The SaltSwitch app enables users to scan the barcode of a packaged food and receive an immediate, interpretive, traffic light nutrition label on screen alongside suggestions for healthier low salt alternatives. Users can also directly compare two or more food products. The SaltSwitch app was originally developed by the George Institute for Global Health in Sydney and has been adapted for New Zealand shoppers using the Nutritrack food composition database. The salt substitute is provided by Nutek Food Science and comprises a blend of potassium salt and sea salt, which provides a 75% reduction in sodium compared to regular table salt.

Signature Page

Author(s):

Authors Name	Signature	Date
Cliona Ni Mhurchu		**03/08/2020**

Note: Dr Helen Eyles is on parental leave March 2020 – February 2021 and Prof Cliona Ni Mhurchu is interim study PI in her absence. Prof Ni Mhurchu revised this version of the protocol in consultation with the SALTS Steering Group, Management Team, and Advisory Group

NIHI Signatory:

Director	Signature	Date
Chris Bullen		3/8/2020

Revision Chronology:

	Date	Type
Protocol Version 1	December 2018	Original
Protocol Version 2	January 2019	Version 2
Protocol Version 3	April 2020	Version 3/ 3.1
Protocol Version 4	July 2020	Version 4

1. Overview

Title of study

SALTS: A parallel, two-arm, randomised controlled trial to determine the effects of a 12-week dietary salt reduction intervention (Saltswitch app + dietary salt substitute) on urinary sodium excretion in adults with high BP.

Investigators and study centres

This study is being designed and conducted at the National Institute for Health Innovation (University of Auckland). The Principal Investigator is Dr Helen Eyles. The Co-investigators are Professor Cliona Ni Mhurchu, Professor Bruce Neal, and Dr Lisa Te Morenga.

Study period

May 2019 to 31 March 2022. It is anticipated that participant recruitment will begin in May 2019.

Clinical phase

SALTS is a phase III randomised controlled trial (RCT).

Objectives

The primary objective of this study is to determine the effects of a 12-week dietary salt reduction intervention (SaltSwitch app + dietary salt substitute) on urinary sodium excretion in adults with high BP.

The secondary objectives are to determine the effects of the dietary salt reduction intervention on: (1) urinary potassium excretion (week 12), (2) systolic blood pressure at week 12 (3) sodium content of packaged food purchases (weeks 11 & 12), (4) the number of participants achieving BP control (≤135/85 mmHg; week 12), and (5) use and acceptability of the SaltSwitch app and dietary salt substitute (week 12).

Additional objectives are to record serious adverse events, and if the intervention is found to be effective then cost-effectiveness and cost-utility analyses will also be completed.

Duration of treatment

12 weeks (preceded by a 2-week baseline phase).

Study design and methodology

SALTS is a 14-week, two-arm, parallel randomised controlled trial. A two-week baseline period (weeks -2 to -1) will be followed by 12 weeks intervention (weeks 1 to 12) Three hundred and twenty six adults (163 per group) with high BP will be randomised in a 1:1 ratio to receive either the salt reduction intervention (SaltSwitch app + dietary salt substitute) or control (generic information about heart-healthy eating), stratified by ethnicity (Māori and non-Māori) and age (<55yrs and 55yrs+). Randomisation will take place at the end of the baseline phase (beginning of week 1). The primary outcome is 24-hour urinary sodium excretion (mg/day) estimated using a spot (casual) urine sample at week 12. Secondary outcomes are (1) urinary potassium excretion (week 12), (2) average systolic BP (week 12),

(3) sodium content per 100g of packaged food purchases (week 12), (4) the number of participants achieving BP control (<135/85 mmHg; week 12)[1], and (5) use and acceptability of the SaltSwitch app and dietary salt substitute (week 12). Serious adverse events will be recorded, and if the intervention is effective then cost-effectiveness and cost-utility analyses will also be completed. Both groups will complete home-based BP measures twice per day (morning and evening) in triplicate during weeks -1, 6 and 12; collect a spot (casual) urine sample at weeks -1 and 12; and scan barcodes of all packaged foods purchased for consumption in the home during the 2-week baseline, and during the 2 weeks at the end of intervention (weeks 11 and 12) using a tailored study smartphone application.

Study population and number of participants

Participants will be 326 free-living adults (18yrs+) with high BP who own a smartphone and are willing to do grocery shopping during the study period. A General Practitioner (GP), healthcare provider, or study staff will have confirmed that they have high BP, and ≥80% will have a recorded systolic BP (SBP) of ≥140 mmHg at screening. Individuals with high BP and on antihypertensive medication will be eligible since effects of dietary salt reduction are additional to drug therapy[2]. The majority of participants (≥70%) will reside in the Auckland region.

Recruitment will be undertaken using four main methods: (1) face-to-face recruitment with a stand to promote the study and offer BP checks for interested participants. This recruitment approach will take place at Green Cross pharmacies, shopping malls, local events and markets, and the Stroke Foundation blood pressure van, (2) at Green Cross GP practices and other primary care providers NIHI has established relationships with e.g. the Fono, (3) using Social Media e.g. advertisements on Facebook to encourage people to register their interest and attend screening clinics at Grafton Campus, (4) via market research panels where a survey is sent to the panel and those who are interested can complete some questions about their eligibility and supply contact details, they are then invited to attend a screening clinic at Grafton Campus. Prospective participants can also obtain measurements required for screening from their local health professional. The health professional must record, sign and date a copy for the individual to send an electronic version to study staff by email to assess and if eligible, complete a referral form. Leaders of Māori communities NIHI has existing relationships with may also be approached to increase recruitment of Māori. Recruitment will be targeted to Auckland regions with higher proportions of Māori and low-income residents but may be expanded to include other regions of New Zealand, if required to meet the recruitment target.

Main criteria for inclusion

Participants will be eligible if they:

- Are aged 18 years or older
- Own a smartphone (iPhone or Android)
- Have a seated SBP of 140-200 mmHg and/or diastolic BP (DBP) of 85-120 mmHg at screening
- Are willing to do grocery shopping during the study period
- Can read and understand English
- Can provide informed consent

Exclusion criteria

Participants will be excluded if they:

- Currently use a dietary salt substitute

- Currently use the FoodSwitch app
- Have a contraindication to changing dietary sodium or potassium intake e.g. severe kidney disease or use a potassium sparing diuretic
- Are taking medication that may lead to hyponatraemia or acute build-up of body water such as furosemide, regular NSAID use, or regular prednisone use
- Have had a stroke or cardiovascular event (hospitalisation for heart attack, coronary artery revascularisation (CABG or stenting), stroke or heart failure) in the previous 6 months
- Have diagnosed heart failure

Eligible participants must provide at least six home-based BP measures during the two-week baseline period (weeks -2 and -1+/- two weeks),) and return a spot (casual) urine sample at baseline (week -1+/- two weeks).

Reference therapy

Dietary advice available from the Heart Foundation of NZ.

Criteria for evaluation

Primary outcome

24-hour urinary sodium excretion (mg per day) estimated using a spot (casual) urine sample at week 12.

Secondary outcomes

1. Urinary potassium excretion (mg per day) at week 12
2. Average systolic BP at week 12
3. Sodium content (mg per 100g) of packaged food purchases (weeks 11 and 12)
4. The number of participants achieving BP control (≤135/85 mmHg; week 12)
5. Use and acceptability of the SaltSwitch app and salt substitute at week 12 (intervention group only)

Serious adverse events will also be recorded during the trial period. If the intervention is found to be effective cost-effectiveness and cost-utility analyses will also be conducted.

Statistical Methods

Study power

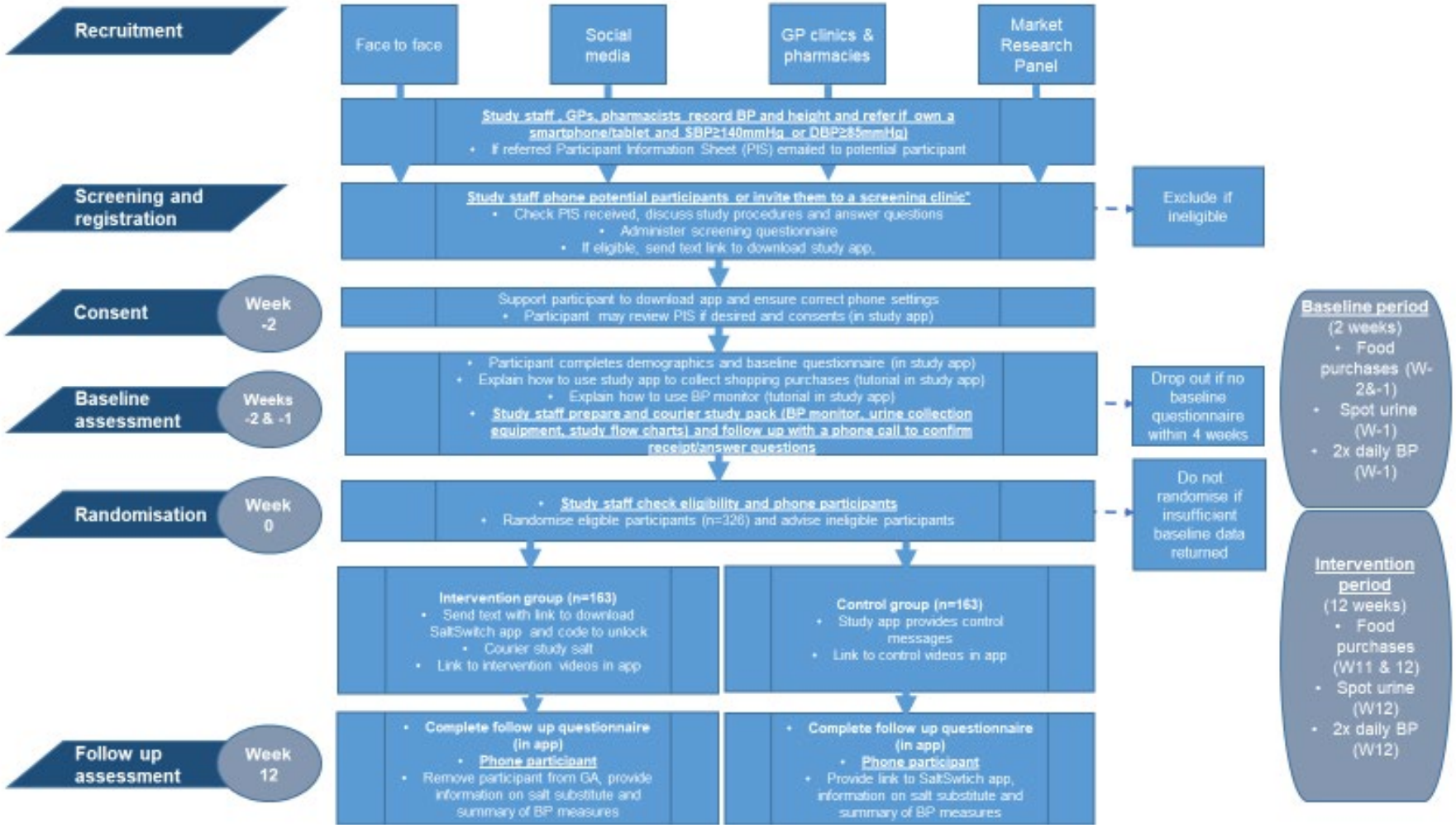
A total of 326 participants (163 per group) will provide 80% power at a 5% level of significance (two-sided) to detect a minimum effect size of 0.33 standard deviation (SD) in the primary outcome measure between groups at week 12 allowing for 10% loss to follow-up. This effect size is based on the SD derived from the SaltSwitch pilot study data (1400mg/day) where estimations of 24hr urinary sodium excretion were calculated using spot urine samples and a standard urine volume of 1.99L.

Statistical analysis

The primary outcome will be analysed using linear regression model adjusting for baseline outcome value and stratification factors. Model-adjusted mean differences between two groups will be estimated with 95% confidence interval and p-value. Multiple imputation will be used on missing primary outcome data in the primary intention to treat (ITT) analysis; this method creates multiple imputed datasets for incomplete outcome variables that are analysed using same regression models and combined for one inference. The Markov chain Monte Carlo method will be used to produce the parameter estimates, assuming the data

are from a multivariate normal distribution and are missing at random. Sensitivity analyses using different assumptions on the missing data, e.g. complete case analysis and last value carried forward, will also be considered to test the robustness of main trial analysis. Per protocol analysis will be performed for participants with no major protocol violations. Generalised linear regression models will be used to analyse secondary outcomes, using a link function appropriate to the distribution of outcome variable. Like the primary outcome analysis, the regression model will adjust for baseline outcome value and stratification factors where appropriate. Model-adjusted group differences will be presented with 95% confidence intervals and p-values. For the primary and key secondary outcomes, the heterogeneity of treatment effects between Māori and non-Māori participants will be tested using an interaction term between treatment group and ethnicity in the main model, and also for participants in two different age groups (<55yrs and 55yrs+). If the intervention is found to be effective, cost-effectiveness and cost-utility analyses will be pre-specified in a separate economic analysis plan and conducted by an Economist at the University of Otago Wellington.

2. Study Plan Schematic



3. Background and rationale

High blood pressure (BP) is the leading cause of premature and preventable death worldwide[1], with the number affected projected to rise from ~0.9 billion in 2000 to ~1.6 billion by 2025[2]. High BP is also a major risk factor for cardiovascular disease (CVD)[3], which in turn is responsible for approximately one third of all deaths in countries belonging to the Organization for Economic Cooperation and Development (OECD) [4].

The relationship between high BP and dietary sodium intake is widely recognised[5] with long-term dietary sodium reduction resulting in a fall in BP for both hypertensive and normotensive individuals, regardless of sex, ethnic group[6-8] or use of BP lowering medication[9]. While larger reductions in dietary sodium are related to larger falls in BP, even modest reductions can reduce BP and the associated morbidity and mortality from CVD[8].

However, most countries globally do not have Government-led salt reduction programs which encourage and enable widespread changes in the food environment[10], and for those that do, the trajectory of change in population sodium intakes has been slow[11, 12]. Therefore, effective, scalable dietary interventions to reduce the sodium intake of individuals are critical, particularly if OECD countries are to realize their 2025 commitment to The World Health Organization (WHO) to reduce population sodium intakes by 30% by 2025[13].

Two promising approaches are mobile health (mHealth) interventions and dietary salt substitutes. Mobile phones and smartphones are becoming synonymous with personal health; global mobile phone ownership was predicted to be 67% in 2019[14], with >90% ownership in most middle and high income countries where 70% or more own a smartphone[15]. A growing body of recent evidence also suggests electronic health and mHealth interventions can support dietary behavior change[16, 17] and reduce BP[17, 18]. However, there have been very few robust randomized controlled trials (RCTs) of app-based interventions for dietary sodium reduction or BP management[18, 19].

In 2014/15 we conducted a pilot trial of the potential six-week effects of the SaltSwitch smartphone app to support adults with diagnosed CVD to make lower sodium food choices[20]. SaltSwitch targets sodium consumed from packaged foods, which contributes ~70% of the sodium (and thus salt) consumed in Western countries[21]. SaltSwitch is a feature within the FoodSwitch app; by selecting this feature users can scan the barcode of a packaged food using their phone camera and receive an immediate traffic light nutrition label alongside a list of healthier, lower sodium options to switch to (Figure 1). The findings of our pilot (n=66) supported a larger trial with longer term follow-up (mean (95% CI) reduction in household purchases of salt: 0.3 (0.58 to 0.03) g/MJ or ~0.7 g per person per day)[20].

However, SaltSwitch does not address discretionary salt added in cooking and at the table, which accounts for ~15% of dietary intakes (the remainder is found naturally in fresh foods)[21]; this need can be met with dietary salt substitutes, which are used in place of regular table salt. Dietary salt substitutes are gaining in popularity because they are higher in potassium and lower in sodium but have a similar taste and flavour, thus reducing BP without requiring a change to habitual discretionary 'salt' use. Dietary salt substitutes have been found to be acceptable and effective in reducing BP in China[22, 23], and evidence from a 2019 meta-analysis (n=21 RCTs) found using a salt substitute can lead to a significant reduction in systolic and diastolic BP (DBP) for both hypertensive and normotensive adults (overall reduction: -7.8 (-9.5 to -6.2) mm Hg and -4.0 (-5.2 to -2.7) mm Hg, respectively)[24]. However, the overall quality of evidence in the 2019 review was considered low, and there were few studies (n=8/21) in high income countries where discretionary salt generally contributes a lower proportion of total salt intake (~15% vs. 76%[25])[21]. Nonetheless, salt substitutes hold promise for reducing sodium intakes because the population benefits far outweigh any risks[26], they are cheap, easy to use, include potassium, and act as a salient reminder of the importance of reducing dietary salt from all sources[27].

4. Objectives

The primary objective of this study is to determine the effects of a 12-week dietary salt reduction intervention (SaltSwitch app + dietary salt substitute) on urinary sodium excretion in adults with high BP.

The secondary objectives are to determine the effects of the dietary salt reduction intervention on: (1) urinary potassium excretion (week 12), (2) systolic blood pressure at week 12 (3) sodium content of packaged food purchases (weeks 11 & 12), (4) the number of participants achieving BP control (≤135/85 mmHg; week 12), and (5) use and acceptability of the SaltSwitch app and dietary salt substitute (week 12).

Additional objectives are to record serious adverse events, and if the intervention is found to be effective then cost-effectiveness and cost-utility analyses will also be completed.

4.1 Hypotheses

The primary hypothesis is that 12-weeks intervention with the dietary salt reduction intervention (SaltSwitch smartphone app + dietary salt substitute) will reduce the sodium intakes (measured using urinary sodium excretion) of adults with high BP, compared with control.

4.2 Secondary hypotheses

12-weeks intervention with the dietary salt reduction intervention (SaltSwitch smartphone app + dietary salt substitute) will, compared with control:

- Increase urinary potassium excretion
- Reduce systolic blood pressure
- Reduce the sodium content of packaged food purchases
- Result in a larger proportion of participants achieving BP control (≤135/85 mmHg)
- Be cost-effective

It is also anticipated that the SaltSwitch app and dietary salt substitute will be used frequently and be acceptable to participants.

5. Study Design

5.1 Inclusion criteria

Participants will be eligible if they:

- Are aged 18 years or older
- Own a smartphone (iPhone or Android)
- Have a seated SBP of 140-200 mmHg and/or diastolic BP (DBP) of 85-120 mmHg at screening
- Are willing to do grocery shopping during the study period
- Can read and understand English
- Can provide informed consent

5.2 Exclusion criteria

Participants will be excluded if they:

- Currently use a dietary salt substitute
- Currently use the FoodSwitch app
- Have a contraindication to changing dietary sodium or potassium intake e.g. severe kidney disease or use a potassium sparing diuretic
- Are taking medication that may lead to hyponatraemia or acute build-up of body water such as furosemide, regular NSAID use, or regular prednisone use
- Have had a stroke or cardiovascular event (hospitalisation for heart attack, coronary artery revascularisation (CABG or stenting), stroke or heart failure) in the previous 6 months
- Have diagnosed heart failure

5.3 Recruitment

Participants will be recruited using four main methods:

(1) Face-to-face recruitment at Green Cross pharmacies, in shopping malls, at local events and markets, and in the Stroke Foundation blood pressure van.
(2) Through Green Cross and other GP clinics/primary care providers that the researchers have existing relationships with e.g. The Fono
(3) Using social media e.g. Facebook, where adverts will be targeted to the characteristics of the intended study population and information given to direct people to Green Cross pharmacies or their local health provider to have their BP taken or a screening clinic at The University of Auckland's Grafton Campus
(4) Via market research panels where a survey is sent to the panel and those who are interested can complete some questions about their eligibility and supply contact details; they will then be invited to attend a screening clinic at Grafton Campus or directed to a Green Cross pharmacy or their local health provider to obtain BP measurements.

We will make every effort to employ Māori and Pacific Research Assistants (RAs) for recruitment of participants in shopping malls, and these same staff members will follow up participants by telephone throughout the study. Text messages inviting people registered with Green Cross for their prescriptions may also be used, and leaders of Māori communities NIHI has existing relationships with may be approached to increase recruitment of Māori. Recruitment will start in the Auckland region but may extend to other regions, if required to meet recruitment targets. Recruitment will be targeted to regions with higher proportions of Māori and low-income residents. Potential participants will watch a short study video and/or have the study explained to them either at the shopping mall, pharmacy or by their healthcare provider. A referral form will be completed where weight, BP, and smartphone ownership will be recorded. Interested people with a SBP

≥140mmHg and/or DBP≥85mmHg who own a smartphone (iPhone or Android) will provide a phone number and email address and consent to their details being forwarded to a study RA, who will call and administer a screening questionnaire to confirm eligibility.

5.4 Study intervention

Both groups (intervention and control) will receive a study smartphone app (compatible with iOS and Android). All participants who are randomised will be allowed to keep the Wi-Fi enabled BP monitor provided during the trial for home-based BP measures.

Intervention group

The intervention group will receive (in addition to the study app) the SaltSwitch smartphone app and a supply of low sodium high potassium dietary salt substitute, each component of the intervention targeted at a different source of dietary sodium.

The SaltSwitch app helps users to select lower salt packaged foods by enabling them to scan the barcode of a packaged food and receive an immediate, interpretive traffic light nutrition label on-screen plus suggestions for lower salt alternatives (Figure 1). Users can also directly compare the salt content and healthiness of two or more food products. The traffic light nutrition criteria underpinning the app are sourced from the UK traffic light nutrition labelling system[28], and the tool used to rank foods by how healthy they are is the Australasian Nutrient Profiling Scoring Criterion (NPSC)[29]. SaltSwitch was originally developed by the George Institute for Global Health in Sydney, and has been adapted for NZ shoppers using the Nutritrack food composition database; it is a filter for the generic FoodSwitch app currently available for free in the NZ app store (iOS and Android). However, the Nutritrack food product database underpinning the app has not been updated since 2016, thus limiting the utility of the publicly available version. Participants in the intervention group will receive a link in a text message to download the SaltSwitch app in the NZ iOS and Android app stores. A code will be provided to unlock the app ensuring participants outside of the study will not contribute to Google Analytics data; this will also decrease the likelihood of participants in the control group accessing the app. Once downloaded the SaltSwitch app will take the user through a brief tutorial on how to use the app to make healthier, lower salt food choices.

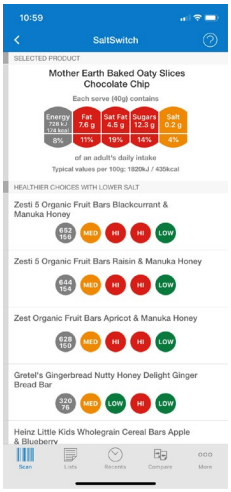


Figure 1: SaltSwitch app

The dietary salt substitute targets discretionary (added) sodium. Participants will receive two 79g bottles of 'Salt for Life' comprising a blend of potassium salt and sea salt, which provides a 75% reduction in sodium compared to regular table salt and comprises 74.5% potassium chloride, 24.5% sodium chloride, and ~1% silicon dioxide (anticaking agent). Two bottles/shakers will enable participants to have one for use in the home, and a second saltshaker for mobile use e.g. to replace salt usually added at a restaurant or café. The salt substitute is shown in Figure 2 in its branded packaging but will be provided in plain packaging for study participants. Nutek are providing the salt substitute for use in the study, but do not otherwise have any involvement in the research. The salt substitute provided in the trial is not currently available for sale in New Zealand pharmacies or any other locations (although similar products such as Mrs Rodgers Low Sodium Salt are available for sale in some New Zealand supermarkets).

Figure 2: Salt for Life salt substitute

Participants in the intervention group will receive weekly notifications to their phone to remind them to use the SaltSwitch app when shopping and replace use of regular table salt with the 'study salt'. The study app will also remind participants to take their BP during the three allocated times of the study (week -1, 6, and 12).

Control group

Participants randomised to the control group will receive the study smartphone app which will send a notification after randomisation (i.e. at week 1) with links to publicly available information on heart-healthy eating information on the Heart Foundation of New Zealand website[30]. The study app will also provide notifications to participants to remind them to measure their BP during the study (week -1, 6, and 12).

5.5 Randomisation

Eligible participants will be randomised at the beginning of week 1 via a centralised randomisation system. All participants will be randomised in a 1:1 ratio to the intervention or control group, stratified by ethnicity (Māori and non-Māori) and age (<55yrs and 55yrs+) using stratified block randomisation with variable block sizes of two or four.

The RA will activate randomisation for each participant, which will ensure receipt of the correct notifications from the study smartphone app (i.e. intervention or control). The RA will text participants to notify them of the group they have been randomised to and provide the intervention group their SaltSwitch access code. The RA will then call participants in the intervention group to help download and unlock the SaltSwitch app and watch the tutorial. Following the randomisation phone call a study RA will courier a supply of study salt to those in the intervention group.

5.6 Blinding

It is not possible to blind study participants or researchers to who receives the salt reduction intervention. The study investigators will have no access to treatment allocations during the study. The primary and secondary outcomes will be measured objectively using home-based BP monitors, urine samples and scanned barcodes of packaged foods and beverages purchased, the latter which will be linked to a packaged food composition database to determine the sodium contents.

5.7 Concomitant therapy

Individuals with high BP and on anti-hypertensive medication will be eligible to participate since effects of dietary salt reduction on dietary salt reduction are additional to drug therapy[2]. Participants taking ACE inhibitors who have normal renal function will be eligible to take part. There is a very small risk of hyperkalaemia (high body potassium) for these participants, but they will be under clinical care, and encouraged to advise their GP of their participation in the study. Participants will be free to take any other medications they have been prescribed. Participants will be asked to list all medications they are currently taking during screening, and will be excluded from the trial at baseline if they are taking any medications which may lead to hyponatraemia or acute build-up of body water including frusemide, regular NSAID use, or regular prednisone use.

5.8 Withdrawal criteria

Participants will be informed that they may withdraw from the study at any time. They may also withdraw their data at any time. Data for withdrawn participants will be included in intention-to-treat analysis. The PI may withdraw a participant from the study if they feel it is in their best interest, or the study is terminated.

5.9 Participant referral

Interested people may be referred during recruitment in shopping malls, events, markets, pharmacies, on the Stroke Foundation BP bus, GP clinics, on social media and via market research panels. Study staff and healthcare providers at venues will complete a short referral form on the DIET website. Participant's height, weight and BP (average of at least two measures) will be collected and recorded along with their name, mobile number, email address, smartphone ownership, and consent to be contacted by the study team. Participants who are referred will be emailed a copy of the PIS. If the participant has expressed interest in the study via Facebook or a market research survey they will be contacted, screened and asked to attend a Grafton Clinic or directed to their local healthcare provider/participating Green Cross pharmacies to obtain required measurements.

5.10 Participant screening

Potentially eligible participants will receive a follow up phone call from a study RA and a screening questionnaire will be administered. The screening questionnaire will collect date of birth and gender (male, female, gender diverse, prefer not to specify), and information on remaining inclusion/exclusion criteria relevant to the screening period: type of smartphone, contribution to household grocery shopping (or willing to for the study period), able to read and understand English, current use of a dietary salt substitute or the FoodSwitch app, contraindication to reducing salt or increasing potassium in their diet, recent stroke or cardiovascular event, or diagnosed heart failure. Eligible participants will be sent a text link to download the study smartphone app.

5.11 Changes to referral and screening process due to Covid-19 – Addition of remote screening option

Due to Covid-19 and closure of The University of Auckland campuses until the end of July, a remote referral and screening process has been devised to allow the study to continue during this period and ensure the safety of study participants and staff. This remote screening option will be offered to any participants recruited through self-referral methods such as market research surveys and Facebook who are not able to attend a clinic for screening measurements. Instead of attending a face to face clinic the participant will be screened over the phone and, if eligible,

asked to self-report their weight and height. They may self-report these measures either by measuring them at home or by calling their GP if they have had a measure in the last three months. If they are unable to provide the measurements, they will be placed on hold until face to face clinics are deemed safe to proceed. If they can provide measurements, they will be couried a blood pressure monitor and guided over the phone by a Research Assistant to take three seated blood pressure measurements (one minute apart as per the protocol) and read these to the Research Assistant. The Research Assistant will then determine if the participant is eligible to proceed with the study based on the eligibility criteria and, if so, support the participant to progress to the consent and baseline phase of the study. If they are ineligible to proceed the Research Assistant will provide guidance on return of the blood pressure monitor. A flow diagram outlining the remote screening option process can be found in Appendix 5.

5.12 Informed consent

Following confirmation of eligibility, a study RA will make sure the participant has read and understood the PIS and will support the participant to download the study smartphone app and complete the consent form (all within the app). The consent form will include one question asking participants if they would be happy to be contacted after the study has finished, to assess longer term outcomes or to be invited to take part in other research studies. Participants who do not consent to this may still take part in the study. Auckland-based participants may be offered face-to-face screening at the University of Auckland Grafton clinics if necessary.

5.13 Baseline assessment

Baseline assessment will comprise four components: (1) the baseline questionnaire, (2) collection of twice-daily home-based BP measures during week -1 (+/- two weeks), (3) return of a spot (casual) urine sample during week -1 (+/- two weeks), and (4) scanning of barcodes for all packaged foods and beverages bought into the home for consumption during weeks -2 and -1 (+/- two weeks), (minimum 10 required).

Baseline questionnaire

Following consent, participants will be prompted in the study app to complete the baseline questionnaire. This may be done with the support of a study RA on the phone, or in the participant's own time. Two text reminders will be sent five days apart if required. If the baseline questionnaire has not been completed within four weeks following consent, the participant will be excluded from the study.

The baseline questionnaire will collect the following information:

1. Initials, date of birth
2. Type of smartphone
3. Discretionary salt intake
4. Preference for salty food
5. Usual take-away consumption
6. Use of nutrition labels when food shopping
7. Existing health conditions
8. Number living in household for which groceries are usually bought each week
9. Concurrent medications
10. Ethnicity participant most identifies with
11. Highest qualification
12. Employment status
13. Annual household income

Collection of a spot (casual) urine sample

Following completion of the baseline questionnaire, participants will be couriered a package containing equipment to collect a spot (casual) urine sample and a Wi-Fi enabled BP monitor (BlipCare). The barcode scanning functionality with the study smartphone app will also be activated at this time. A study RA will text/phone participants and guide them through short tutorials within the study smartphone app on how to collect urine samples, measure BP, and scan the barcodes of purchased packaged foods and beverages (or tutorials may be watched in the participants own time).

The spot (casual) urine sample will be collected by the participant at any time of the day during week -1 +/- two weeks), except first void. Participants will collect urine in a beaker with a pouring facility, which will be used to transfer ~5mL into a pre-labelled 10mL tube. Participants will freeze the sample before couriering it to researchers at The University of Auckland. Participants will be provided with a small bubble wrapped bag for the urine sample, and a same-day courier bag. Participants may keep their urine sample cool with a freezer pack rather than store it in the freezer or send it immediately by courier if they prefer. A study RA will log urine samples and store them at -4deg before couriering bulk samples to The University of Otago for analysis. Two text reminders to collect the urine sample will be sent per week for the two-week baseline period. If a urine sample has not been returned for the baseline period, these data will be considered missing.

Collection of BP

Blood pressure will be collected by the participant on a home-based automated Wi-Fi enable BP monitor using methods adapted from the PATHWAY-2 trial and according to European Society of Cardiology guidelines[31,32]. Participants will collect BP measures in triplicate after 5 mins rest, 1 minute apart. Measures will be taken both morning and evening, ideally at the same time each day during week -1 +/- two weeks). Participants will receive twice-daily notifications to their phone to remind them to collect their BP. If no BP measures have been received by researchers within one week of the phone call to confirm receipt of the monitor, reminder notifications will be sent and the participant will receive a phone call from a study RA to ensure they are confident in using the monitor. If less than six BP measures have been received within two weeks following courier of the BP monitor, BP data will be considered missing, the participant will be excluded, and the BP monitor will returned to researchers. Blood pressure measures will be received in real time directly from participant's monitors via an Application Programming Interface (API). Consistently elevated SBP (>180mmHg for three consecutive days including any missing days), consistently low SBP (<90mmHg for three consecutive days including any missing days), or major changes in SBP from baseline (>20mmHg) will trigger a notification to be sent to the study staff. The RA will confirm this by investigating the raw data and call the participant advising them that their BP measure is outside the normal range and it is recommended that they visit their GP as soon as possible. The RA will send a letter to notify a participant‘s GP where required.

Collection of barcodes for packaged food purchases

Participants will scan the barcode of all packaged foods and beverages bought into the home for their consumption during the two-week baseline period (weeks -2 and -1 +/- two weeks). Weekly notifications will be sent to their phone via the study smartphone app to remind them to complete the scanning. Barcodes will be used as unique product identifiers for linking with the Nutritrack supermarket food composition database[30] to determine the sodium content of food purchases. If no shopping purchase information has been returned for the baseline period, these data will be considered missing.

5.14 Follow-up assessment

Follow up assessment will comprise four components: (1) the follow up questionnaire, (2) return of a spot (casual) urine sample during week 12 (+/- one week)., (3) collection of home-based BP

measures during week 12 (+/- one week), and (4) collection of barcodes for all packaged foods and beverages bought into the home for consumption during weeks 11 and 12 (+/- one week)..

Follow up questionnaire

At the end of the 12-week intervention period, participants will be prompted by the study app to complete the follow up questionnaire. Two text reminders will be sent five days apart. If the follow up questionnaire has not been completed within four weeks of the end of the intervention period, then follow up data will be considered missing.

The follow up questionnaire will collect the following information:

1. Change in habits regarding salt added to food and/or take away consumption
2. Change in the in the number of participants household food is usually purchased for
3. Change in body weight (self-reported)
4. Use and acceptability of the SaltSwtich smartphone app (intervention group only)
5. Use and acceptability of the dietary salt substitute and left-over study salt (intervention group only – weighed if possible or estimated if not possible)
6. Left-over regular table salt (control group only - weighed if possible or estimated if not possible)
7. Details of any cardiac event in the past 12 weeks (prompt to complete Serious Adverse Event form if appropriate)
8. Number of visits to the Dr and/or hospital during the study period, and number of these visits which are primarily due to their BP or medication for their BP
9. Use of meal boxes during the study period e.g. My Food Bag, WOOP.

Collection of BP, urine and packaged food purchases

A spot urine sample (week 12 +/- one week) home-based BP measures (week 12+/- one week), and barcodes for packaged food and beverage purchases (weeks 11 and 12 +/- one week). will be collected as per the baseline phase. Participants will be couriered enough equipment at baseline for collection and return of the second spot urine sample.

5.15 Unique study code allocation

Participants will be automatically allocated a unique study code (USC) at referral to enable linkage of information for each participant throughout the trial. USC numbers will be between 00001 and 09999 and allocated randomly. Separate referral and registration numbers will also be allocated to track study numbers at each phase of the trial. All data from the app, including questionnaires and barcodes for shopping purchases, will be exported to protected Drupal database on secure servers at The University of Auckland.

5.16 Physical measurements

Blood pressure, height and weight at screening

Blood pressure, height and weight will be measured at referral by either a trained GP, nurse, pharmacist, or RA. Height will be measured using a standard stadiometer to the nearest 1cm. Blood pressure will ideally be measured seated after 5 minutes rest using an automated BP monitoring device. Three BP measurements will be taken from which the average of the second two measures will be calculated. However, to minimise burden on GPs, nurses, and pharmacists, at least two measures will be enough for referral.

Urine sample collection

Baseline and follow up spot (casual) urine samples will be collected as described for the baseline phase of the study.

Home based BP measures

Baseline and follow up home-based BP measures will be collected as described for the baseline phase of the study.

5.16 Data collection tutorials

Participants will receive tutorials within the study smartphone app on how to collect BP measures and urine samples, and how to scan the barcodes of packaged foods and beverages bought into the home. A study RA will be available to answer any questions on the tutorials over the phone during the registration phone call, via text message or email. Auckland-based participants who require face-to-face tutorials may be offered these at The University of Auckland Grafton Clinics.

Following the registration phone call and completion of the baseline questionnaire, participants will be couriered a package containing:

- A flow chart showing the processes in the study and the data to collect each week
- Urine collection equipment for 2x spot urine samples
- Wi-Fi enabled BP monitor set up to automatically send readings to University of Auckland servers (via an API)
- Pre-paid courier bags and small bubble-wrapped bags to return tubes containing frozen urine samples (x2)

Following receipt of the package, participants will receive a text from a study RA checking that they are comfortable with how to collect their BP; collect, freeze and courier their urine sample; and collect barcodes for packaged food purchases. The RA will call participants who request support completing the data collection. Participants will also be able to phone, text or email if they have any further questions on how to collect any of the study data.

5.17 Primary outcome measure

24-hour urinary sodium excretion (mg per day) estimated using a spot (casual) urine sample at week 12.

5.18 Secondary outcome measures

1. Urinary potassium excretion (mg per day) at week 12
2. Average systolic BP at week 12
3. Sodium content (mg per 100g) of packaged food purchases (weeks 11 and 12)
4. The number of participants achieving BP control (≤135/85 mmHg; week 12)
5. Use and acceptability of the SaltSwitch app and salt substitute at week 12 (intervention group only)

Serious adverse events will also be recorded during the trial period. If the intervention is found to be effective cost-effectiveness and cost-utility analyses will also be conducted.

5.19 Schedule of intervention and follow-up

Participants will be notified by a study RA (via telephone) as to their treatment allocation.

Intervention participants will be sent a text with a link to download the SaltSwitch smartphone app in the iOS or Android app stores, and a code to unlock the app. They will also be sent a supply of study salt (dietary salt substitute) via courier and a link to the intervention tutorial/video (via a notification from the study smartphone app), the latter which will explain how to use the two components of the BP lowering intervention. Intervention participants will receive weekly notifications reminding them to use the SaltSwtich app when shopping for household food, and to use the study salt in place of regular table salt (but not to increase their intake/use of salt).

Control participants will receive one notification at the beginning of the intervention phase (via email) containing a link to information on heart-healthy eating on the Heart Foundation of NZ website, and will be advised not to change their regular salt intake.

At the end of the intervention period participants in the intervention group will receive instructions to ensure they are able to continue using the SaltSwitch smartphone app, but their study data will cease to be collected/recorded in Google Analytics. Control group participants will receive a information on how to download the SaltSwitch app. Both groups will be given information about how to purchase the dietary salt substitute (or a similar product available for sale in New Zealand). Participants will be allowed to keep their BP monitor and will be provided with information on how to download the BP monitor smartphone app to receive a summary of their BP measures collected during the study (and any additional BP measures they collect after study end).

Participants in the intervention group who complete and return their final urine sample will also be eligible to enter a draw to win one of five $100 grocery vouchers. To enter the draw, participants must indicate your interest on the consent form and complete and return their final urine sample. Winners will be contacted by phone and email at the end of the study (estimated date March 2021). If no response is received within 14 days of notification, another winner will be drawn at random.

5.20 Detail of contact points with participants

Eligibility (contact 1 – phone call)

Potentially eligible participants will receive a phone call (call 1) from a study RA who will administer a screening questionnaire in Drupal software to confirm eligibility. The screening questionnaire will incorporate relevant inclusion/exclusion criteria.

Support to download study smartphone app, complete consent and baseline questionnaire, and watch study tutorials (contact 1)

Following screening, the RA will ensure participants have received and read the Participant Information Sheet (emailed following referral). The RA will then send a link to download the study smartphone app and an access code with instructions to complete the consent form and baseline questionnaire via text message. The RA may stay on the telephone to guide participants to download the study smartphone app and to complete the consent form and baseline questionnaire (in app). Participants are directed to watch study tutorials on how to collect shopping purchases, urine, and BP data and advised that study staff are available to answer any questions if needed during the study period. However, the participant may choose to hang up and complete these tasks in their own time or may book an appointment to come into the University of Grafton Campus Clinic to complete these tasks face-to-face. If the participant chooses to complete consent in their own time and consent has not been completed within five days, one notification and follow-up phone call will be made to the participant. Following call 1 and completion of the consent form and baseline questionnaire, a study RA will courier the participant a study pack including the BP monitor, urine collection equipment and a study flow

chart. If the baseline questionnaire has not been completed within one-week follow-up phone call(s) (call 1b & c) may be required.

Follow up on receipt of study pack (contact 2 – phone call or text message)

Following courier of the study pack, the RA will phone or text message the participant (contact 2) a few days later to check they have received it and to offer support on collection of BP measures, returning a spot urine sample, and scanning barcodes of shopping purchases. Participants will also be reminded of the study phone number to call or text, and email address to ask any further questions, as well as the study video tutorials explaining procedures.

Notification of randomisation (contact 3 – text message)

At the end of baseline (end of week -1), a study RA will confirm eligibility (minimum of six BP measures received, one urine sample, and 10 scanned food purchases) and text the participant (contact 3) to notify them of the group they have been allocated to. The RA will activate the participants study smartphone app to receive the appropriate notifications, based on their allocation. The RA will call participants in the intervention group to support them download the SaltSwitch smartphone app, enter a code to 'unlock' it, and watch a short tutorial (within the app) on how to use it. The intervention group will be notified that they will receive a supply of study salt in the mail.

Study end (contact 4 – a. Phone call and b. Email/Letter)

Participants will receive a notification via the study app at the end of week 12 to complete the follow-up questionnaire. If the follow up questionnaire has not been completed within one week following the end of the study, a follow-up phone call(s) (contact 4a.) may be required. On completion of the follow up questionnaire participants will receive a notification thanking them for their participation, a summary of their BP measures over the study, and more information about the dietary salt substitute. A study completion email or letter (contact 4b.) will also be sent to participants which will include instructions (1) to download the BlipCare smartphone app to monitor their BP measures post study-completion (2) to change the settings in their phone to enable them to continue using the SaltSwitch app but to cease collection of their use of the app by Google Analytics if in the intervention group (3) to download the SaltSwitch app (control group) and on how to purchase the dietary salt substitute. The RA will disconnect the participant's blood pressure monitor from the study system to stop data being sent to the study team.

5.21 Table 1: Summary of SALTS trial stages and procedures

Assessment	Referral	Screening	Baseline	Randomisation	Mid study	Follow-up
Timing	**Recruitment**	**Pre-baseline**	**Week -2/-1**	**Week 1**	**Week 6**	**Week 12**
Method of contact and data collection	**Face-to-face (malls, pharmacies, GP clinics)**	**Contact 1**	**Contact 1, API, courier, study smartphone app**	**Contact 3, courier**	**API**	**Contact1, API, courier, study smartphone app**
Referral						
Name, initials, phone number, email	√					
Eligibility 1 (smartphone ownership, BP)	√					
Physical measures (height, weight, BP)	√					
Referral number allocated	√					
Participant Information Sheet emailed	√					
Screening						
Verbal consent to screening		√				
Gender		√				
Eligibility 2 (type of smartphone, date of birth, English, contribute to household shopping, current FoodSwitch use, recent CVD event, heart failure, contraindications, holidays)		√				
Screening number linked to referral number		√				
Informed consent						
PIS read and understood, consent in app		√				
Registration number allocated and linked to screening number		√				
Study smartphone app downloaded						

Assessment	Referral	Screening	Baseline	Randomisation	Mid study	Follow-up
Timing	**Recruitment**	**Pre-baseline**	**Week -2/-1**	**Week 1**	**Week 6**	**Week 12**
Method of contact and data collection	**Face-to-face (malls, pharmacies, GP clinics)**	**Contact 1**	**Contact 1, API, courier, study smartphone app**	**Contact 3, courier**	**API**	**Contact1, API, courier, study smartphone app**
Tutorials completed for collection and return of BP, urine, shopping purchase data		√				
Baseline questionnaire						
Initials, date of birth			√			
Discretionary salt			√			
Preference for salty food			√			
Use of nutrition labels			√			
No. household members groceries bought for			√			
Existing health conditions			√			
Concurrent medications			√			
Ethnicity			√			
Employment			√			
Household income			√			
GP contact information			√			
Study pack 1 sent to participant						
BP monitor, urine collection equipment, study flow chart			√			
Baseline measures						

Assessment	Referral	Screening	Baseline	Randomisation	Mid study	Follow-up
Timing	**Recruitment**	**Pre-baseline**	**Week -2/-1**	**Week 1**	**Week 6**	**Week 12**
Method of contact and data collection	**Face-to-face (malls, pharmacies, GP clinics)**	**Contact 1**	**Contact 1, API, courier, study smartphone app**	**Contact 3, courier**	**API**	**Contact1, API, courier, study smartphone app**
Twice daily home-based BP measures during week -1			√			
1x urine sample couriered to researchers			√			
Barcodes scanned using study app			√			
Randomisation						
Randomisation recorded				√		
Study pack 2 sent to participant						
Dietary salt/salt substitute				√		
Mid study measures						
Twice daily home-based BP measures during week 6					√	
Follow up measures						
Twice daily home-based BP measures during week 12						√
1x sample couriered to researchers						√
Barcodes scanned using study app						√
Follow up questionnaire						
Salt added to food (change)						√
No. household members groceries bought for						√

Assessment	Referral	Screening	Baseline	Randomisation	Mid study	Follow-up
Timing	**Recruitment**	**Pre-baseline**	**Week -2/-1**	**Week 1**	**Week 6**	**Week 12**
Method of contact and data collection	**Face-to-face (malls, pharmacies, GP clinics)**	**Contact 1**	**Contact 1, API, courier, study smartphone app**	**Contact 3, courier**	**API**	**Contact1, API, courier, study smartphone app**
Weight						√
Use and acceptability SaltSwitch app (intervention group only)						√
Use and acceptability of study salt, and remaining salt substitute/salt						√
Details of adverse events						√
Visits to the Dr and/or hospital, and visits due primarily to BP or medication for BP						√
Use of meal boxes e.g. My Food Bag						√

6. Statistical Considerations

6.1 Sample size

A total of 326 participants (163 per group) will provide 80% power at a 5% level of significance (two-sided) to detect a minimum effect size of 0.33 standard deviation (SD) in the primary outcome measure between groups at week 12 allowing for 10% loss to follow-up. This effect size is based on the SD derived from the SaltSwitch pilot study data (1400mg/day) where estimations of 24hr urinary sodium excretion were calculated using spot urine samples and a standard urine volume of 1.99L.

6.2 Statistical analysis

Statistical analysis will be performed on an intention-to-treat (ITT) basis, using SAS version 9.4 (SAS Institute Inc. Cary NC, USA). All statistical tests will be two-sided at 5% significance level. Trial results will be reported according to CONSORT 2010 guidelines for parallel group randomised trials.

6.2.1 Baseline characteristics

Baseline characteristics of all randomised participants will be summarised using descriptive statistics. Continuous variables will be described as numbers of observed and missing values, mean ± standard deviation. Categorical variables will be described as numbers and percentages. Results will be presented for each of the two treatment arms overall, and by ethnicity (Māori vs non-Māori) and age group (<55yrs and 55yrs+) separately as stratification factors. Since any differences between randomised groups at baseline could only have occurred by chance, no formal significance testing will be conducted.

6.2.2 Treatment effects

The primary outcome will be analysed using linear regression model adjusting for baseline outcome value and stratification factors. Model-adjusted mean differences between two groups will be estimated with 95% confidence interval and p-value. Multiple imputation will be used on missing primary outcome data in the primary intention to treat (ITT) analysis; this method creates multiple imputed datasets for incomplete outcome variables that are analysed using same regression models and combined for one inference. The Markov chain Monte Carlo method will be used to produce the parameter estimates, assuming the data are from a multivariate normal distribution and are missing at random. Sensitivity analyses using different assumptions on the missing data, e.g. complete case analysis and last value carried forward, will also be considered to test the robustness of main trial analysis. Per protocol analysis will be performed for participants with no major protocol violations. Generalised linear regression models will be used to analyse secondary outcomes, using a link function appropriate to the distribution of outcome variable. Similar to the primary outcome analysis, the regression model will adjust for baseline outcome value and stratification factors where appropriate. Model-adjusted group differences will be presented with 95% confidence intervals and p-values. For the primary and key secondary outcomes, the heterogeneity of treatment effects between Māori and non-Māori participants will be tested using an interaction term between treatment group and ethnicity in the main model, and also for participants in two different age groups (<55yrs and 55yrs+).

6.2.3 Cost-effectiveness analysis

If the intervention is found to be effective, cost-effectiveness and cost-utility analyses will be pre-specified in a separate economic analysis plan and conducted by an Economist at the University of Otago Wellington.

6.2.4 Interim analysis

No interim analysis will be undertaken in this trial.

6.3 Data Management

The design and management of all databases associated with this trial (aside from the databases used for recruitment) will be undertaken by the study data manager (JF) and statistician (YJ) in collaboration with the PI (HE) and study co-investigators.

7. Ethical Approval and Consent

7.1 National ethics approval

Ethics approval was granted by the Health and Disability Ethics Committees (HDEC) on 17th February 2019 (Ref 18/NTB/239).

7.2 Scott committee approval

No medication will be administered as part of this study. Therefore, SCOTT approval is not required.

7.3 Informed consent

Maintenance of confidentiality and compliance with the Privacy Act will be emphasised to all study participants. Participation in the study will be entirely voluntary. A Participant Information Sheet (PIS) and Consent Form will be provided to all eligible potential participants. The consent form will include a question asking participants if they would be happy to be contacted up to two years after the study has finished, to assess longer term outcomes. Participants who do not consent to this question may still take part in the study. Electronic consent will be obtained at the baseline assessment within the study smartphone app. Prior to consent all participants will have had the opportunity to read the PIS and ask questions.

8. Assessment of Safety / Adverse Event Reporting

8.1 Adverse events

8.1.1 Definition of an adverse event

An adverse event (AE) is any untoward clinical occurrence in a participant which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study treatment, whether or not it is considered related to the product. An AE will include any illness, sign, symptom, or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under study.

AEs will not be recorded in this trial.

8.2 Serious adverse events

8.2.1 Definition of a serious adverse event

A serious adverse event (SAE) is any untoward clinical occurrence in a participant that does not necessarily have a causal relationship with the treatment. SAEs are those that result in: death, are life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), require hospitalisation or prolongation of hospitalisation, cause persistent or significant disability/incapacity, result in congenital abnormality, are an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject/subject or may require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

SAEs will be recorded in this trial.

8.2.2 Contact for notification of serious adverse events

Participants will be informed on the PIS and consent form that they will be asked to report any SAEs that occurred during the study period, at the end of the study. The RA will report all SAEs immediately to the PI and PM who will then report them in the form of a safety update to HDEC, on a quarterly basis. The PI will have the overall responsibility of ensuring that all events are reported to the regulatory authorities in the appropriate timeframes and that the process is not breached.

8.3 Reporting safety information

As the SaltSwitch smartphone app and dietary salt substitute are considered low risk, SAEs will not be collected in real time, and data for participants experiencing SAEs will not be removed from the study. All SAEs will be recorded on the follow-up questionnaire within the study smartphone app and if necessary will be follow-up with a phone call to ensure completeness and accuracy of SAE information. If known, the name of the underlying illness or disorder (i.e. the diagnosis) will be recorded, rather than its individual symptoms. All reported SAEs will be assessed within 24hours by an authorised medical representative: Dr Chris Bullen (or delegate) will determine whether the AE is an SAE.

8.4 Unblinding

Participants will not be blinded to receipt of the dietary salt reduction intervention. The study investigators will have no access to treatment allocations during the study. If unblinding is required this will be undertaken by an independent researcher.

8.5 Data safety and monitoring

Ellenburg et al. (2002) provide guidelines for deciding whether or not to establish a Data Safety and Monitoring Committee (DMC) for a trial. They propose that if two or more of the following criteria are met then a DMC is required[39].

1. The trial is intended to provide definitive information about the effectiveness and/or safety of a medical intervention.
2. There are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity.
3. The trial is evaluating mortality or another major endpoint such that inferiority of one treatment arm has safety as well as effectiveness implications.
4. It would be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not fully addressed.

The SALTS trial does not meet two or more of the above criteria. Consequently, a DMC will not be established for the trial.

9. Relevance to Health

High BP alone accounts for 8.3% of health loss in New Zealand (NZ)[10] and is a major risk factor for cardiovascular disease (CVD). One in five NZ adults currently has high BP, 17% take BP-lowering medication, and ~172,000 are living with CVD.[16] Cardiovascular disease is the leading cause of health loss for NZ males and the second ranked cause for NZ females, accounting for 10% and 6% of health loss respectively[10]. Furthermore, the burden of CVD is disproportionally attributed, with Māori and Pacific peoples suffering a greater proportion of the burden, particularly in the younger age groups (35 to 50 years)[17]. In 2006, CVD was estimated to account for 17.5% of the total national disease burden, with coronary heart disease (CHD) the leading specific cause of health loss accounting for 9.3% of disability adjusted life years (DALYs) lost by the population[10]. The costs of CVD to the healthcare system are also substantial; in 2011/12, hospitalisations for IHD cost $228 million, for stroke $67 million, and for high BP, $6 million[18].

However, a considerable amount of CVD risk is potentially modifiable by reducing dietary salt intake[19], and in NZ there is substantial room for improvement; salt intake ranks as the second largest contributor to health loss[10], and our current population salt intake is ~40% higher than WHO recommendations (~8.4g (3,373mg sodium)/day compared with 5g (2,000mg sodium)/day, respectively)[21]. Further, despite being a signatory to the global 2013 WHO target to reduce population salt intake by a relative 30% towards 5g per day by 2025.[20], we do not (in contrast to 75 other countries internationally) have a government-led national salt reduction strategy. The Heart Foundation has worked with food manufacturers to reduce salt in low cost, high volume foods such as bread, but the trajectory of change to date suggests NZ will fall far short of realising our 2025 WHO commitment[14]. Therefore, more effective, scalable salt reduction interventions such as that being tested in the SALTS study (SaltSwitch app + dietary salt substitute) are urgently needed.

This research directly addresses four of the 10 key targets for NCDs were set by member nations at the 2012 World Health United Nations Assembly: (1) 25% relative reduction in overall mortality from CVD, cancer, diabetes or chronic respiratory disease; (2) 25% relative reduction in prevalence of raised BP; (3) 30% relative reduction in mean adult population intake of salt, with the aim of achieving recommended level of less than 5g/day; and (4) a minimum of 80% availability of affordable, quality-assured essential NCD medicines and technologies in public and private sectors[40]. Further, this research has the potential to reduce health inequalities. Māori, Pacific and those from lower socio-economic groups have similar dietary salt intakes to the general population[21] but are more likely to be affected by CVD than non-Māori, non-Pacific and those from higher socio-economic groups. With lower-cost smartphones being available to the market, the fact that the SaltSwitch app, once downloaded, does not require Wi-Fi or data to work, and the cheap cost of the dietary salt substitute, it is possible that this intervention could adequately reach Māori, Pacific and lower socio-economic groups. If found to be effective the intervention package being tested in the SALTS trial could be rolled out nationally at a relatively low cost.

10. Dissemination of Results

10.1 Trial registration

The trial will be registered with the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/), an organisation that maintains a database of trials in progress to assist with the synthesis of controlled trials.

10.2 Study participants

At the end of the study, all participants will receive a notification thanking them for their time and contribution to the study. They will also be given a summary of their BP measures during the trial. Participants who request on their consent form will also receive a brief summary of the results, an outline of their significance, and plans for publication (at study completion).

10.3 The general public

It is anticipated that the general public will be informed about the trial via local media coverage, social media (NIHI and DIET programme twitter and Facebook accounts) and publicly accessible websites including the DIET programme website, and the NIHI website.

10.4 Academic / professional colleagues

Academic and professional colleagues will be informed about the trial via articles submitted to national and international peer-reviewed medical and nutrition journals, reports and presentations to Government and Non-Government organisations, presentations at national and international medical and nutrition conferences, and news releases to the mass media.

10.5 Health service funders and providers

Health service funders and providers will be kept informed about the trial via presentations at conferences. Reports and presentations with any recommendations arising out of the study will be sent to the Ministry of Health, Non-Government Organisations (including the Heart Foundation, cardiac rehabilitation groups, District Health Boards, and Primary Health Organisations) to assist in promoting evidence-based practice and the development of future research.

10.6 Iwi / Māori

Consultation with co-investigator Dr Lisa Te Morenga, (Ngapuhi, Ngāti Whātua, Te Rarawa)) will be on-going throughout the study to ensure relevance to Māori, engagement with Māori stakeholders, potential for informing Māori health development, and appropriate dissemination pathways.

11. Administrative Section

11.1 Adherence to the protocol

Except for a change that is intended to eliminate an immediate hazard to participants, the approved protocol will be conducted as described. Any significant protocol deviation will be documented in a new protocol version which will be sent as a variation to HDEC for ethical approval.

11.2 Protocol revision procedures

All revisions will be discussed with, and approved by, the Study Steering Committee. If the revision is an “administrative letter”, the PI will submit it to the appropriate Ethics Committee for their information. If the revision is an “amendment”, the PI will sign it. The PI will submit the amendment to the appropriate Ethics Committee for review and approval or favourable opinion prior to implementation. Documentation of approval signed by the chairperson or designee of the Ethics Committee will be sent to the PI. This will be filed in the study files and copies where appropriate sent to relevant collaborators.

If an amendment substantially alters the study design or increases the potential risk to the subject:

- the consent form will be revised and submitted to the Ethics Committee for review and approval or favourable opinion;
- participants currently enrolled in the study, if they are affected by the amendment, will be contacted by telephone and the amendment discussed and verbal consent re-obtained;
- the revised consent form will be posted to participants currently enrolled in the study if they are affected by the amendment

11.3 Procedures for referral form, screening form, consent, questionnaires, tutorials, and randomisation

The referral form will be completed during a face to face interview with potential participants by study RA’s, pharmacists, and GP’s. Referral forms will be completed on-line in Drupal survey software with results visible to study researchers via a secure user interface. A registration number and a referral number will be automatically applied in Drupal for all potential participants. All referred participants will be automatically emailed the PIS and will verbally consent to screening.

The screening form will be completed by a study RA during phone call 1. Screening forms will be completed on-line in Drupal survey software with results visible via a secure user interface. Screening forms will be linked to referral forms for same potential participant via the registration number.

Eligible participants will be supported (during phone call 1) to download the study smartphone app. On opening the app for the first time, participants will be able to view and re-read the PIS, ask questions, and complete electronic consent by ticking a box. Consent will activate the app and direct participants to complete the baseline questionnaire (within the app).

Participants may complete the baseline questionnaire while still on phone call 1 or in their own time. On submission of the baseline questionnaire (when the participant is in a Wi-Fi zone or as data on their phone) the app will link with the on-line database at NIHI and upload the information to secure servers.

On submission of the baseline questionnaire the study app will also prompt the user to watch three tutorials (BP, urine, and barcode data collection), which they may do during phone call 1, or during their own time. Tutorials will be available to participants via their study app, throughout the entire study period.

Eligible participants will be contacted two weeks after the baseline questionnaire has been completed (allowing time for receipt of the BP monitor) to advise them of the group they have been allocated to. Randomisation will take place at this time. The study app will be activated to send notifications appropriate for their allocated group. Participants allocated to the intervention group will be supported to download and unlock the SaltSwitch app from the app store (iOS or Android) and ensure they can access it via the study app. The SaltSwitch app will prompt the user to complete a short tutorial the first time they open it, which will also be available throughout the entire study period.

Twelve weeks after randomisation participants study apps will prompt them to complete the follow-up questionnaire. The questionnaire will be completed within the secure study app. On submission of the follow-up questionnaire (when the participant is in a Wi-Fi zone or as data on their phone) the app will link with the on-line database at NIHI and upload the information to secure servers. Participants will receive a notification thanking them for their participation, information about their BP over the study etc. The participant will also receive a final email or letter on completion of the study with instructions on how to change SaltSwitch app code and create a Blipcare account for their blood pressure monitor. The participant will also be notified that their blood pressure monitor has been disconnected from the study system. These actions will stop data being sent to the study team, whilst allowing the participant to continue using devices.

There will be no source data to check study outcome data against. However, all study outcome data will be stored securely on NIHI servers at The University of Auckland, which are backed-up every evening.

11.4 Data confidentiality and security

Data will be entered, stored and backed-up in a secure manner via the NIHI internet data management system.

11.5 Reporting schedule

The PI will provide yearly reports of the progress, or completion, termination or discontinuation of the study to the HDEC committee and to the Health Research Council (HRC) of New Zealand, the principal funder of this trial. Aggregate safety data will be reported to HDEC at two intervals throughout the trial (approximately 12 months, and end of the trial). All SAEs will be reported to the HDEC on a quarterly basis in the form of a safety update issued by the PI.

11.6 Record retention policy

At the end of the study, all electronic data will be stored in a ‘read only’ format at NIHI; the data will still be accessible to the study team. However, previous access restrictions will be retained. Electronic data will be stored for 15 years from the date of study termination, as per the NIHI Standard Operating Procedures for archiving.

11.7 Insurance

Participants may be entitled to compensation from the Accident Compensation Corporation (ACC) for personal injury suffered as a result of treatment given as part of the trial. ACC cover is not automatic and each case is assessed by ACC, according to the provisions of the ACC Compensation Act 2001. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury.

11.8 Ownership of data and publication policy

Individual study data will remain the property of individual study participants. NIHI will have the responsibility for storage, protection and retrieval of study data. The Steering Committee will have the responsibility for the safe guardianship and use of the data. All access, analyses and dissemination of Māori-specific data will be the joint responsibility of the Steering Committee, including Māori representation.

All publications will be approved by members of the Steering and Advisory Committees, who will be named on all reports. Study participants, RAs, members of the Management Committee who are not part of the Steering Committee, and study sponsors will be acknowledged in the final report and in all publications and presentations resulting from this trial.

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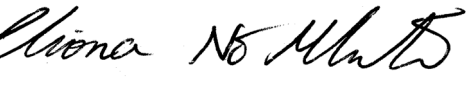
13. Study Acknowledgement

STUDY ACKNOWLEDGMENT

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the treatment and the study.

I understand that the study may be terminated, or enrolment suspended at any time if it becomes necessary to protect the best interests of the study participants.

Prof Cliona Ni Mhurchu  _____ *8 April 2020*

Principal Investigator's printed name and signature Date

Address of study site:

National Institute for Health Innovation
Building 507
Grafton Campus
The University of Auckland
22-30 Park Ave
Auckland
New Zealand

14. Appendix 1 – Terms of Reference

14.1 Steering committee

The Steering Committee will consist of Dr Helen Eyles, Prof Cliona Ni Mhurchu, Prof Bruce Neal, Dr Yannan Jiang and Dr Lisa Te Morenga, and will be responsible for providing strategic guidance for the trial including developing and maintaining the study design, approval of the protocol, statistical analysis, presentation and publication of results. The Committee will be supported with expert advice from the Study Advisory Committee consisting of Dr Rachael McLean, Dr Robert Doughty, and Prof Anthony Rodgers. The Steering and Advisory Committees will meet as required during study development, then at least quarterly (or more frequently if required) from start-up to review problems and issues raised by the Study Management Committee. Members who live outside of Auckland may attend the meetings or participate via conference call.

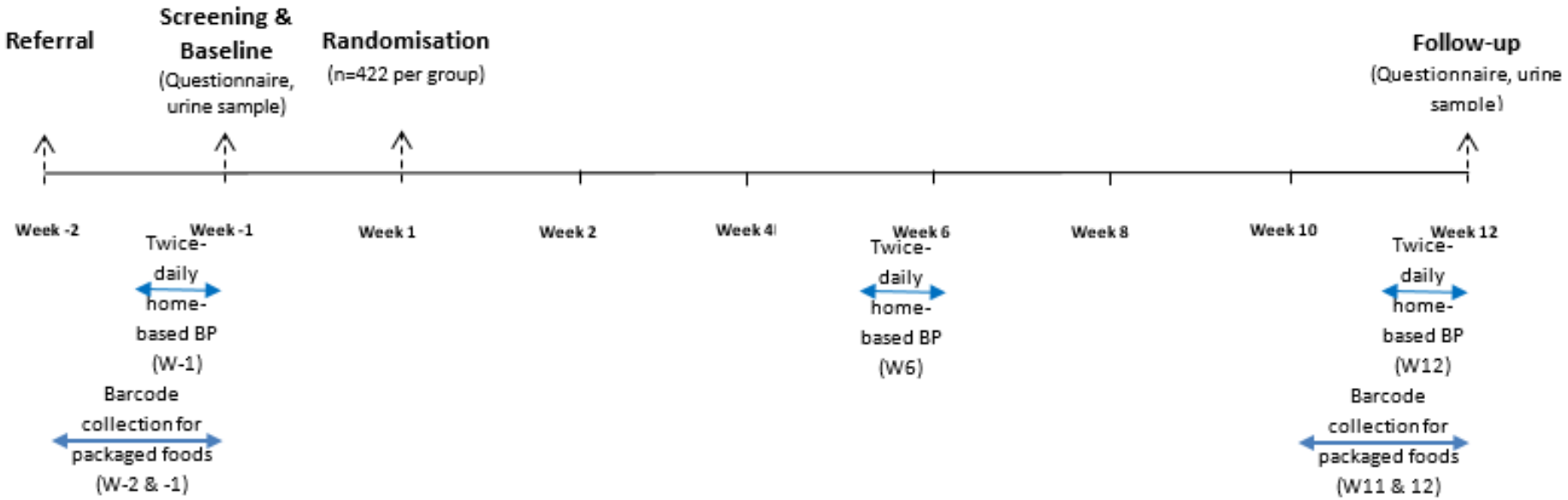
14.2 Study management committee

The Study Management Committee will be responsible for the daily operation of the study, and will develop study materials, deal with study problems, recruitment, and logistical issues. Meetings will be held weekly while the study is in development, then as required when the study is underway.

15. Appendix 2 – Summary of Forms and Questionnaires

Form	Purpose	When administered	Administered
Referral form	To collect contact information, height and weight, and to assess preliminary eligibility (BP and smartphone ownership)	At recruitment	By study RA, pharmacist, or GP
Screening form	To collect participant details and assess eligibility against full list of inclusion/exclusion criteria.	Contact 1	Study RA
Baseline questionnaire	To collect demographic information, current shopping practices, use of discretionary salt, GP contact, and relevant household information.	Contact 1 or participants own time (week 0)	Self-administered (with RA support during contact 1 if desired)
Follow up questionnaire	To collect information on any changes in shopping practices, Dr and hospital visits, relevant household information, and use and acceptability of dietary salt substitute/salt and any SAEs. For the intervention group data will also be collected on use and acceptability of the SaltSwitch app and dietary salt substitute.	Participants own time (week 14)	Self-administered. SAEs will be signed by an authorised medical representative at NIHI.

16. Appendix 3 - Flow Diagram of Study Design



17. Appendix 4 – Summary of Protocol Amendments

Version	Section heading	Amendment
2	6.7 Concomitant therapy	Participants taking ACE inhibitors with normal renal function will be advised that there is a very small risk of developing hyperkalaemia.
2	6.9 Participant referral and 6.11 Informed Consent	Participants will be emailed the Participant Information Sheet immediately following referral (as well as have it available in the study smartphone app for review). One BP measure rather than the average of three will be sufficient for referral. A maximum of one reminder notification and phone call for Consent will be sent.
2.1	6.20 Detail of contact calls to participants	Participants will be asked if they have received the PIS by email and if they have any questions prior to Consent.
2.1	1.0, 6.2, 6.12 Eligibility criteria	Eligibility criteria at baseline altered: Participants must now have a minimum of 10 rather than 30 scanned barcodes for packaged foods. This was changed to take into account participants who use meal boxes but ensures the technology can still be used.
2.1	6.13, 6.21 Follow up questionnaire	New questions added to follow up questionnaire to assess use of meal boxes (see above), and to collect information for economic analysis (Dr and hospital visits due to high BP or medication for BP).
3.0	1.0, 3.0, 4.0, 5.17, 5.18 Primary outcome 1.0, 6.1 Study power and sample size 5.3, 5.9 Recruitment methods	Study primary outcome changed from Systolic Blood Pressure (SBP) to Dietary Sodium Intake (measured via urinary sodium sample). Secondary outcomes changed accordingly and to include SBP. Study power and sample size revised to reflect change in study primary outcome. Recruitment methods modified to focus on most efficient and productive methods.
3.1	5.11 Changes to referral and screening process due to Covid-19 Appendix 5 – Flow diagram for Covid-19	Due to Covid-19 a remote referral process has been devised so the study can continue.
4.0	Page 5 - Co-ordinating Centre Study Staff (NIHI) 5.19 Schedule of intervention and follow-up	Update of SALTS project team Addition of paragraph on SALTS prize draw for participants who will complete and return their final urine sample

	5.20 Detail of contact points with participants	Fixed wording for sentence 4 onwards of Study end (contact 4 – a. Phone call and b. Email/Letter)

18. Appendix 5 – Flow Diagram for remote referral and screening option process.