



Seong, J., Newcombe, R. G., Matheson, J., Weddell, L., Edwards, M., & West, N. X. (2020). A randomised controlled trial investigating efficacy of a novel toothpaste containing calcium silicate and sodium phosphate in dentine hypersensitivity pain reduction compared to a fluoride control toothpaste: Calcium silicate/phosphate paste for DH. *Journal of Dentistry*, *98*, Article 103320.
<https://doi.org/10.1016/j.jdent.2020.103320>

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[10.1016/j.jdent.2020.103320](https://doi.org/10.1016/j.jdent.2020.103320)

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A randomised controlled trial investigating efficacy of a novel toothpaste containing calcium silicate and sodium phosphate in dentine hypersensitivity pain reduction compared to a fluoride control toothpaste.

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Short title: Calcium silicate/phosphate paste for DH

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Key Words

Dentine hypersensitivity, calcium silicate and sodium phosphate, occlusion, toothpaste, pain

Conflict of Interest and Funding Statement

This study was carried out by the Clinical Trials Unit at Bristol Dental Hospital. The study was funded by Unilever Oral Care and ME, JM and LW are employees of Unilever Oral Care and contributed to the design of the study. NW and JS were the authors of the protocol. The study was carried out, analysed and prepared for publication by RN, JS and NW.

We would like to acknowledge Emma Macdonald and Nikki Hellin from the Clinical Trials Unit at Bristol Dental Hospital who also contributed to the study

The study was registered on ClinicalTrials.gov: Identifier NCT03244618

Abstract

Objectives: To compare a calcium silicate and sodium phosphate toothpaste (CSSP) with a fluoride negative control toothpaste for dentine hypersensitivity (DH) pain reduction after 14, 28 and 29 days.

Methods: This was a double blind, parallel study in 247 healthy adults with DH (Schiff score >2, tactile 10-20g) in 2 teeth in different quadrants of the mouth. After acclimatisation, participants were randomised to CSSP or control toothpaste. After measuring baseline sensitivity products were applied twice-daily by toothbrushing, and once daily massaging into the sensitive teeth. Sensitivity was assessed following airblast (Schiff and VAS) and tactile (Yeaple probe) stimuli at baseline, 14 and 28 days, and at 29 days, 12 hours after last product application. Participants completed a quality of life questionnaire at each study visit up to day 28.

Results: After 14, 28 and 29 days the CSSP group had significantly lower Schiff, lower VAS and higher Yeaple probe scores compared to control (VAS at 14 days, $p<0.04$; all other comparisons, $p<0.001$). Quality of life scores improved in both groups, but no significant differences between groups were observed.

Conclusions: The CSSP toothpaste was more effective than the fluoride control toothpaste at reducing DH pain with benefit persisting 12 hours following application.

Clinical Significance

This novel calcium silicate and sodium phosphate toothpaste (CSSP) toothpaste is an effective twice-daily treatment when brushed on the teeth for dentine hypersensitivity sufferers compared to brushing with a conventional fluoride paste. Twice-daily brushing provides a sustained effect for long-lasting pain relief from dentine hypersensitivity.

Introduction

Dentine hypersensitivity (DH), the short sharp pain experienced in response to triggers such as cold air or pressure is common in adults [1]. While a wide range of prevalence figures have been reported (1.34% - 98%)[1], figures obtained from general adult populations have indicated that 27% of adults in Europe suffer from DH [2] with similar figures reported following clinical exam in Xi'an city, China (25.5%)[3], and Andhra Pradesh, India (32%)[4]. DH has a negative impact on oral health related quality of life (OHQoL) [5,6], with treatment of DH demonstrated to improve OHQoL scores [7].

For dentine to become sensitive it must be exposed to the oral cavity with dentine tubules open through to the pulp [8]. Dentine exposure occurs by 2 main mechanisms, gingival recession whereby the gingival margin migrates apically exposing cementum which is rapidly abraded away, or following toothwear, generally erosive, in which the enamel surface of the crown is lost exposing dentine [9]. Tubule patency is achieved by removing of the smear layer, which dietary acids effect [10]. The hydrodynamic theory of DH [11] is generally accepted in which fluid movement within dentine tubules triggers a pain response from the pulp.

Treatments for DH include over the counter and professionally applied products. Professionally applied products include lasers, adhesive systems and varnishes that deliver active agents to the site of DH [12] (2015). Although systematic reviews have been unable to confirm the efficacy of professionally applied agents due to their diverse nature and different modes of application, randomised controlled trials have demonstrated efficacy of individual agents such as calcium fluoride [13]. Over the counter products include toothpastes, offering the benefit of home use and routine twice-daily application. Treatments either interrupt nerve impulses or prevent tubule fluid movement by occluding dentine tubules. While systematic reviews have supported efficacy for both methods of treating DH [12, 14], no early or immediate effects on the reduction of pain by products that target the nerve response have been reported [12,15]. By contrast, products containing occluding agents can often act rapidly after application [16,17]. A disadvantage of occluding treatments however is that they are exposed to abrasion and dietary acids in the oral cavity, with evidence for acid dissolution of some formulations such as arginine calcium carbonate [18,19] or some oxalate complexes [20]. As a result there is a need for-occluding treatments that robustly withstand the insults of the oral cavity since they are likely to perform better.

A novel toothpaste has been developed combining calcium silicate and sodium phosphate (CSSP). The formulation augments the natural mineralisation processes of human saliva by providing additional calcium and phosphate which nucleate hydroxyapatite formation. In vitro this formulation occludes dentine tubules, levels of occlusion increasing over time [21]. This suggests that this novel toothpaste might be effective in

the relief of DH in vivo. The present study investigated the efficacy of this CSSP toothpaste for the reduction of dentine hypersensitivity compared to a negative control fluoride toothpaste. The primary objective was to measure the efficacy of the CSSP toothpaste as compared to a negative control toothpaste for the reduction in DH after 28 days of use, and the primary outcome of the study was Schiff score [22] after 28 days following an evaporative air blast. The null hypothesis was that there would be no difference in the efficacy of the two toothpastes for the reduction of DH after 28 days of treatment.

Methods

Study Design

This was a double-blind parallel study in otherwise healthy adult volunteers with DH, undertaken in a UK dental school. The study was approved by an NHS Research Ethics Committee (Ref 17/SW/0007) and the Health Research Authority, and conducted in accordance with Good Clinical Practice guidelines. Participants who gave informed consent and fulfilled study eligibility criteria were given a standard fluoride toothpaste and toothbrush to use for the acclimatization period. Participants returned to the study site 4-6 weeks later for their baseline visit. Those with continued eligibility were randomized to either test or control toothpaste. During the treatment phase participants returned to the study site after 14, 28 and 29 days for assessments of DH. The primary outcome of the study was the 28-day Schiff score [22] following an evaporative air blast. At screening, baseline and 14 and 28 day visits participants also completed an OHQoL questionnaire rating their overall DH, and rated various aspects of their allocated toothpaste including taste and freshness. Throughout the study, participants were instructed to refrain from undertaking routine dental treatment.

Recruitment and screening of study participants

Potential participants were recruited through local advert and the study site database of individuals who had expressed an interest in taking part in dental clinical trials. Volunteers were given a participant information sheet and invited to an enrolment appointment (visit 1). Those who gave informed consent were invited to a screening visit. For this and all subsequent study visits participants were asked to refrain from all oral hygiene procedures, chewing gum and eating and drinking, except tap water during the 4 hours prior to their appointment time. Tap water could be sipped until 30 min before the appointment.

At the screening appointment (visit 2) potential participants were given an oral soft tissue (OST) exam and assessed for study eligibility. Eligible participants were adults aged 18 or over with, in two quadrants of the mouth, at least one hypersensitive tooth (Schiff score 2 or 3), anterior to the molars excluding adjacent central incisors which had no evidence of pathology such as caries/extensive restoration. A visual analogue score (VAS) pain score was also recorded for the hypersensitive teeth following the evaporative air stimulus.

Individuals who had used sensitivity products or undergone vital tooth bleaching within 4 weeks preceding screening, were currently undergoing dental treatment or receiving medication that might affect DH such as regular use of analgesics or anti-histamines were excluded. Participants were also excluded if they had aphthous ulceration, severe gingivitis or periodontitis, diabetes or any other medical condition that could affect DH. Current and recent smokers or e-cigarette users (previous 12 months) and those who used a power toothbrush at least 4 times per week were also ineligible.

For each eligible participant one sensitive tooth (not molar) was selected as a study tooth in two quadrants of the mouth. They completed an OHQoL instrument, the DHEQ15 [23] and were asked to rate their overall DH. They were then provided with an acclimatisation fluoride toothpaste (1450ppm), toothbrush and a toothbrushing diary which they were asked to complete (timings of twice-daily product application) until their next appointment.

Baseline and treatment Visits

Participants returned to the study site 4-6 weeks after screening for the baseline visit (visit 3), given an OST exam, and their designated study teeth assessed for sensitivity following an airblast (Schiff and VAS), and tactile stimulation (Yeaple probe). Only participants with evaporative air Schiff scores of >2 and tactile sensitivity of 10-20g on both study teeth remained eligible to continue. Compliance with acclimatisation toothpaste application was confirmed by toothbrushing diary review. Participants who had not used the toothpaste according to the instructions or who had used too little (<17g) or too much (>53g) of the acclimatisation toothpaste were also withdrawn.

Participants with ongoing eligibility were randomised (stratified by gender), according to their screening number, allocated based on their arrival for screening at the study site, to receive either a control or the test toothpaste containing calcium silicate and sodium phosphate (CSSP). Both toothpastes contained 1450ppm fluoride as sodium monofluorophosphate. The randomisation table was provided by the sponsor's statistician, randomisation was undertaken by study staff. Participants were given written instructions for product use which included a picture of lips and teeth on which their chosen study sensitive teeth were indicated, and asked to brush their teeth following these instructions as if they were brushing their teeth in the evening. Participants were to brush for at least 2 minutes twice-daily using their normal routine, minimise swallowing and finally expectorate the remaining slurry. The instructions for evening application then instructed participants to apply a pea sized amount of toothpaste onto a clean, dry fingertip and massage the toothpaste gently onto the surface of each study sensitive tooth for 30 seconds. Participants were then asked to complete the OHQoL questionnaire and rate their overall oral sensitivity. They were also

asked to rate their allocated toothpaste for flavour, freshness after use, freshness during use, level of foam and how smooth it left their teeth feeling, each on 7-point scales from strongly disagree, to strongly agree. They were then given their allocated toothpaste, a new toothbrush and a toothbrushing diary to record their toothbrushing routine and fingertip application at home.

Participants returned to the study site after 2 weeks' product use (visit 4). Compliance with study product application was confirmed by review toothbrushing diary review, an OST exam was undertaken and study teeth assessed for sensitivity following an airblast (Schiff and VAS), and tactile stimulation (Yeaple probe). Participants were then asked to complete the OHQoL questionnaire, rate their overall oral sensitivity and aspects of their allocated toothpaste, and given a new toothpaste diary and additional study product for use for a further 2 weeks. Participants returned to the study site again after 4 weeks' product use (visit 5) and the assessments undertaken at visit 4 were repeated, participants were also instructed that they should clean their teeth for the final time at between 12 and 14 hours prior to their final appointment (visit 6). Visit 6 took place the day after visit 5 and aimed to determine whether relief from DH was retained 12 hours after product usage. Compliance with study toothbrushing procedures was assessed from the diary, an OST exam was undertaken and DH assessed on study teeth following an airblast (Schiff and VAS), and tactile stimulation (Yeaple probe).

Assessments of DH

Evaporative air sensitivity was assessed by Schiff and VAS score. After shielding adjacent proximal teeth, a one-second blast of air was directed onto the exposed buccal root surface of the tooth from a distance of one centimetre, at 60 psi. (± 5 psi) and 19-21°C. Sensitivity was recorded using the Schiff sensitivity scale: 0 = Tooth/Participant sensitivity does not respond to air stimulation; 1 = Tooth/participant responds to air stimulus, but does not request discontinuation of stimulus; 2 = Tooth/participant responds to air stimulus, and requests discontinuation or moves from stimulus; 3 = Tooth/participant responds to air stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus. For VAS assessment of sensitive teeth, participants rated their sensitivity on a scale from 0mm (no pain) to 100mm (extreme pain).

Tactile sensitivity was assessed 5 minutes later by Yeaple probe (calibrated daily) [24]. The probe tip was passed over exposed dentine of designated teeth at a force of 10-20g (baseline) or 10-60g (treatment phase), the force being increased by 10g each pass, until the participant indicated discomfort.

Participants were asked to rate global sensitivity on a bar coloured from green through yellow to red (Figure 1).

For tactile sensitivity, high scores and increases are favourable; for other measures, low scores and decreases are favourable.

Statistical Analysis

No previous data exists to estimate the sample size accurately to test the efficacy of this new technology (CSSP) with regards to sensitivity after 4 weeks as assessed by Schiff air blast, thus the power calculation for the current study was based on published studies of other effective DH technologies [25-27]. Sufficient participants were recruited to ensure that there were 100 per group, which provided 80% power to detect a difference of 0.40 standard deviation between the treatment groups for the continuous variables at a two-sided 5% significance level, relative to the control toothpaste [28].

The main analyses comparing the products after 14, 28 and 29 days were performed on an intention-to-treat basis using on all analysable data at each time point. No participant's data was excluded due to protocol deviations, so per-protocol analyses would be identical. For each of Schiff, tactile, and VAS scores, summary statistics are presented and data as analysed by ANCOVA with treatment and gender as factors and adjusted for baseline scores. Data were also analysed by ANOVA, but due to stronger than expected baseline response correlations it was deemed preferable to incorporate baseline covariance in the analysis and present this here. Study findings were the same when data analysed by ANOVA. The air blast response (Schiff score) was also dichotomised, and analysed by a method appropriate for 2 teeth scored per mouth [29,30] to assess the percentage reduction in number of sensitive teeth using CSSP toothpaste relative to control toothpaste. All analyses report treatment differences with 95% confidence intervals as well as p-values.

A composite score for the OHQoL data was calculated from scores for each question which were averaged and rescaled from -1 to +1. Figures are based on participants with 28 day data. The differences in composite sensitivity-related quality of life score at day 14 and day 28 between groups adjusted for gender and corresponding score at baseline were analysed by ANCOVA.

Results

Participant flow through the study (June 2017–June 2018) is shown in Figure 2, 272 participants enrolled and 247 completed the study. Participant mean age was 36 years, and 54% were female. Age and race were well balanced between treatment groups. 22 non-product related, non-serious adverse events were recorded.

DH scores at screening, baseline and 3 treatment visits are shown in Table 1. For both treatments DH severity decreased over time, but improvements were greater in the group receiving the CSSP toothpaste.

When the treatment groups were compared after 28 and 29 days DH was significantly lower in the group receiving the CSSP toothpaste by all measures ($p < 0.001$, Table 2). The differences between products found for the Schiff score were larger than those assumed in the power calculation. Significant differences in favour of the CSSP toothpaste were also seen at day 14, but were more marked for clinically determined Schiff and Yeaple measures $p < 0.001$, than for participant-reported VAS ($p = 0.040$).

After 28 days CSSP product use (visit 5), 35.2% of teeth remained sensitive (Schiff > 2), compared to 70.1% that had been treated with the control product, a relative risk reduction of 49.8% (95% CI: 37.2% to 60.1%, $p < 0.001$). Interestingly, there were very strong correlations between 28 day Schiff scores for the two study teeth, +0.59 and +0.65 for the CSSP and control groups respectively, both $p < 0.001$, indicating that responses to treatment were not independent for the two teeth studied.

In contrast to VAS scores for study teeth, there was no significant difference in participant-reported whole mouth VAS scores between those who received CSSP and those who received control product although scores improved in both groups from screening to 28 days, and slightly favoured the CSSP product ($p = 0.104$, 14 days; $p = 0.328$, 28 days; Table 3).

Similar to global VAS, OHQoL scores improved in both participant groups, but there were no differences between the groups at days 14 or 28 for any of the questions, and no significant differences when the data was combined to give an overall OHQoL score ($p = 0.272$, 14 days; $p = 0.574$, 28 days; Table 4), although scores were improved slightly more in the CSSP group.

In both groups overall participant scores indicated that slight agreement that they liked the flavour, freshness, level of foam and how smooth their allocated toothpaste left their teeth feeling. Differences in the ratings for the two toothpastes were small and not significant, but did marginally favour the control group for all questions.

Discussion

This study disproved the null hypothesis and demonstrated that the new toothpaste formulation containing calcium silicate and sodium phosphate (CSSP) reduced DH as measured by Schiff score in response to an airblast after 28 days to a significantly greater degree than the control toothpaste. The reduction in DH

achieved by the new toothpaste was progressive over the 29 day treatment phase. The difference between the toothpastes was evident by 14 days DH being reduced more in the group receiving the test toothpaste than in the group receiving the control. This difference was highly significant for clinical scores, and significant ($p < 0.05$) for participant-reported VAS. After 28 days, the differences in DH pain scores between the groups were highly significant in favour of the CSSP product for all measures, furthermore, this difference persisted for 12 hours after the final application of the toothpaste. These findings suggest that this toothpaste formulation is a suitable treatment for DH and that its effect is maintained for at least 12 hours after brushing and massaging the toothpaste into the exposed dentine of the sensitive tooth, and therefore it should provide DH sufferers with a consistent, continuous reduction in DH pain when used in a twice-daily application regimen. Although differences between the products were significant at all time points, improvements in DH scores for all measures were also observed in the control group. This finding is likely due in part to the placebo effect [31], and also a result of regression towards the mean [32], which occurs since DH fluctuates in sufferers [1] and in studies such as this, participants are only eligible if they have marked sensitivity at the start of the study. For at least some of the participants this baseline sensitivity will be higher than their long-term average sensitivity and they are, therefore, likely to show improvements in DH pain over the course of the study as their sensitivity returns towards this average.

Although participant-reported pain scores improved significantly more in the CSSP group than in the control group no significant difference in global VAS scores were seen, although scores favoured the CSSP toothpaste. This is likely due to the large fluctuation in this score between visits indicating that global VAS is not a sensitive measure to detect the advantage of one product over the other. Similarly, there were no significant differences in OHQoL scores between products, although scores favoured the CSSP product. This may also be due to the lack of sensitivity of the measure for this type of study. Perceived OHQoL benefits are likely to accumulate over time as participants realise their DH is not affecting everyday activities so much, but 29 days may be too short a time period for participants to be sure/fully aware that activities are being affected less.

The design of this study was robust and appropriate for the research question. Sufficient participants were randomised to treatment groups, and they were balanced for gender, ethnicity and age. Participants were excluded if they had used a desensitising product within the 4 weeks prior to screening and there was a minimum of 4-week acclimatisation period to ensure the groups were as similar as possible at baseline to reduce carry over effects. In line with guidelines for the conduct of DH studies, 3 measures of DH were used, and both participants and examiners were blinded to the treatments given [33]. Although the study employed a negative control, comparison with a positive control with recognised efficacy such as arginine calcium carbonate [14,34], stannous fluoride [35] or potassium nitrate/stannous fluoride [36,37] would have

indicated whether the CSSP product was as good as, or better than over the counter products on the market that have been shown to provide relief from DH. Comparison with another product containing calcium as an active, such as a calcium fluoride varnish which been shown to be effective in the reduction of DH pain over the same period of 4 weeks [13] and significantly better than a gel containing 6% potassium nitrate/0.11% fluoride after 1 and 3 months [38] would also be of benefit. However, as this was the first randomised controlled trial (RCT) of this product, the first goal was to demonstrate it was better than a standard fluoride toothpaste at reducing DH pain, which proved to be the case. We found that although the 2 teeth with DH selected for assessment were in different quadrants of the mouth, their responses to treatment were far from independent. This suggests that the perceived response to the toothpaste is largely at participant level rather than tooth level, suggesting there would be little advantage to selecting a larger number of teeth per participant in future trials. This is further supported by a study by Midwood et al [39] where patients were reasonably aware of whether they had a DH issue, but unable to identify which teeth were affected. The favourable efficacy of the CSSP toothpaste that occludes dentine tubules through the formation of hydroxyapatite, compared to a negative control toothpaste for the reduction of DH pain in this RCT is in line with findings for calcium and phosphate containing occluding toothpastes, such as calcium sodium phosphosilicate (CSPS). When anhydrous CSPS toothpaste is exposed an aqueous environment, calcium, phosphate and sodium ions are released and promote 'hydroxyapatite-like' crystal growth, dentine mineralisation and dentine tubule occlusion [40,41]. Systematic reviews of CSPS containing toothpastes for treatment of DH support their efficacy for DH pain reduction compared to negative control toothpastes [33,41] supporting the value of formulations that aim to mimic the action of hydroxyapatite in vivo. In the present study utilising a CSSP toothpaste that has been shown to form hydroxyapatite in vitro not only were differences in pain reduction between control and CSSP toothpaste significant in favour of the CSSP formulation, they were maintained after 12 hours [42].

In conclusion, the present study demonstrates that a novel fluoride toothpaste containing calcium silicate and sodium phosphate is able to reduce the pain of DH more than a fluoride negative control toothpaste and that its effects last for at least 12 hours, making it a suitable treatment for obtaining consistent pain relief following twice-daily toothbrushing and application by massaging into sensitive dentine. Further studies are warranted to determine whether this treatment is better than other formulations for which systematic reviews have demonstrated efficacy for the management of DH.

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Table 1. Schiff, VAS and Yeaple scores at screening (visit 2), baseline (visit 3) and treatment visits 4, 5 and 6 (14, 28 and 29 days).

Visit	n	Control			n	CSSP		
		Schiff (score) Mean (SD)	Yeaple (g) Mean (SD)	VAS (mm) Mean (SD)		Schiff (score) Mean (SD)	Yeaple (g) Mean (SD)	VAS (mm) Mean (SD)
2	131	2.275 (0.373)	-	57.8 (16.6)	132	2.205 (0.321)	-	54.2 (17.8)
3	131	2.256 (0.336)	16.5 (3.8)	50.0 (20.4)	132	2.193 (0.336)	17.4 (3.5)	48.7 (20.4)
4*	125	1.908 (0.533)	24.0 (10.3)	44.2 (21.4)	128	1.582 (0.601)	30.4 (12.1)	38.9 (21.4)
5**	122	1.811 (0.624)	27.5 (11.7)	42.0 (22.1)	125	1.268 (0.723)	38.2 (14.4)	31.1 (22.8)
6***	122	1.713 (0.671)	29.7 (11.9)	38.1 (22.7)	125	1.044 (0.773)	41.5 (14.2)	27.2 (23.2)

*14 days, **28 days, ***29 days

Table 2. Differences in averaged Schiff, Yeaple and VAS score at visits 4 to 6 between CSSP and control groups. All analyses are adjusted for gender and for the corresponding score at baseline visit 3 (ANCOVA).

Visit (days)	n	Schiff		VAS		Yeaple	
		95% CI	p-value	95% CI	p-value	95% CI	P-value
14	253	-0.411 to -0.162	<0.001	-8.4 to -0.2	0.040	+2.8 to +7.9	<0.001
28	247	-0.673 to -0.349	<0.001	-14.4 to -5.2	<0.001	+6.5 to +12.7	<0.001
29	247	-0.818 to -0.464	<0.001	-14.5 to -4.9	<0.001	+7.6 to +13.9	<0.001

Table 3. Differences global VAS scores at visits 4 and 5 between CSSP and control groups, adjusted for gender and corresponding score at baseline visit 3.

Visit (days)	n	Estimate	95% CI	p-value
14	253	-2.8	-6.3 to +0.6	0.104
28	247	-2.1	-6.3 to +2.1	0.328

Table 4. Differences in composite sensitivity-related OHQoL at visits 4 and 5 between groups CSSP and control groups, adjusted for gender and corresponding score at baseline visit 3.

Visit (days)	n	Estimate	95% CI	p-value
14	247	-0.028	-0.078 to +0.022	0.272
28	247	-0.018	-0.081 to +0.045	0.574

Figures

Figure 1: Scale on which global VAS was recorded. Participants were asked: On this scale where would you rate your sensitivity?

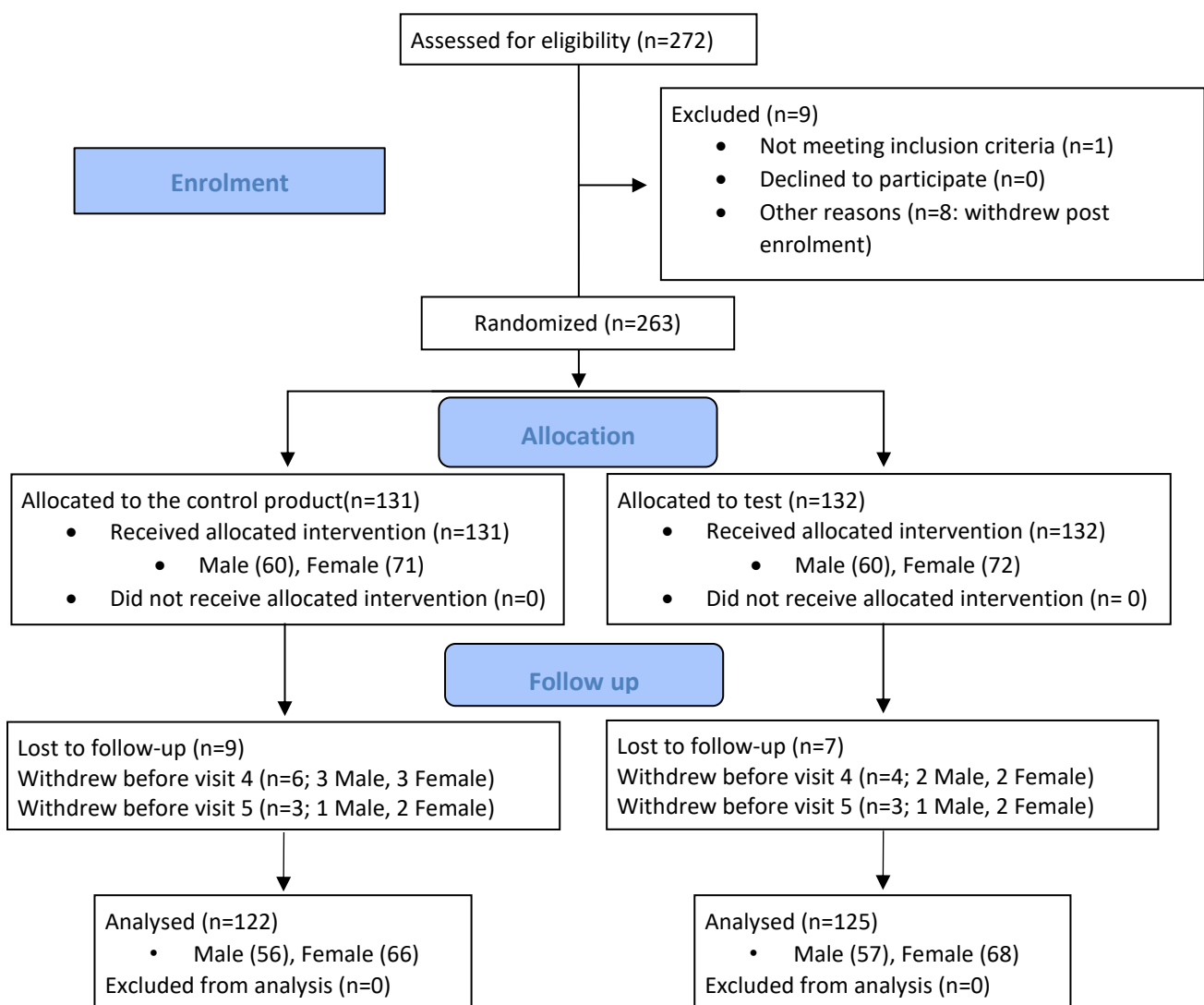


Figure 2. Participant flow through the study