

# BMJ Open Protocol: carrageenan for the prevention of oral HPV infection – a feasibility randomised clinical trial

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## ABSTRACT

**Introduction** Head and neck cancers (HNCs) are a significant health burden worldwide. Oral human papillomavirus (HPV) infection is a major risk factor for HNCs. Unfortunately, currently available prophylactic vaccines have limited coverage and potential for HPV type replacement. Carrageenan, a natural product extracted from marine red algae, has demonstrated potency as an HPV inhibitor and could offer a potential alternative to prevent HPV-related diseases, including oral HPV infection. However, there is a lack of clinical studies on the effect of carrageenan on oral HPV infections. As a first step to address this gap, we propose a randomised controlled trial (RCT) to evaluate the feasibility of conducting a larger multicentric RCT to investigate the effect of a carrageenan mouthwash on oral HPV infection.

**Methods and analysis** We will conduct a placebo-controlled triple-blinded feasibility RCT with two parallel arms, each arm consisting of 20 participants. Participants will complete a single in-person visit at baseline and conduct biweekly follow-ups from home by completing a web-based questionnaire and sending saliva self-samples via mail. During the 6-month period trial, participants will gargle with the mouthwash morning and night, and around sexual activities. The study will evaluate several factors including recruitment and retention rates, the feasibility of data collection procedures, compliance with study procedures, acceptability of RCT procedures and intervention and safety data on carrageenan use in the oral cavity. We will estimate the standard deviation of outcome measures, including time to the incidence of oral HPV infection and time to clearance of prevalent oral HPV infection. The trial primary outcome is whether to proceed to a definitive trial based on prespecified progression criteria.

**Ethics and dissemination** The protocol was approved by the McGill University institutional review board. Study results will be presented at scientific conferences and published in academic journals.

**Trial registration number** NCT05746988.

## BACKGROUND

Half a million cases of upper aerodigestive tract cancers (oral, oropharynx and larynx cancers), also known as head and neck cancers (HNCs), occur annually worldwide.<sup>1</sup> Compared with more common cancers (eg, breast), these cancers have a much lower

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Biweekly sample collection for oral human papillomavirus (HPV) testing allows for better tracking of oral HPV status.
- ⇒ Single in-person baseline visit with at-home self-sampling for follow-up rather than biweekly visits may encourage study uptake and reduce attrition.
- ⇒ At-home completion of follow-up sexual-related questionnaire improves compliance and reduces recall and social desirability bias.

probability of survival (5 years, <50%)<sup>2</sup> and have one of the highest morbidity and suicide rates of all cancers.<sup>3 4</sup> HNCs are among the most expensive solid tumours to treat,<sup>5</sup> inflicting a heavy financial toll on patients and the healthcare system.

Two distinct aetiological pathways for the multistage carcinogenesis of HNCs have been suggested: one is linked to the mutagenic effects of tobacco smoking and alcohol. At the same time, the other is related to human papillomavirus (HPV) mediated transformation. HNCs related to oral HPV infection (HPV-HNCs) predominantly affect the oropharynx and the base of the tongue.<sup>6</sup> The HPV viruses linked to them are acquired principally through oral sexual activities.<sup>7–12</sup> With an increase of HPV-HNCs, as much as 225% since the 1980s,<sup>13 14</sup> these cancers have reached epidemic proportions in North America, surpassing the annual incidence and mortality of cervical cancers—the most well-known HPV-related cancer in Canada.<sup>15</sup>

There are more than 140 HPV genotypes, which are broadly divided into cutaneous and mucosal HPV.<sup>16</sup> Mucosal HPVs infect the upper aerodigestive tract and anogenital mucosa and are classified according to their carcinogenic potential into ‘low risk’ (eg, HPV-6, HPV-11) and ‘high risk’ (eg, HPV-16, HPV-18).<sup>16</sup> Low-risk HPV can lead to benign lesions (eg, genital warts, laryngeal papilloma),<sup>16</sup> while the high-risk types may lead to invasive carcinomas of the cervix, anogenital



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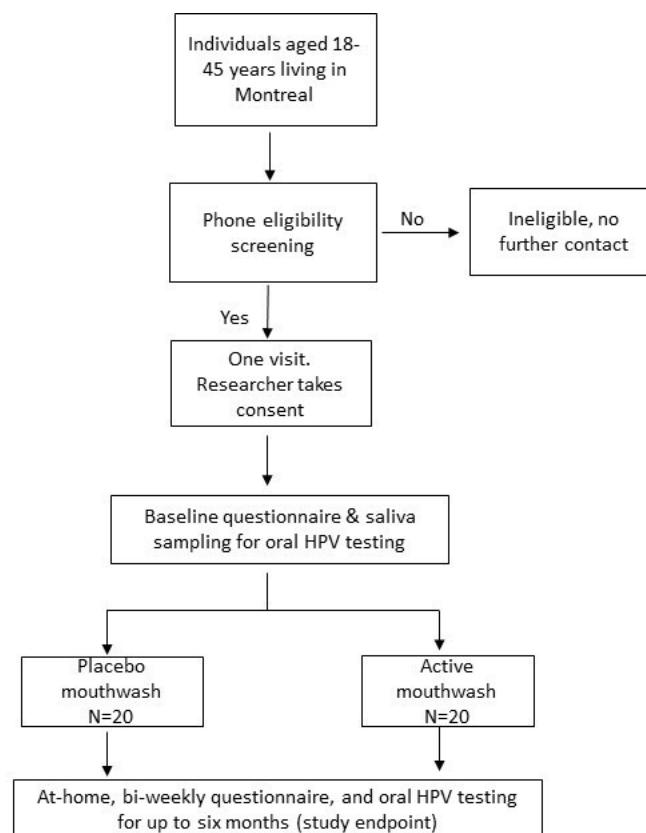
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and upper aerodigestive tracts, particularly if the infection persists.<sup>16</sup>

While HPV prophylactic vaccination programmes are in place in several countries, their coverage and uptake are low, with huge socioeconomic and gender disparities.<sup>17–19</sup> Moreover, currently available vaccines are effective only against a few HPV types, and there is a potential for HPV type replacement, that is, a gradual change in HPV type distribution within vaccinated populations due to vacated ecological niches occupied by HPV 16/18 (the common HPV types currently targeted by the vaccines).<sup>20</sup> Finally, lesions caused by HPV can be treated, but the causal oncogenic HPV types in a population have never been eradicated and thus remain a risk factor. Clearly, there is a need for alternative strategies to prevent oral HPV infections and to reduce the future burden of HPV-HNCs.

Carrageenan, a natural product extracted from marine red algae, is approved as an organic additive in food, baby formulas and cosmetic products.<sup>21</sup> Carrageenan is a potent HPV inhibitor and offers a potential alternative to prevent HPV-related diseases. Although this product is at different stages of clinical testing to prevent cervical and anal cancers, to the best of our knowledge, there are no clinical studies examining the effect of carrageenan on preventing oral HPV infection. Moreover, there are no data on carrageenan use in the oral cavity, which is a unique milieu where complex interactions occur between various elements (eg, soft/hard tissues, food and micro-organisms). This ever-changing environment includes many compounds that may interact with carrageenan and oral HPV infections. Given the high prevention potential of carrageenan, we propose a feasibility randomised controlled trial (RCT) to evaluate the safety and the possibility of conducting a larger multicentric RCT investigating the effect of a carrageenan mouthwash on oral HPV infection. However, several RCTs fail due to a lack of knowledge of the essential aspects of the study design.<sup>22</sup> Therefore, the need for a feasibility study to prevent RCT failure should not be discounted.<sup>23 24</sup>

Our overarching research question is: to what extent is it feasible to conduct a definitive trial of a carrageenan mouthwash to prevent oral HPV infection? Specific key questions related to study procedures that we will answer include: (1) Can we recruit a sufficient number of participants into two parallel arms to allow the completion of a full study in a timely fashion? (2) Can we retain a sufficient proportion of these participants in both arms? (3) Are study measures feasible? To answer these questions, we set a series of objectives following the Consolidated Standards of Reporting Trials (CONSORT) and other guidelines for feasibility trials.<sup>25 26</sup> Our primary aims are to: (1) implement and evaluate the standardised recruitment and data collection procedures, including (A) recruitment strategies and rates; (B) retention rates; (C) feasibility of data collection over the phone and via a web application; (2) assess the feasibility of completing study measures, including (A) mailing of mouthwash supplies to participants; (B) self-collection and transfer of biweekly



**Figure 1** Trial schema.

mouth rinse samples for HPV-genotyping; (C) rates of compliance with study procedures; (3) assess acceptability of the RCT procedures and intervention; (4) estimate the SD of outcome measures: time to the incidence of oral HPV infection and time to clearance of prevalent oral HPV infection; (5) elaborate strategies to optimise study procedures for the main RCT. Our secondary aim is (6) to obtain preliminary safety data on carrageenan use in the oral cavity in humans.

## METHODS AND ANALYSIS

We propose to conduct a feasibility placebo-controlled triple-blind parallel design RCT to assess the feasibility of conducting a large trial testing the effect of carrageenan on oral HPV infection outcomes. This study is ongoing, with recruitment started in May 2023 and an anticipated study end date of March 2024. This report is made using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guideline.<sup>27</sup>

### Study population

The study population will consist of individuals aged between 18 and 45 years living in Montreal, Canada, with no history of HNCs (figure 1).

Inclusion criteria: Individuals who are (1) oral sexually active (defined as having at least one oral sexual activity in the past 6 months) with the intention to continue to have oral sex for the foreseeable future, (2) understand English or French, (3) able to sign the consent form and

agree to fully adhere to the study instructions, (4) live and plan to be in Montreal for at least a 6-month period post-study enrolment and (5) have access to or own a digital device.

Exclusion criteria: Individuals who (1) are vaccinated against HPV or (2) have a history of HNCs.

### Sample size

To estimate the required sample size for this trial, we followed the approach illustrated by Whitehead *et al.*<sup>28</sup> We assume a future main trial will detect a ‘medium’ difference in efficacy for a carrageenan mouthwash between two arms (standardised difference =  $0.3 \leq \delta < 0.7$ ) at 90% power. Therefore, we require a minimum of 15 participants in each arm for this feasibility trial.<sup>28</sup> We round up this sample size to 20 participants per arm to account for a 33% drop-out rate in each arm.

### Recruitment

Our recruitment strategy will emulate the EXPLORE trial.<sup>29</sup> This will include placing advertising flyers at bars, bathhouses, sex clubs, health clubs, magazines, medical clinics, community organisations and the University Student Health Services. Furthermore, recruitment flyers will be distributed in household mailboxes across the island of Montreal. We will also post advertisements on the Faculty of Dental Medicine and Oral Health Sciences, McGill University website and run Facebook/Instagram ads. Eligible individuals will be randomly assigned to one of the two arms (intervention and placebo) at a ratio of 1:1 using permuted block randomisation with varying block sizes. Participants will be compensated.

### Intervention

The intervention (n=20) and control (n=20) groups will receive treatment with a first-in-class formulation of carrageenan mouthwash and a matching placebo mouthwash, respectively. The base mouthwash is a sodium lauryl sulfate-free composition of the most common ingredients found in OTC mouthwash preparations with or without carrageenan as the active ingredient (Petra Hygienic Systems, Concord, Ontario, Canada). Participants in both groups will be instructed to gargle vigorously for 30–60 s with their assigned mouthwashes daily (morning and night) as an adjunct to regular toothbrushing and before and/or immediately after sexual activities. Both types of mouthwash will have the same taste and ‘mouth feel’ and will be packaged in similar plastic bottles and study bags. Study participants, investigators and outcome assessors (ie, HPV testing laboratory) will be blinded to intervention allocation.

### Data collection

Participants who respond to the study advertisement will be screened for eligibility over the phone and invited to visit the dental clinic at the Faculty of Dental Medicine and Oral Health Sciences, McGill University. If eligible to participate, the study’s aim and overall procedure will be explained verbally, and they will be invited to read and

sign a consent form. The research assistant in the study will do this. Afterwards, they will be explained how and when to use the mouthwash and how to self-collect saliva samples for HPV testing during the follow-up period. They will then give their baseline saliva sample and complete the self-administered baseline questionnaire in a private room at the clinic. This will be the only study visit. Subsequently, we will follow the participants for up to 6 months, and saliva specimens for HPV DNA testing will be collected biweekly for the study period (up to 12-time points). The saliva specimen for this testing will be self-collected by the participants. This simple and safe procedure involves participants spitting approximately 1 mL of saliva into OMNIgene•ORAL (OM-501) kit (DNA Genotek, Ottawa, Ontario, Canada) following recommendations from the manufacturer. The samples will then be sent to our lab for HPV analysis through the Canada Post return envelopes given to the participants. Importantly, all vials will be clearly marked using different colours and labels and plastic bags specifically used to transport biological material will be provided. We will provide written and verbal instructions on the study procedures (ie, mouthwash, oral samples, specimen self-collection).

Study participation for each participant will end at one of the following endpoints: (1) first positive HPV result following a negative HPV test at baseline; (2) first type-specific HPV negative test result following a positive HPV test at baseline or (3) end of follow-up period at 6 months from baseline. Individual participants will be informed of their HPV test results at their endpoints.

Participants will continue to complete a biweekly self-administered questionnaire during the follow-up period. These follow-up questionnaires contain a shorter list of questions. They are intended to not only evaluate recent sexual behaviours but also to corroborate the responses given during the baseline visit. These questionnaires will measure known and potential oral HPV risk factors (including sexual activities) and compliance with the intervention (including using the mouthwash around sexual activities) and monitor safety and tolerability. All questionnaire data will be collected with the MyCap mobile application on participants’ phones and managed through the REDCap (Research Electronic Data Capture) tool hosted at McGill University.<sup>30 31</sup> MyCap is a secure mobile application companion to REDCap, which is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; (4) automated study reminder to complete biweekly tasks and (5) procedures for data integration and interoperability with external sources. Collecting this potentially sensitive data this way, and at the participant’s home comfort, has been shown to be effective for logging sexual-related research data, and superior to questionnaires completed only during physical study visits for reducing recall bias,



ensuring high compliance, and improving the quality of data.<sup>32</sup> Responses will be important for the purpose of evaluating adherence and assisting us in developing our main trial.

To preliminary assess safety, participants will also record pain on 10-point Visual Analogue Scale (VAS), other discomforts related to the mouthwash (eg, taste, inflammation), and instances of recurrent aphthous stomatitis (RAS). Importantly, participants who report RAS (a chronic condition) prior to study enrolment will be monitored throughout the trial for any aggravation of the condition.

### Outcome measures

The primary outcomes of this study are as follows:

1. Recruitment rate: This will be measured by the total number of participants recruited into the study. The investigators intend to recruit 40 participants. The recruitment rate will be calculated as number of participants per month.
2. Drop-out rate: The proportion of individuals who enrolled on the study but left before the end of the study will be documented.
3. Adherence rate for mouthwash use: This will be calculated as the proportion of participants who completed the study and complied with the mouthwash use regimen.
4. Adherence rate for self-sampling: This will be calculated as the proportion of participants who completed the study and complied with the biweekly self-sampling procedure.
5. Acceptability of study procedures as assessed by satisfaction on a VAS: Qualitative and quantitative assessment

will be used to evaluate participants' experience with the RCT through the follow-up questionnaire and an exit question. Participants will be asked to rate their satisfaction with the study procedure on a scale of 1–10 (10 being the highest level). This will focus on the level of satisfaction of the participants with mouthwash use around sexual activities and the level of satisfaction of the participants with the biweekly self-sampling.

The secondary outcome measures are as follows:

1. Mouthwash safety (pain score) as assessed by the VAS: The mean pain score (for any pain ascribed to the mouthwash, eg, burning mouth, RA) measured on the VAS<sup>1–10</sup>; 10 being the worst pain will be recorded.
2. Time to oral HPV infection: Time to type-specific oral HPV infection will be recorded for participants with negative type-specific oral HPV status at baseline.
3. Time to oral HPV clearance: Time to type-specific oral HPV clearance will be recorded for participants with positive type-specific oral HPV status at baseline.

### Data confidentiality

The confidentiality and security of participant data and specimens are of utmost importance in this study. To ensure privacy and protection, all laboratory tests results and questionnaire responses will be treated with strict confidentiality. No names or other information that could identify a participant will be released. All the data from this study will be analysed in aggregate statistical form only, with no names linked to any data. Specimens will be securely stored for as long as they are needed for the verification of laboratory results, testing with additional methods and for research audit purposes. Access to specimens will only be granted only to investigators involved

**Table 1** Progression criteria

	Red (consider not progressing with the main trial or substantial changes to the trial protocol)	Amber (discuss and implement improvement strategies but lean towards proceeding with the main trial)	Green (go ahead with the main trial)
Recruitment			
Proportion of individuals deemed eligible for the study and agree to participate	<30%	30%–50%	>50%
Retention			
Proportion of participants remaining in the study at 6 months	<45%	45%–60%	>60%
Adherence rate for mouthwash use			
Proportion of participants who completed the study and complied with the mouthwash use regimen around sexual activities	<50%	50%–70%	>70%
Adherence rate for self-sampling			
Proportion of participants who completed the study and complied with the biweekly self-sampling procedure	<50%	50%–70%	>70%

in the study. Electronic versions of the data will be stored on a private server of the principal investigator hosted at the Faculty of Dental Medicine and Oral Health Sciences, McGill University, while hard copies of data will be stored in a secure locker and room located in the same Faculty. Access to the study data, both the electronic and hard copies, will be restricted to those directly involved in the study. Furthermore, members of the McGill Institutional Review Board (IRB, a research ethics board), person/s designated by the McGill IRB, or persons authorised by McGill University may access the study data to verify the ethical and responsible conduct of the study.

### Data analysis

We will use descriptive statistics (eg, rates, proportions and means) to fulfil our primary objectives. For example, we will document the success in recruitment strategies, participation and retention rates, the proportion of mouthwash and oral rinse vials lost due to shipment, the proportion of participants who completed the study but did not comply with the biweekly self-collection of mouth rinse samples, among others. We will use an exit satisfaction survey to evaluate participants' experiences with the RCT. Moreover, we will obtain precise estimates to calculate the sample size required for the main RCT. For pain, the within-participant correlation of VAS scores will be estimated using intraclass correlation coefficients. The between-subject SDs of VAS scores will be estimated separately for each time point of measurement. The mean difference between the intervention arms will be estimated for RAS. All 95% CI will be estimated through non-parametric bootstrapping.

Based on the best guidelines for designing and reporting pilot and feasibility trials,<sup>25 26</sup> the overall aim in evaluating these outcomes is to determine whether and how to proceed with a main RCT based on a priori thresholds for specific feasibility, acceptability and safety criteria. These thresholds based on the red, amber and green coding methodology are described for our progression criteria in [table 1](#). We will also collect information on satisfaction of the participants with study procedures, including the mean level of satisfaction with mouthwash use around sexual activities and the biweekly self-collection of mouth rinse samples, using a 10-point VAS (10 being the highest satisfaction level). For these secondary measures, the study sample size is too small to allow a reliable analysis of the effect of the intervention on outcomes. Therefore, no hypothesis testing will be performed, and the analysis will be limited to estimates of effect size and measures of uncertainty where appropriate using bootstrapping.

### Ethics and dissemination

This study will be conducted based on the ethical principles outlined in the 2013 Declaration of Helsinki. Ethics approval has been obtained from the McGill University Institutional Review Board, and consent forms will consider the participants' well-being, free will and respect, including their respect for privacy. The protocol was

approved on 12 April 2022. Study results will be published in peer-reviewed academic journals and presented at relevant clinical conferences and societies.

### Patient and public involvement

This feasibility trial protocol was not designed with public's involvement. However, participants will be asked to complete an exit questionnaire about their experience with the study and make suggestions for improvement. This information will be incorporated into the design of the definitive trial.

### DISCUSSION

The overarching goal of this feasibility RCT is to provide important insight into the feasibility and acceptability of the proposed design as well as essential data on variances and effect sizes to inform the sample size calculation for the multicentric RCT.<sup>33</sup> This information is essential in determining the feasibility of the main trial, informing the design of a larger trial, and for securing financial support to conduct it.

Currently, there is no effective treatment for oral HPV infections. If this study demonstrates feasibility and a carrageenan mouthwash proves effective in preventing and/or clearing oral HPV infections in a main trial, it will have enormous immediate public health implications. Although vaccination programmes are important to prevent HPV, it will take a long time before we can observe any real decrease in HPV-HNCs related to the vaccine. Indeed, a recent estimate suggests no such effect will be seen for at least 25 years.<sup>34</sup> In the meantime, there exists a large population of at-risk people who have never been vaccinated and who may benefit from alternative prevention strategies. Moreover, carrageenan can be a useful adjunct to HPV vaccination because it tackles a broad spectrum of HPV types.

Furthermore, in the USA alone, 201 million people reported using some form of mouthwash in 2019, suggesting that this intervention would have acceptability and adherence. Given that oral HPV infection is mainly transmitted through oral sex,<sup>7–12</sup> if our study demonstrates feasibility and we proceed to a main RCT, findings from the main RCT would make feasible the use of a mouthwash to prevent oral HPV infections (and, by extension HPV-HNCs). This would provide an affordable, easy-to-use, yet effective complement to HPV vaccines in HPV-HNCs prevention.

**Contributors** BYA, SM and BN designed the trial. BYA drafted the initial version of the manuscript and is responsible for the statistical analysis plan. BN, SM, SDT and BYA critically evaluated the study design, contributed to manuscript writing and approved the final version. BN, SM and BYA obtained funding for the study.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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