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Oral cancer screening using mobile phone-based(mHealth) approach versus conventional oral examination approach, protocol of a cluster randomized study with cost-effectiveness analysis

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ABSTRACT

Introduction: Oral cancer is a significant health problem in India. Diagnosis is often delayed. The effectiveness of conventional oral screening has been shown in the Trivandrum oral cancer screening study. The present study will be a step forward to test a mobile phone-based (the mHealth approach) comparing it with the conventional approach. The purpose of this paper is to report the protocol for this study. The primary objective will be to compare both methods in diagnosing oral potentially malignant disorders and cancers. The secondary objective would be to study the cost-effectiveness.

Methods and analysis: This will be a cluster-randomized clinical trial of the population in Ernakulam district of Kerala state in India. They will undergo oral cancer screening by community health workers, who will be pre-assigned to the randomly allotted intervention (mHealth) or control (conventional method) clusters. We will enrol a minimum of 9696 subjects from all 6 clusters over 18 months. The cost-effectiveness of the two strategies for oral screening will be determined using data from this randomized controlled trial. The incremental cost per oral cancer/high-risk dysplasia detected, and the incremental cost per life saved will be reported. We will conduct sensitivity and scenario analysis to evaluate the robustness of the findings.

Ethics and dissemination: When completed, this will be the first cluster randomized population-based study to test the technology-based approach in India. The knowledge from this study will indicate whether specialists can make a remote diagnosis of oral lesions accurately based on the information gathered using a mobile phone health application and whether the mHealth strategy will be cost-effective in Oral cancer screening. The study will follow the ethical guidelines and will be published in an indexed journal.

1. Introduction

Oral cavity cancer is a significant public health problem in India due to the prevalent habits of tobacco, betel quid and alcohol. India accounts for one-third of the global burden (119,992 of 354,864 new cases) of the lip and oral cavity cancer [1,2]. We propose a mobile phone-based approach (m-Health approach) in oral cancer screening to improve the ability of community health workers (CHWs) in rural settings to prevent and diagnose oral cancer at an early stage. We hypothesize that the m-Health approach will enable CHWs using a mobile phone application with decision algorithms to assess risk, diagnose oral potentially malignant disorders (OPMDs) and oral cancer early, and improve the adherence of individuals to follow up in resource-restricted settings.

The effectiveness of conventional oral screening has been shown in the Trivandrum oral cancer screening study [3]. mHealth approach [4] has been validated in a study, that showed that CHWs were equally effective as specialists in oral screening [5]. A recent

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publication has summarized our experience with the mHealth. The approach also has proved to be effective in 45,754 subjects [6]. The present study will be a step forward to test the mHealth approach in a cluster-randomized two-armed study comparing it with the conventional approach. The purpose of this paper is to report the protocol for this study.

2. Material and methods

The trial will follow the CONSORT guidelines for the conduct of cluster randomised trials [7] and will be registered in the national (http://ctri.nic.in) and international trial registry before the start of the study.

2.1. Objectives and outcomes

The primary objective will be to compare the mHealth approach and the conventional clinical examination method in diagnosing oral, potentially malignant lesions and cancers. The secondary objective would be to study the cost-effectiveness of the above two strategies to diagnose oral, potentially malignant and malignant lesions. The primary outcome measure will be the number of high-risk dysplasia or cancers detected. The secondary outcome measures will be, 1) Incremental cost per case of high-risk dysplasia/ cancers detected. 2) Incremental cost per life-year saved. 3) The number of individuals who adhere to diagnostic and surveillance protocols from enrollment to completion of the study after physical examination by CHWs (Compliance rate).

3. Study design

3.1. Design for primary objective

This will be a cluster-randomized clinical trial of the population in the clusters (7 Taluks-administrative subdivisions of the district) in Ernakulam district of Kerala state in India to form 6 clusters; two of the taluks with lesser population will together form a single cluster) since the population in these taluks is less) will undergo oral cancer screening by CHWs. As per the Census India 2011, Ernakulam district has 8,14,011 households and population of 32,82,388. The annual estimated incidence is 5400 of new cancers in the district. There is no definite data regarding the incidence of oral cancer and potentially malignant lesions in Ernakulam district [8].

3.1.1. Randomization

The study population will be recruited from the Taluks. 3 of the 6 clusters will be randomly exposed to the intervention (mHealth) and the remaining 3 to control (Conventional method) for Oral Cancer Screening by FHPs. The CHWs will be pre-assigned to the randomly allotted intervention (mHealth) or control (conventional method) clusters. The CHWs assigned to the mHealth clusters will be using the mobile phones with an oral cancer application that has decision algorithms for risk assessment, oral lesion diagnoses and follow up care. Remote specialists at the cancer centre at the district headquarters (CCRC) will aid in the diagnosis through the mobile-based approach. The participants in the control clusters will undergo oral cancer screening by CHWs using the conventional method (Fig. 1).

3.1.2. Inclusion and Exclusion criteria

Participants will include 1) men and women of 18 years or older who are at risk for developing oral cancer in the Ernakulam District of Kerala, 2) self-identified with current or previous use of tobacco and tobacco-related products, alcohol use, betel quid/areca nut use, 3) able and willing to give informed consent to willing to participate in the study. Individuals excluded would be those 1) suffering from an acute illness, 2) undergoing treatment for tuberculosis, 3) diagnosed or undergoing treatment for oral cancer, and 4) pregnant women.

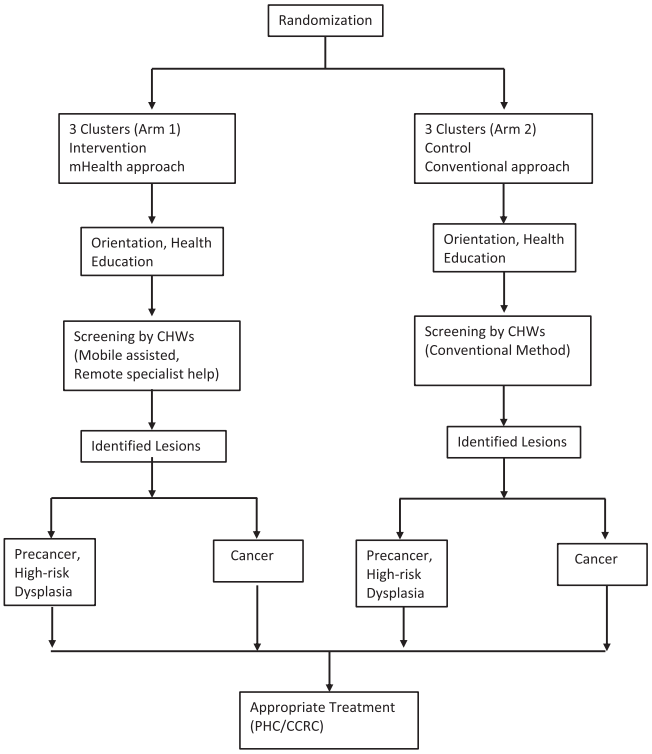

Fig. 1. Study Design, CHWs-Community Health Workers PHC- Primary Health Center CHC– Community Health Center.

3.1.3. Study Procedures

The CHWs will conduct Oral Cancer Awareness and Screening Programs at the selected Primary Health Centers (PHC) and Community Health Centers (CHC) in their assigned clusters using the mHealth or conventional methods. The participants, with a high prevalence of risk habits, will be chosen based on a questionnaire. The triaging will be based on the presence of any of the following three factors: a history of risk habits (smoking tobacco, chewing betel leaf or gutka [combination of areca nut with or without tobacco], or regular use of alcohol), older than 40 years, and clinical signs (nonhealing ulcers, red or white patches of the mouth that last more than three weeks, restriction of mouth opening, and swelling of the neck) [4,6]. A single round of screening will be done, and the screen-detected positive patients would be followed up or appropriately treated. The study design is a hub-and-node based model (Fig. 2). The hub is located at the tertiary cancer center (CCRC, Kochi, India), and the nodes are the PHCs/CHCs under a taluk hospital. The project will be presented for approval by the appropriate institutional review boards and ethical committees. Informed consent will be obtained from all participants. The workflow will involve the use of an Android mobile phone and a screening software operational with a clinical decision algorithm for the risk assessment and diagnosis (Fig. 2). The gold standard diagnostic test for oral lesions is a core tissue biopsy. The subjects who are not diagnosed with any oral lesions will be monitored by the CHWs once every three months for one year by clinical examination and habit cessation counselling. Patients with oral lesions recommended for biopsy by remote expert's review will be referred to

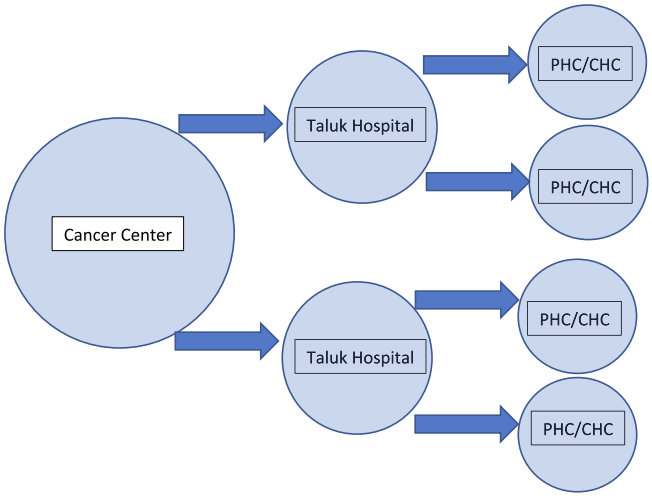

Fig. 2. Node and hub model for the trial workflow PHC- Primary Health Center CHC– Community Health Center.

oral cancer specialists in the PHCs/CHCs [4,6]. Patients with non-neoplastic lesions were discharged after anti-tobacco counselling. In contrast, those with low-risk lesions will be counselled for habit cessation and follow-up. Patients with high-risk lesions and invasive cancer will be referred to the tertiary cancer centre for surgery and adjuvant treatment according to the established cancer treatment guidelines. Compliance with biopsy and the treatment at nodal and cancer centre will be checked. Fig. 3 shows the timelines for the project.

3.1.4. Technology platform

Mobile application which complies for best practices for securing data will be used. All communications between the mobile apps, server and other solution components are encrypted using encryption technologies. Authentication is typically managed via integration with a backend user directory. All data will be uploaded to a secure server, which is HIPPA compliant, A webpage will facilitate remote consultation, appointment schedule and referrals.

3.1.5. Workflow

In arm 1 (Interventional arm, mHealth), the software on mobile phone will generate patient registration number, date of registration, and demographic details. Each participant will be interrogated using a risk evaluation questionnaire incorporated in the application. The details will consist of demographics, risk factors, and symptoms. The data obtained through the mobile phones, along with photographs of the suspicious lesions, will be uploaded to the system through a secure server. The system will then create a queue that will be reviewed at the coordinating center by the oral cancer specialist. The specialist will review the image and will judged it as interpretable or not interpretable. The interpretable images will BE clinically stratified as nonneoplastic, potentially malignant, or malignant. For oral potentially malignant and malignant lesions, the patients will undergo biopsy. Text messages (also known as short messaging services, or SMS) with follow-up instructions will be sent to the respective CHWs. On receiving the message, the CHWs will refer the patients with suspected lesions to the nodal centers (PHCs/CHCs) for biopsy. In the control arm (Conventional method), all the above procedures including the registration, record keeping, the questionnaire, the clinical details will be done through a conventional paper-based method.

Histologic evaluation: Participants with oral lesions will be seen by the specialist at the health center. The gold standard diagnostic test for oral lesions is a core tissue biopsy. The histopathologic reporting of the OPMDs will be carried out or reviewed by specialist pathologists at the central pathology laboratory of the cancer center. The reporting will be carried out as per the World Health Organization classification; oral epithelial precursor lesions will be classified into categories (mild, moderate, and severe dysplasia; invasive carcinoma) [9]. For treatment decisions, we will adopt the binary system developed by Kujan and colleagues [10]. Accordingly, nondysplastic lesions will be combined with mild dysplasia as low-risk lesions, while moderate and severe dysplasia will be the high-risk lesions.

3.1.6. Sample Size

The data from the Trivandrum oral screening study by Sankaranarayan et al [3] (for the conventional approach) and the reports our previous publications on mHealth approach were used for calculation of the sample size. In the Trivandrum study, the intervention arm (the control arm in our study) could identify 2389 oral precursor lesions or cancers from an eligible high-risk population of 45,601 (5%). The pilot study from our group had a study population (n = 3440) included a targeted cohort (n = 2000) and an opportunistic cohort (n = 1440) screened by CHWs and dental professionals, respectively. A total of 236 (130(6%) in the targeted group and 106(7%) in the opportunistic group, lesions were detected out of the total 3440 screened (6%). In our earlier study that summarized the screening in different settings by mHealth approach [5], the prevalence of OPMDs ranged from 0.8 to 62% at different cohorts, with a mean of 12.6%. The sample size was calculated to detect at least a 2% difference between the arms. Assuming that 5% of the subjects in the reference population have the factor of interest, and after applying continuity correction, the study would require a minimum sample size of 2309 for each group, to

Q1, Q2, Q3, Q4 -Quarters of the year

Activity	Q1, YI	Q2, Y1	Q3, Y1	Q4, Y1	Q1 Y2	Q2, Y2	Q3 Y2	Q4 Y2	Q1 Y3	Q2 Y3	Q3 Y3	Q4 Y3
Planning												
App refinement and												
Staff training and orientation												
Participant recruitment, screening												
Follow-up and treatment												
Data base development and entry												
Data review and analysis												
Economic evaluation data collection												
Economic data review and analysis												
Abstract and manuscript												

Y1, Y2, Y3- Year one, two and three

Fig. 3. Study Time line.

achieve a power of 80% for detecting a difference in proportions of 0.02 between the two groups (test - reference group) at a two-sided p-value of 0.05. We inflated the sample size assuming a design effect of 2 for intra-cluster correlation, providing us with a sample 4618 in each group. Considering a dropout rate of 5%, the sample size would increase to 4848 for each group. (i.e. a total sample size of 9696 assuming equal group sizes).

We will enrol a minimum of 9696 subjects from all 6 clusters over 18 months. In each cluster, at least 1616 subjects at the selected sites (PHCs and CHCs) will undergo oral cancer screening by CHWs. Each cluster will be assigned to a group of CHWs (m Health/SOC) to screen at least 80 participants per visit. The number of referable lesions for biopsy will be approximately double of the expected number of positive biopsies (according to data from Sankaranarayan et al. [1]). Accordingly, in the mHealth arm, it will be 678(14%), and in the control arm, it will be 484(10%). The expected number of patients who will be referred for biopsy will be 1162 over 18 months).

3.2. Design for secondary objective

In this study, the cost-effectiveness of the two strategies for oral screening will be determined using data from this randomized controlled trial.

3.2.1. Cost estimation

The cost estimation will include, the costs of the screening program (cost of recruiting health-care workers and screening the subjects), costs of diagnosing and treating the oral cancers detected, and of research activities. The cost from a societal perspective by including the cost of the time spent by the patient for undergoing diagnosis and treatment and the cost due to the productivity loss will also be included. An activity-based approach will be used to calculate the costs associated with the various components of the program. Activity-based costs will be derived by assigning the costs of the resources used to specific activities involved in implementing the screening program. These program activities included recruitment or invitation of screening participants, screening, data collection, research, and management and administration. Data on all the resources used will be obtained from the financial database that will be maintained by the screening program. Details of the staff employed by the program and of the equipment and supplies purchased will also be obtained from the database. The costs of equipment, staffing, consumables and travel allocated to program activities based on the expenditure incurred for each activity will be calculated. The costs of the mobile devices, the technology platform, the development and maintenance of the software and the cost of storing the data will be included. The cost of training involved in both the arms also will be included. Indirect costs and the overhead costs for program activities will be obtained. Also, the costs of biopsies and treatment were derived from the information contained in the program financial database and hospital records at the CCRC. The cost of a patient's time will be estimated from the time spent undergoing diagnostic tests and receiving treatment. Estimated daily wages of the subjects will be used. The average cost per individual in both intervention and control arms will be calculated, and the incremental cost of the intervention will be derived by comparing the two figures [8].

3.2.2. Effectiveness assessment

The effectiveness of the screening will be assessed using the number of cancers/high-risk dysplasia detected in each arm. At the end of the study, there will be data on 1. The number of high-risk dysplasia in each arm and the 2. The number of cancers in each arm. From this point, a decision-analytic model will be built till death or cure, based on the malignant transformation rates (available in the literature) of the dysplasia. Cost of treatment of the dysplasia (will be obtained from the study) cost of treatment of cancers (cost for early cancer will be obtained from the study, and that of the advanced cancers will be obtained from the hospital records). Mortality rates of oral cancers (available in the literature) Indirect costs of treatment period can be obtained from the study. Cost of the life lost is also available (the life expectancy rates of the district is available).

3.2.3. Incremental cost effectiveness ratio (ICER)

The incremental (i.e. the difference between intervention and control arms) cost per oral cancer/high-risk dysplasia detected and the incremental cost per life saved will be reported. We will conduct sensitivity and scenario analysis to evaluate the robustness of the findings from this cluster randomized trial. Probabilistic Sensitivity Analysis will be done.

4. Discussion

Trivandrum oral cancer screening study [3] was a randomized controlled trial performed in population clusters in the Trivandrum district of Kerala in India. Seven of the 13 clusters were randomly allocated to three rounds of oral, visual inspection by health-care workers; six of them got the standard care and educational messages (the control arm). Findings of the initial report published in 2005 [3], showed that, out of the 96 517 participants in the intervention group, 87,655 (91%) were screened at least once. Of the 5145 screen positive individuals, 3218 (63%) complied with the referral. 95 356 participants in the control group received standard care. 205 oral cancer cases and 77 oral cancer deaths were reported in the interventional group compared with 158 cases and 87 deaths in the control group (mortality rate ratio 0·79 [95% CI 0·51–1·22]). In individuals with tobacco or alcohol habits or both, the intervention arm (the control arm in our study) could identify 2389 oral precursor lesions or cancers from an eligible high-risk population of 45,601. A cost-effectiveness analysis was done based on the above study [11]. The incremental cost per life-year saved was US$ 835 for all individuals eligible for screening and US$ 156 for high-risk individuals. Oral cancer screening by visual inspection was performed for under US$ 6 per person [9].

mHealth approach [4] has been validated in a study, that showed that CHWs were equally effective as specialists in oral screening [5]. A recent publication has summarized the experience with the mHealth. The approach was tried in 45,754 subjects [6]. 5406 subjects with potentially malignant disorders were identified. The prevalence of oral potentially malignant disorders ranged from 0.8 to 62% at different cohorts, with a mean of 12.6%. The present study will be a step forward to test the mHealth approach in a cluster-randomized two-armed study comparing it with the conventional approach.

We expect the project will result in the early detection of oral precancer and cancer. Individuals with lifestyle-related habits (tobacco use, alcohol use) will become more aware of the risk factors of oral cancer. Diagnosis of a precancer lesion can avoid delay in diagnosis of oral cancer and thereby improve patient treatment outcomes. The long-term benefits include early detection of oral cancer and precancer lesions by CHWs, increase in awareness of oral cancer risk factors among the rural population, decrease in cost to patients and health care system, and improved access to specialist care. The knowledge from this study will indicate whether specialists can make a remote diagnosis of oral lesions accurately based on the information gathered using a mobile phone health application. This will be useful in an era when health records have become electronic, and the cost of health care per

consultation visit is high. The limitation of the study is that, it is a short term study in the community to detect the high-risk dysplasia or cancers. The detected patients will be treated, but no long term follow-up is planned. Ideally, the primary endpoint should be survival. But it may not be feasible to follow up all the patients with premalignant lesions for an event like survival.

5. Conclusion

The effectiveness of conventional oral screening was tested and shown in Trivandrum oral cancer screening study in India. The study proposes a mobile phone-based approach (m-Health approach) to improve the ability of health workers (CHWs) in rural settings to prevent and diagnose oral cancer at an early stage and to improve individual's adherence to follow up after oral cancer screening. This will be a cluster randomized population-based study to compare mHealth approach versus the conventional approach of oral examination method in oral cancer screening. When completed, this will be the first cluster randomized population-based study to test the technology-based approach in India. The study covers the population of a district in Kerala in India. This trial also plans to do a health economic evaluation, the cost-effectiveness analysis, along with the trial.

6. Source of funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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