A systematic review of medical interventions for oral submucous fibrosis and future research opportunities

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Group 3

Management Issues in Oral Submucous Fibrosis: a Systematic Review of Medical Interventions and Recommendations for future research.

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<u>Notes from Saman to Reviewers & Consultants</u>: please would you add your affiliation as brief as possible here? To be incorporated by us to title. After the first 4 names (section head and 3 consultants) I propose to arrange other co-authors listed alphabetically.

1. Background

Oral submucous fibrosis (OSF) is a chronic, insidious disease that affects the lamina propria of the oral mucosa and, as the disease advances, it involves tissues deeper in the submucosa of the oral cavity with resulting loss of fibroelasticity. The disease manifests with blanching and stiffening of the oral mucosa leading to limitation in opening of the mouth. The presence of fibrous bands in lips, cheeks and soft palate is a hallmark of the disease. Oral submucous fibrosis predominantly affects South, South Asian and East Asian populations and is seen in India, Pakistan, Bangladesh, Nepal, Sri Lanka, southern parts of China, Taiwan, Melanesia and Micronesia and in the pacific islands. The disease is also reported among Asian migrant communities living in the South and East Africa, parts of Europe, and in North America.

OSF was first described by Schwartz in 1952 among five Indian females living in Kenya and he coined the term Atrophia idiopathica (trophica) mucosae oris. Several other descriptive terms have been attributed, submucosal fibrosis of palate and pillars, diffuse oral submucous fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, and sclerosing stomatitis. The etiology of the disease was thought to be multifactorial and several agents have been reported, including local irritants (chillies), nutritional deficiency, genetic predisposition, and auto-immune disease. There is now conclusive evidence that OSF is caused by areca nut, a masticatory substance used by Asians (Gupta & Warnakulasuriya, 2002; IARC, 2004). Several mechanisms and biological pathways have been proposed for the pathogenesis of the disorder, all based on the constituents of areca nut and genetic susceptibility to the disease (Tilakaratne et al., 2006, Rajalalitha & Vali, 2005). In essence the disease could be described as a collagen metabolic disorder with changes observed in the extracellular matrix of the lamina propria and

submucosa of the oral cavity due to both increased collagen synthesis and/ or reduced collagen degradation. Areca nut is the fourth most addictive substance in the world (Gupta & Warnakulasuriya, 2002), a dependency syndrome has been described (Winstock, 2002) and unlike for tobacco cessation, interventional programmes have neither been adopted nor evaluated. There is a significant variation in the prevalence of OSF in different countries and communities directly attributable to the patterns of areca nut use, age of onset of the habit and regional variations in the available product. Regional variations in the prevalence of the disease has been observed in India. Reports on the frequency of encountering OSF suggests that the disease has rapidly risen in India from an estimated 250,000 in 1980 to 2 million cases in 1993. The reasons for the rapid increase of the disease is hypothesised due to commercial marketing strategies of the pan masala industry that produces and markets freeze-dried preparations of areca nut, and an increased uptake of this habit by young people (Gupta et al., 1998). The disease has even been identified in infancy, since a 4 year old child was reported to have developed OSF in Canada (Hayes, 1985). At the same time the pattern of use of areca nut has also changed in other parts of south Asia. For example, in Thailand and Cambodia the use of areca nut has been decreasing for many decades.

Malignant potential in OSF was described by Pindborg and Sirsat in 1966 (Pindborg & Sirsat, 1966). In a long term follow up study the annual transformation rate was approximately 0.5% (Murti et al., 1985). OSF is now a well recognised potentially malignant disorder of the oral cavity (Warnakulasuriya et al., 2007). Various classification systems for OSF based on clinical and histopathological criteria were reviewed by Ranganathan and Mishra (2005). There are no established markers to identify who may be predisposed to the disease, nor to identify the risk of malignancy in affected individuals.

The treatment of OSF has been reviewed previously, including a narrative review by Jiang and Hu (Jiang & Hu, 2009) and a Cochrane review by Fedorowicz et al (Fedorowicz et al., 2008). The review by Jiang and Hu dealt with 'the role of drugs' in the treatment of OSF. The review included a total of 15 publications (involving 1,224 patients), six of which were classed as randomized controlled trials, four as controlled clinical trials, and five as 'other experimental studies'. However, it is unclear how these papers were selected for inclusion in the review. Overall, the authors concluded that the 'effect' of various drug treatments was 'not satisfactory' and that the research in this field was insufficient.

The Cochrane review by Fedorowicz et al. had the objective to 'assess the effectiveness of interventions in the management of pain and restricted jaw opening or movement occurring as a result of oral submucous fibrosis'. Only randomized controlled clinical trials of patients with trismus or restricted jaw movement and a confirmed diagnosis of OSF (by clinical examination and biopsy) were considered. Pre-specified primary outcomes included (i) resumption of normal eating, chewing and speech, (ii) change or improvement in maximal jaw opening, measured as interincisal distance, (iii) improvement in range of jaw movement utilizing any validated assessment tool, and (iv) change in severity of oral/mucosal burning pain using any recognized validated pain scale. Secondary outcome measures included (i) postoperative discomfort or pain as a result of the intervention: patient assessed using any validated pain scale, (ii) length of hospital admission, (iii) quality of life (QOL) as assessed by any validated questionnaire, either generic or oral health specific, and (iv) patient satisfaction assessed by validated questionnaire. In addition, healthcare costs and adverse effects were to be considered. After review of potentially eligible studies, 2 studies involving 87 participants were included. The validity of both of the included studies was rated as having a high risk of bias, i.e., plausible bias that

seriously weakens confidence in the results. In terms of results regarding the primary outcome measures, both trials included measurements of change of interincisal distance; however incomplete reporting of results hampered the ability of reviewers to draw quantitative conclusions or to corroborate the reported scores. No data on resumption of normal eating, chewing and speech, or range of jaw movement were reported in either of the included studies. Changes in severity of oral/mucosal burning pain were not assessed using validated pain scales and data were considered of insufficient quality to draw any conclusions. No data regarding any of the secondary outcome measures or costs, and no quantitative data regarding adverse events were reported in either of the studies. The authors concluded that the uncertain validity of a limited amount of available data would not appear to support the view that any of the evaluated interventions were effective, beneficial or safe. The authors also highlighted several issues regarding the design and reporting of future trials, including recommendations for stratified randomization or minimization for treatment allocation based on baseline disease severity, for rigorous blinding and improved methods of outcome assessments and the use of validated instruments to ascertain relevant outcomes, as well as reporting of trials in accordance with CONSORT standards (Moher et al., 2001). However, the authors also acknowledge the challenges and difficulties faced by investigators in low and middle income countries in which OSF is prevalent.

Study of the natural history of OSF show that it is an insidious disorder that progresses with time. In clinical practice there are a number of treatments for OSF, ranging from medical interventions, surgical interventions, physical therapy, and of course habit control (ie cessation of areca nut use). Often a combination of strategies is used.

In general, chronic chewers with OSF seem to complain of two problems: inability to open their mouths and function normally, and a burning sensation and intolerance to spicy foods that are often the mainstay of the diet, leaving an individual handicapped both physically and psychologically. The severity and blend of signs and symptoms of OSF is highly variable. Patients with mild early disease, marked by a strong inflammatory component, are less likely to have fibrosis and more likely to complain of burning. This is in marked contrast to those with severe advanced disease where irreversible fibrosis and loss in function predominates. As such the aims of treatment are to reverse or ameliorate these signs and symptoms, and in addition, to minimize the risk for malignant transformation. There is a dizzying array of reported medical interventions including dietary supplementation (vitamins, anti-oxidants), anti-inflammatory agents (principally corticosteroids) and proteolytic agents (such as hyaluronidase and placental extracts) and anti-cytokines. Such agents may be administered orally, topically or via submucosal injection. Surgical interventions are generally reserved for more advanced cases of OSF. Physical therapy may be used as a single modality intervention or combined with other interventions (principally surgical interventions).

2. Objectives

Our objectives are:

a. To develop a systematic map on the current medical (ie non-surgical) interventions available for the management of OSF.
b. To update the evidence on the medical interventions for the management of OSF.

c. To develop a structure implication for a low-cost research protocol for future clinical trials in this field, with an emphasis on conducting studies in regions of the world where OSF is prevalent.

3. Review Methodology

Search Strategy:

Detailed automated searches of PubMed were conducted using “oral submucous fibrosis” as the key words up to September 2010. Interventional studies were then selected from the abstracts. Additional searches of the Indian and Chinese literature were manually conducted. Chinese studies of interest were translated into English. The initial pool of intervention studies and review articles were searched for references leading to additional papers missed in the automated searches. Articles that were case reports and statements of expert opinion were only included if they offered some possible insight.

Inclusion Criteria:

Interventional studies were then categorized by study type, including randomized controlled studies (RCTs), observational studies, or case series reports. To meet the criteria for RCTs, the study had to be prospective, include a control group and state that subjects were randomly assigned to the control and interventional groups. Observational studies included uncontrolled (or poorly controlled) and/or non-randomized prospective study of a single intervention OR retrospective studies comparing two or more different interventions. A case series constituted a retrospective series of cases based on a single intervention. Participants included individuals in any age group with a confirmed diagnosis, by clinical examination and/or biopsy of OSF. Types

of interventions included habit intervention, surgical procedures, medical treatments (ie systemic, submucosal injection or topical agents, or physical therapy. The primary outcomes explored were the (i) objective change or improvement in maximal jaw opening, measured as the inter-incisal distance, (ii) subjective change in severity of oral/mucosal burning pain using any recognised validated pain scale, (iii) subjective change in quality of life using any questionnaire, whether validated or not, and (iv) reduction in the rate of malignant transformation.

The secondary outcomes explored were any other objective or subjective changes, such as adverse events, and improvement of anaemia and co-morbidities.

Data collection and extraction:

Studies selected were evaluated independently by three reviewers (RK, TD & AM), and a data extraction table was developed for this purpose. For each study the following data was captured: study period, publication language, country, study setting, number of subjects, study type, intervention types, design details (ie control group, randomisation, blinding, timing of visits), description of population (gender, age, diagnostic criteria for OSF, baseline disease severity, habit profile), outcomes measured (subjective and objective), follow-up information, and details about statistical analyses.

Quality assessment:

The quality of evidence for each study was assessed using the Risk of Bias table (Higgins, Green, 2009).

Data synthesis:

Due to clinical heterogeneity of the studies and missing data, we were not able to pool the data of the included RCTs and provided a narrative synthesis of the data

GRADING the overall quality of evidence:

The overall quality of evidence for each outcome was assessed and reported using the GRADE approach (Guyatt et al., 2008a), (Guyatt et al., 2008b), (Guyatt et al., 2008c), (Guyatt et al., 2008d), (Jaeschke et al., 2008).

Developing Recommendations:

The quality of evidence for the questions were presented and discussed in the consensus group. The balance between risk and benefits, necessary cost and resources and patients values and local contexts has been taken into consideration. The final recommendations were graded from strong or weak based on the judgment of all participating experts.

4. Results

50 publications were included in the pool of investigations on the treatment of OSF, of which 23 were surgical in focus (and will be reported elsewhere by our group). Of the remaining studies, 22 were medical, 3 were medical/surgical, one was medical/physical, and one was medical/surgical/physical. The earliest study was reported in 1980 from India, and approximately half were undertaken after the year 2000. Three were reported in Chinese and the rest in English. Of these 27 studies, about half were conducted in India, about a third in Taiwan/China, a small number in other South Asian countries, and two among immigrants living abroad (one each in the UK and USA). All of the reported investigations were hospital/institution based and none were conducted in community settings.

In most of the 27 investigations, the diagnosis of OSF was based on the classic clinical presentation. Histopathology was used to confirm diagnosis in 12 of the investigations. Enrolled populations had a wide spectrum of OSF (ie from early to advanced), and yet stratification of the study group by OSF stage/severity rating was defined at baseline in only approximately half of the studies, most of these by reporting baseline opening, although some studies grouped subjects by range of opening (Ariyawardana et al., 2005), (Maher et al., 1997) and (Lai et al., 1995), or by using various rating scales (Khanna & Andrade, 1995), (Gupta et al., 1992), (Talsania et al., 2009) and (Singh et al., 2010).

Baseline demographic information, such as age, gender was reported in 60% of studies. Baseline patterns of areca nut use were reported in 30% of investigations, and those of alcohol and/or tobacco were reported in 22%. Baseline assessment of nutritional or dietary habits was reported in a single study (Tai et al., 2001), and laboratory assessment of hematologic status was made in 30% of studies.

A summary description of the study types is set out in Table 1. Only four studies (Rajendran et al., 2006), (Kumar et al., 2007), (Cox & Zoellner, 2009) and (Jirge et al., 2008) met our criteria for an RCT (including the two (Rajendran et al., 2006) and (Kumar et al., 2007) previously reported in the Cochrane review), and all were run at a single center. There was one other prospective controlled study that lacked randomization (Lin & Lin, 2007). The rest were rated as observational or retrospective studies.

Tables 2 and 3 highlight the different interventions and how they are alleged to work. There were no studies that looked at the effect of habit control alone as the primary endpoint, ie cessation of areca nut habits. The methodology of 14 studies included the advice to quit the habit, although only two of these described specific measures for cessation. In these studies subjects

were given a dental cleaning at baseline to remove staining and then re-examined at follow-up visits for any new staining (Ariyawardana et al., 2005) and (Kumar et al., 2007). No serum markers for metabolites of areca nut were utilized.

15 studies used a single agent, and the rest studied combinations of agents. 22 studies included the use of nutrients, micronutrients and/or anti-oxidants, 21 studies included the use of immunomodulatory agents that reduced the inflammatory component, principally injected corticosteroids (16 studies). 19 studies included the use of proteolytic enzymes to reduce fibrosis of which 7 used hyaluronidase. 4 studies included agents to promote blood flow. Agents were delivered orally for systemic absorption, intra-lesionally, or topically.

Outcome measures reported in these studies were highly variable both in the type and the manner in which they were measured. In terms of objective measures, mouth opening (generally measured as inter-incisal opening) was the most consistently and reliably measured outcome across all studies. Other objective measures included changes in tongue movement (ie ability to protrude), degree of suppleness of the tissues, amount of blanching of the mucosa, presence of ulceration/vesicle formation, and amount of dorsal tongue papillation, although the methodology for measuring these other objective outcomes was poorly defined and of questionable unreliability. In terms of subjective measures, oral burning/pain was the most consistently measured subjective outcome, although very few studies reported using validated pain assessment instruments, such as a visual analogue pain rating scale. Other subjective measures included change in taste, oral dryness, and ability to chew, swallow, or speak. None of the studies used validated instruments evaluating quality of life of subjects with OSF, nor could we find any such instruments in the published literature.

22 investigations did not specify whether or not subjects completed a given treatment regimen. Of the remaining studies, 17 reported >75% of the subjects completed the study regimen. Follow-up of subjects after treatment was highly variable, with only 19 studies reporting follow-up beyond 1 year.

Randomized Controlled Studies:

There were three RCTs describing investigation of medical interventions: pentoxifylline (Rajendran et al., 2006), lycopene (Kumar et al., 2007) and levamisole with anti-oxidants (Jirge et al., 2008). Rajendran et al. divided the 29 participants into two groups that took either oral pentoxifylline or multi-vitamins. All those enrolled completed the 7 month study period. The authors reported statistically significant improvements in the oral pentoxifylline group (n=14) compared to controls with respect to objective criteria (mouth opening, tongue protrusion and relief from circum-oral fibrotic bands) and subjective criteria (intolerance to spices, burning sensations, tinnitus, difficulty in swallowing, and difficulty in speech).

Kumar et al. recruited 83 participants who were divided between study groups that received either oral lycopene (n=21; group A), oral lycopene with intralesional corticosteroids (n=19; group B) or an oral placebo (n=18; group C). The two-month intervention period was completed by 58 people. Objective measurement of mouth opening was reported to be significantly improved with an average increase of 3.4mm, 4.6mm and 0mm for groups A, B and C, respectively. The increases were maintained at 3 and 6-months review. All patients who took lycopene reported relief from burning sensations within 2 weeks, whereas only one patient from the placebo group reported a similar improvement.

The 45 participants reported by Jirge et al. were divided equally between three study groups: oral levamisole (group I), an oral antioxidant (group II), or oral levamisole with antioxidant (group III). On conclusion of the intervention period (approximately 15 weeks) there was improvement of mouth opening of 7.1%, 6.7% and 8.0% in groups I, II and III, respectively. These gains were maintained on further evaluation two months later. There was also a significant reduction in burning sensations in all study groups.

Cox and Zoellner enrolled 54 Nepali subjects into 3 groups: physiotherapy, injections with combination hyaluronidase/steroids, and a control group. After 4 months, subjective and objective measures were compared to baseline. The physiotherapy group showed a significant increase in opening but had no superior effect on subjective measures.

Re-analysis by the working group of the published data from these four RCTs using the GRADE criteria identified significant limitations with each report and challenged the conclusions reached by the authors (Table 4) .

5. Future Studies

The review team, echoing the sentiments of other reviewers, appreciates the opportunity and importance to offer suggestions and recommendations for future research. Clinical research methodology has evolved rapidly in the industrialized world, yet not all parts of the world have the experience, nor the necessary infrastructure, to design let alone run randomized controlled trials. While the methodological issues in the published literature we reviewed offer weak evidence at best to make recommendations for the management of patients with OSF, there is much valuable insight to be gained from the studies we reviewed.

Moving away from the perspective of a systematic review, and focusing on mining the studies for information to help direct future research, we developed a list of objectives (adapted from (Brown et al., 2006)), and summarized in Table 6.

a. What populations should be researched?
b. What types of interventions are needed?
c. What types of outcomes should be measured?
d. What study designs are needed?
e. What infrastructure is required to conduct studies?

Populations:

The populations for research on OSF are dictated by where the areca nut habit is prevalent. Studies must be conducted in both in South East Asia (India, Pakistan, Nepal, Bangladesh, Sri Lanka), and in Chinese populations (Taiwan and Southern China) where studies have already been performed and the research infrastructure is developing. Numerous other countries have high rates of areca nut use (Burma, parts of Malaysia, Pacific islands and others) although very little literature suggests that clinical studies are ongoing. Additional studies conducted in immigrant populations, such as the UK, US, or Australasia, are secondary, yet have the potential to overcome some of the methodological flaws inherent in countries where clinical research infrastructure is lacking.

Given the variable spectrum of the signs and symptoms of OSF, subpopulations of patients grouped by disease severity/stage should be studied separately because different interventions may be effective at different stages of pathogenesis. For simplicity, there are two distinct populations: those with advanced-stage disease hallmarked by irreversible and debilitating fibrosis, and those who have not reached advanced-stage. Studies must define

specific inclusion and exclusion criteria to foster the enrollment of subjects suited to the type of intervention. In terms of demographics, studies are needed not only in adult populations, but also in children who are regularly using areca nut products (particularly gutkha) (Gupta & Ray, 2003). There may also be differences in OSF populations related to the habits and types of areca-nut preparations used.

Interventions Needed:

We hypothesize that habit cessation alone as an intervention may have a large effect, more so on the symptoms of OSF rather than reversing fibrosis. The almost complete lack of studies incorporating habit control suggests that investigators have difficulty managing the dependence on areca nut products. Indeed the introduction of gutkha into the marketplace in India has led to even higher rates of dependence and OSF (Gupta, 1998). Future interventions must incorporate a standardized preventive plan even if a high relapse rate is anticipated, and include methodology to allow investigators to control for relapse during the study and follow-up during data analysis. Serial measures of serum areca alkaloids might be the gold standard to detect relapse or continued use of areca products during the studies, although simple strategies such as performing a baseline dental prophylaxis to remove extrinsic staining and re-evaluate for new staining might be an excellent surrogate.

Our current understanding of the pathogenesis of OSF (Tilakaratne et al., 2006) includes overlapping phases, an early inflammatory phase and the later fibrosis phase, suggesting that interventions can be tailored to the severity of disease. At one end of the spectrum, new studies for the treatment of advanced disease are needed. We know that surgical excision of fibrosis will provide short-term improvement in function. Yet, there are a number research questions

remaining. At what stage of fibrosis is surgery indicated? Would habit control and pre-operative physical therapy lead to a subset of advanced staged patients not requiring surgery? Which post-operative interventions lead to favourable long-term outcomes? Which surgical procedures offer excellent immediate post-operative outcomes and with minimal hospitalization, complications and cost? These questions will be reviewed by our group elsewhere. At the other end of the spectrum, early and intermediate stage disease may be amenable to a combination of existing and novel medical therapies. Which medical therapies are best indicated for which stage of disease? Does a combination of medical therapies provide the best outcomes? Which agents can slow down (or even reverse) fibrosis? What are the best delivery systems for medical therapies (ie topical vs submucosal injection vs systemic agents) in terms of compliance/adherence to treatment? What role do anti-oxidants or nutritional supplements play? The injection of corticosteroids was the most frequently studied medical therapy and in clinical practice it remains the first line of treatment for symptomatic patients with OSF, and yet unfortunately there is not a single controlled clinical trial.

Another major area of research is to consider specific anti-inflammatory agents (eg COX-2 inhibitor, Celecoxib) and molecular targets to stabilize the disease in early stages and to impact on the malignant potential of OSF. Scientific rationale for such potential interventions are based on laboratory findings in OSF that are reviewed elsewhere (Tilakaratne et al., 2006); (Rajalalitha & Vali, 2005). As seen in Figure 1 one of the key molecules in the initiation of fibrosis is TGF-β, a multifunctional cytokine known to be activated in fibrotic disorders. In addition to its key role in fibrosis TGF-β has a range of biological effects including cell proliferation and differentiation, immune regulation, production and deposition of extracellular matrix, and effects on inflammation. Anti-TGF-β drugs in the form of an antibody would inhibit the function of the

cytokine by interacting with it. Given the integral role of TGF-β in fibrosis as well as later malignant transformation, various components of the TGF-β signaling pathway offer potentially attractive therapeutic targets for treatment of OSF. Both small and large molecule drugs are currently in development that target TGF-β, its receptor and down stream steps along its signaling pathway that could be used as novel therapies for OSF. Such clinical trials could form the basis of a high-cost approach suitable for use in developed countries on selected migrant populations with OSF. Other molecular targets may be of relevance to inhibit malignant potential. αVβ3 integrin is highly expressed in OSF and in carcinoma arising thereof. Therapeutic trials are underway to target αVβ3 integrin in other cancers and OSF researchers might explore these new avenues of therapy.

Curcumin (diferuloymethane) found in turmeric, a natural yellow pigment mostly used as a curry powder in Asian cooking exhibits anti-oxidant, anti-inflammatory and anti-cancer properties (Chainani-Wu, 2003), (Epstein et al., 2010). Curcumin has recently been advocated in phase ll and lll clinical trials for a variety of cancers including multiple myeloma, pancreatic and colon cancer (Shehzad et al., 2010). Sixteen clinical trials on curcumin are currently listed in the National Cancer Institute web site. As such it may fulfill two roles in the putative treatment of OSF, both as an anti-inflammatory agent and as a chemopreventive agent. It also provides the basis for a simple, safe, acceptable and cost effective intervention for earlier stage OSF. After completion of this systematic review and while writing this report, a paper describing the use of curcumin in the treatment of oral precancer including 25 patients with OSF was retrieved. This study again was not an RCT but reported that OSF was “cured by curcumin” due to increase of local and systemic antioxidative status (Rai et al., 2010).

Outcome Measures:

In terms of important outcome measures one must first consider the perspective of the patient. We have acknowledged the absence of any qualitative research on quality of life measures in this patient population, and the need to develop and validate such instruments. Little is known about the social implications associated with OSF. Are there issues in the workplace or at home? What are the issues with children and youth with OSF? The morbidity associated with OSF is related to pain/burning, intolerance to spicy foods/beverages, and as the fibrosis progresses it is related to inability to function, such as opening wide enough to masticate, speak, and in some cases swallow. Until QOL instruments are developed and validated, subjective outcome measures must include validated pain scales, such as numerical visual analogue scales or pain-intensity scales (Wewers & Lowe, 1990). Consideration must be given to the cultural differences in pain perception and tolerance, and existing validated instruments need to be modified to the population being studied. Inter-incisal opening seems to be the single most reproducible objective measure for OSF. Whether measured by Vernier calipers or a metal ruler, the only room for error is if the patient is missing anterior teeth, in which case an adjustment must be made. Ideally, measurements should be made by blinded investigators and with intra and inter-rater reliability assessments. Other objective measures seem less reproducible, such as tongue protrusion, the extent of cheek puffing, palpation of fibrous banding, degree of tissue blanching etc. Development of new objective measures will be important and could include sensors to assess tightness of banding or vascular changes. Many of the OSF patients present with anemias and nutritional deficiencies. It is not clear how these conditions are related to OSF, although it seems prudent to consider laboratory testing as a secondary objective measure, particularly if designing a medical intervention involving the use of micronutrients, vitamins, or nutritional

supplements. From a public health perspective there are additional considerations, including the presence of premalignant lesions and risk for malignant transformation. A percentage of patients with OSF will have concomitant oral lesions at baseline or develop them over time. Protocols for standardized examinations to detect potentially malignant oral diseases, followed by a diagnostic algorithm leading to a histopathological diagnosis are of paramount importance (Warnakulasuriya et al., 2007).

The issue of areca nut dependence is another major public health issue. It is necessary to use evidence from the literature on the effectiveness of pharmacological, psychological and public health interventions in the management of other substance use disorders to inform potential innovative therapeutic interventions for those who habitually and harmfully consume these inexpensive and widely available areca nut products. Legislation and education by appropriately targeted health campaigns and mass media communication will underlie any effective strategy to reduce its overall use in the community and associated morbidity. Potential approaches for cohort studies may include, individual, family and group interventions based upon Cognitive Behavioural Therapy, relapse prevention and aspects of motivational enhancement therapy in combination with potential substitute therapies and flavoured gums.

Study Design:

Study design will be dependent on the type of intervention. All study methods will require a habit assessment and cessation component and the ability to assess and control for relapse during treatment. Depending on budget and infrastructure, cessation could range from a brief intervention repeated at all visits, to intensive counseling (+/- pharmacotherapy). Separate studies are needed to assess which strategies might work and is beyond the scope of this review.

Randomized double-blinded placebo-controlled study design is ideally suited to explore the efficacy of medical agents, particularly studies testing agents taken orally where it is feasible to manufacture placebos. It is rather more difficult to control for agents that have to be injected submucosally, although one could control for the agent by mixing it with local anesthetic and having the placebo injection with local anesthetic alone. Other acceptable designs could be comparison RCTs in which two or more different agents are compared. In such cases, power calculations are important to generate conservative sample sizes to account for differences between active group and controls. Assigning subjects to a "no treatment" arm (ie habit control alone) may also be useful.

Establishing specific inclusion and exclusion criteria is important. How to diagnose and grade OSF? Is histopathology needed or could a set of validated clinical criteria suffice, thereby saving patient discomfort, time and cost? Defining the population depending on the agent being investigated, such as excluding advanced cases, including those patients with a range of restricted opening, or those with a certain threshold of pain, or those who use gutkha versus betel quid or other non-industrialized preparations. Preparation of the research infrastructure with IRB approval should include a study protocol, consent forms, data entry forms, a budget, and the hiring of personnel with training the area of human subjects research. Once enrollment begins, informed consent must be given. This is major problem in developing countries since subjects may speak different dialects, or are not educated enough to read or sign the consent or understand the concepts of the study. Where possible, consent forms should be translated into different languages and, in cases where subjects cannot understand, a family member or designated person must act on behalf of the patient.

Randomization, by various acceptable techniques, may be simple or based upon quotas for various severity groups (ie early/mild vs moderate/intermediate OSF) or other variables. Subjects would then receive a cleaning and oral hygiene and dietary instruction before receiving the treatment. All investigators performing procedures (measuring outcomes) must be also be blinded to the treatment arms. Subject incentives are an important consideration. Many cultures are suspicious about receiving monetary incentives, and investigators may need to be creative about how to incentivize enrollment and retention without coercion. In studies with multiple visits, a bonus for completing the trial can help reduce drop-outs. Higher incentives are required for studies with long visits, or where invasive procedures are conducted (ie blood draw, biopsies, injections). Studies with long-term follow-up are important to assess relapse and the development of potentially malignant oral lesions. Loss to follow-up is a major issue and creative approaches are needed. A checklist for these and other steps for running a clinical trial may be found through CONSORT (Moher et al., 2001).

None of the interventions reported so far have examined any improvement in oral health-related quality of life among patients treated for OSF. Both burning and trismus can affect oral function, oro-facial appearance and social interaction. We propose that future studies should include questionnaires designed specifically to evaluate how well those treated for OSF can perform common functions. Study questionnaires could be devised from existing QOL questionnaires, such as the following:

- EORTC QLQ – H&N 35 (Bjordal et al., 2000)
- International Classification of Functioning, Disability and Health (ICF) questionnaire for patients with Head & Neck Cancer (Tschiesner et al., 2010)
- Performance Status Scale (List et al., 1996)

Other new questions added to gain more information in relation to specific aspects related to OSF and oral function. However, such new adapted questionnaire should be pilot tested among a cohort of OSF patients before research use.

The WWOM V Working Group will help investigators develop research protocols for the management of OSF and facilitate centralized data collection and analysis. We propose to convene a consortium of interested investigators to design and run multi-center studies in high incidence countries.

6. Conclusions

We found a low grade of evidence to support recommendations for the management of OSF. However, using the information from the review, our working group developed a framework to propose multi-center research in countries where OSF remains a serious public health issue.

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8. Tables & Figures:

Table 1: Types of studies (excluding surgical studies)

Single centre prospective RCT	4
Observational studies	19
Retrospective case-series	4
Total	**27**

Table 2: Summary of studies including physical therapy

Group	Rationale	Examples of Interventions		Example references
Physical therapy	Modify tissue remodelling through promotion of physical movements and localised heat	Physiotherapy	Physical exercise regimen (including post-surgery)	(Lai et al., 1995), (Cox & Zoellner, 2009)
			Splints or other devices (including post-surgery)	(Patil & Parkhedkar, 2009), (Nayak et al., 2009), (Le et al., 1996), (Huang et al., 2008)
			Microwave diathermy	(Gupta et al., 1980), (Gupta et al., 1992) (Chen 2006)

Table 3: Summary of studies including medical therapy

Group	Rationale	Examples of Interventions		Example references
Nutrients, micronutrients and anti-oxidants	Correct deficiency states and promote normal cellular processes present in health that help to protect against adverse events including carcinogenesis	Systemic	Vitamin A (chewable tablets also give some topical application)	(Borle & Borle, 1991), (Kumar et al., 1991)
			Vitamin A and vitamin B complex	(Khanna & Andrade, 1995)
			Vitamin B complex	(Lai et al., 1995)
			Vitamin B complex (with iodine injection)	(Gupta et al., 1992)
			Vitamins A, B complex, C, D & E plus minerals iron, copper, zinc, magnesium and others	(Maher et al., 1997)
			Ferrous fumarate	(Borle & Borle, 1991)
			Zinc	(Kumar et al., 1991)
			Antoxidants (β-carotene, vitamins A, C & E , zinc, copper, manganese & selenium)	(Jirge et al., 2008)
			Glucosidorum tripterygii totorum, vitamins A & E, nicotinic acid	(Liu et al., 1999)
			Tea pigment, vitamins A, B complex, D & E	(Li & Tang, 1998)
			Lycopene	(Kumar et al., 2007)
			Placental extract	(Kakar et al., 1985), (Gupta & Sharma, 1988), (Katharia et al., 1992), (Rananjaneyulu & Rao, 1980), (Gupta et al., 1992)
			Papain (cysteine protease) with keratolytic action of urea:	(Gupta et al., 1992)
Biogenic stimulation	Homograft stimulates favourable metabolic processes that promote non-fibrotic tissue regeneration	Intralesional injections	Collagenase	(Lin & Lin, 2007), (Chen & Lin, 1986)
Proteolytic enzymes	Proteolytic enzymes breakdown the inappropriate connective tissue fibrosis	Intralesional injections	Hyaluronidase	(Kakar et al., 1985), (Gupta & Sharma, 1988), (Borle & Borle, 1991), (Lai et al., 1995), (Cox & Zoellner, 2009), (Singh et al., 2010)
			Chymotrypsin	(Gupta & Sharma, 1988)

Immune modulation	Immune modulation that diminishes pro-fibrotic inflammation and enhances pro-fibrolytic immune-mediated pathways	Topical	Corticosteroid	Betamethasone	(Borle & Borle, 1991)
				Triamcinolone acetonide	(Lai et al., 1995)
		Intralesional injections	Corticosteroid	Dexamethasone	(Kakar et al., 1985), (Gupta & Sharma, 1988), (Borle & Borle, 1991), (Lai et al., 1995), (Liu et al., 1999)
				Triamcinolone diacetate	(Lin & Lin, 2007), (Borle & Borle, 1991), (Khanna & Andrade, 1995), (Chen & Lin, 1986), (Singh et al., 2010)
				Methylprednisolone	(Ariyawardana et al., 2005)
				Betamethasone	(Kumar et al., 2007)
				Hydrocortisone	(Cox & Zoellner, 2009), (Kumar et al., 1991), (Singh et al., 2010)
			Other	Interferon gamma (IFN-γ)	(Haque et al., 2001)
		Systemic	Levimasole		(Jirge et al., 2008)
			Immune milk from cows immunised with multiple human intestinal bacteria		(Tai et al., 2001)
Promotion of blood flow	Promote blood flow to ischaemic tissues via multiple mechanisms including vasodilatation and mild anti-coagulant effects with other biological actions including immunomodulation and anti-oxidant functions	Systemic	Pentoxifylline		(Rajendran et al., 2006)
			Nylidrin Hydrochloride		(Sharma et al., 1987)
			Buflomedial hydrochloride		(Lai et al., 1995),
			Danxuan Koukang (DXKK)		(Tan et al., 2006)

Table 4: GRADE summary of RCTs

Question: Should oral lycopene vs placebo be used for oral submucous fibrosis? (Kumar et al., 2007)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral lycopene	placebo	Relative (95% CI)	Absolute	Quality	
Clinical assessment of maximum opening (follow-up 2 months; measured with: Interincisal distance (mm); Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21	18	-	MD 1.15 higher (4.42 lower to	⊕OOO VERY LOW	CRITICAL

										6.72 higher)		
Burning sensation (follow-up 2 months; subjective reporting by the patients)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/21 (4.8%)[3]	17/18 (94.4%) 94.4%[4]	RR 0.05 (0.01 to 0.34)	897 fewer per 1000 (from 623 fewer to 935 fewer) 897 fewer per 1000 (from 623 fewer to 935 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] The method of randomisation was not clear. It was not blinded. It was not clear whether the allocation was concealed. The study has 30% drop out.
[2] The sample size was very small. The participants were first 83 patients and a number were lost to follow up and only 58 continued to participate in the trial.
[3] The authors report that in the lycopene group and the lycopene with betamethasone group, only one patients had still burning sensation. It was not clear whether the patients was from the lycopene or the lycopene with betamethasone group, therefore, we assumed the worse case scenario for this comparison and put 1 event for the lycopene group.
[4] This is derived from the mean baseline risk in the control group of this study and assumes that there is a high baseline risk (94.4) that patients with oral submucous fibrosis would have burning sensation.

Question: Should oral lycopene vs oral lycopene and betamethasone be used for oral submucous fibrosis? (Kumar et al., 2007)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**oral lycopene**	**oral lycopene and betamethasone**	**Relative (95% CI)**	**Absolute**	**Quality**	
Clinical assessment of maximum opening (follow-up 2 months; measured with: Interincisal distance (mm); Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21	19	-	MD 6.35 higher (1.04 to 11.66 higher)	⊕OOO VERY LOW	CRITICAL
Burning sensation (follow-up 2 months; subjective reporting by the patients)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/21 (0%)[3]	0/19 (0%)	Not estimable[4]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] The method of randomisation was not clear. It was not blinded. It was not clear whether the allocation was concealed. The study has 30% drop out.
[2] The sample size was very small. The participants were first 83 patients and a number were lost to follow up and only 58 continued to participate in the trial.
[3] The authors report that in the lycopene group and the lycopene with betamethasone group, only one patients had still burning sensation. It was not clear whether the patients was from the lycopene or the lycopene with betamethasone group, therefore, we did not put any data in this comparison.
[4] Both groups had burning sensation before the treatment and this disappeared after the treatment.

Question: Should oral lycopene and betamethasone vs placebo be used for oral submucous fibrosis? (Kumar et al., 2007)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oral lycopene and betamethasone	placebo	Relative (95% CI)	Absolute	Quality	
Clinical assessment of maximum opening (follow-up 2 months; measured with: Interincisal distance (mm); Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	18	-	MD 5.20 lower (9.85 to 0.55 lower)	⊕OOO VERY LOW	CRITICAL
Burning sensation (follow-up 2 months; subjective reporting by the patients)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/19 (5.3%)[3]	17/18 (94.4%)	RR 0.06 (0.01 to 0.38)	888 fewer per 1000 (from 586 fewer to 935 fewer)	⊕OOO VERY LOW	IMPORTANT
								94.4%[4]		887 fewer per 1000 (from 585 fewer to 935 fewer)		

[1] The method of randomisation was not clear. It was not blinded. It was not clear whether the allocation was concealed. The study has 30% drop out

[2] The sample size was very small. The participants were first 83 patients and a number were lost to follow up and only 58 continued to participate in the trial.

[3] The authors report that in the lycopene group and the lycopene with betamethasone group, only one patients had still burning sensation. It was not clear whether the patients was from the lycopene or the lycopene with betamethasone group, therefore, we assumed the worse case scenario for this copmrison and put 1 event for the lycopene + betamethasone group.

[4] This is derived from the mean baseline risk in the control group of this study and assumes that there is a high baseline risk (94.4) that patients with oral submucous fibrosis would have burning sensation.

Question: Should levamisole vs antioxidant (multivitamin) be used for oral submucous fibrosis? (Jirge et al., 2008)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	levamisole	antioxidant (multivitamin)	Relative (95% CI)	Absolute	Quality	
Clinical assessment of maximal opening (changes in interincisal distance) end of the treatment (follow-up 6 weeks[1]; measured with: cm; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 0 higher (0.11 to 0.11 higher)	⊕OOO VERY LOW	CRITICAL

Clinical assessment of maximal opening (changes in interincisal distance) after 60 days follow up (follow-up 60 days; measured with: cm; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	mean 0.10 higher (0.03 to 0.17 higher)	⊕OOO VERY LOW	CRITICAL
Burning sensation (follow-up 6 weeks[1]; measured with: VAS scale; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	mean 9.10 lower (16.23 to 1.9 lower)	⊕OOO VERY LOW	IMPORTANT

[1] Six weeks was the treatment (5th visit after starting the treatment) and 60 days follow up with two visits each 30 days (7th visit).
[2] No clear description of methods of randomisation, concealment of allocation or blinding.
[3] The sample size was small and included only 45 patients.

Question: Should pentoxifylline and local heat therapy vs multivitamin capsule and local heat therapy be used for oral submucous fibrosis? (Rajendran et al., 2006)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pentoxifylline and local heat therapy**	**multivitamin capsule and local heat therapy**	**Relative (95% CI)**	**Absolute**		
Clinical assessment of maximum opening (follow-up 6-12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14	15	-	MD lower (0 to 0 higher)[3]	⊕OOO VERY LOW	CRITICAL
Burning sensation (follow-up 6-12 months; unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/14 (0%)[3]	0/15 (0%)[3]	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] Methods of randomisation, concealment of allocation and blinding is unclear. Not of all of the patients were included in the analysis.
[2] The study only included 29 patients. The sample size was very small.
[3] The data were not transparently reported and we were not able to do further calculation.

Question: Should physiotherapy be used for oral submucous fibrosis? (Cox & Zoellner, 2009)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**physiotherapy**	**control**	**Relative (95% CI)**	**Absolute**		
Clinical assessment of maximum opening (follow-up 4 months; Better indicated by lower values)												
1	randomise	very	no serious	no serious	serious[2]	none	16	8	-	MD 0	⊕OOO	CRITICAL

	d trials	serious[1]	inconsistency	indirectness						higher (0 to 0 higher)[3]	VERY LOW	

[1] The study did not adequately conceal the allocation of patients in two groups, it was not blinded and 52% of the patients were lost to follow up.
[2] The study included 54 patients at the beginning and only 28 came for the final evaluation. The sample size is small.
[3] The data were not adequately reported and we could not include them in further calculation.

Question: Should physiotherapy vs hyaluronidase and steroid injections be used for oral submucous fibrosis? (Cox & Zoellner, 2009)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	physiotherapy	hyaluronidase and steroid injections	Relative (95% CI)	Absolute		
Clinical assessment of maximum opening (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	4	-	MD 0 higher (0 to 0 higher)[3]	⊕OOO VERY LOW	CRITICAL

[1] The study did not adequately conceal the allocation of patients in two groups, it was not blinded and 52% of the patients were lost to follow up.
[2] The study included 54 patients at the beginning and only 28 came for the final evaluation. The sample size is small.
[3] The data were not adequately reported and we could not include them in further calculation.

Question: Should hyaluronidase and steroid injections be used for oral submucous fibrosis? (Cox & Zoellner, 2009)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	hyaluronidase and steroid injections	control	Relative (95% CI)	Absolute		
Clinical assessment of maximum opening (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4	8[3]	-	MD 0 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL

[1] The study did not adequately conceal the allocation of patients in two groups, it was not blinded and 52% of the patients were lost to follow up.
[2] The study included 54 patients at the beginning and only 28 came for the final evaluation. The sample size is small.
[3] The data were not adequately reported and we could not include them in further calculation.

Table 5: Disease Grading System – OSF

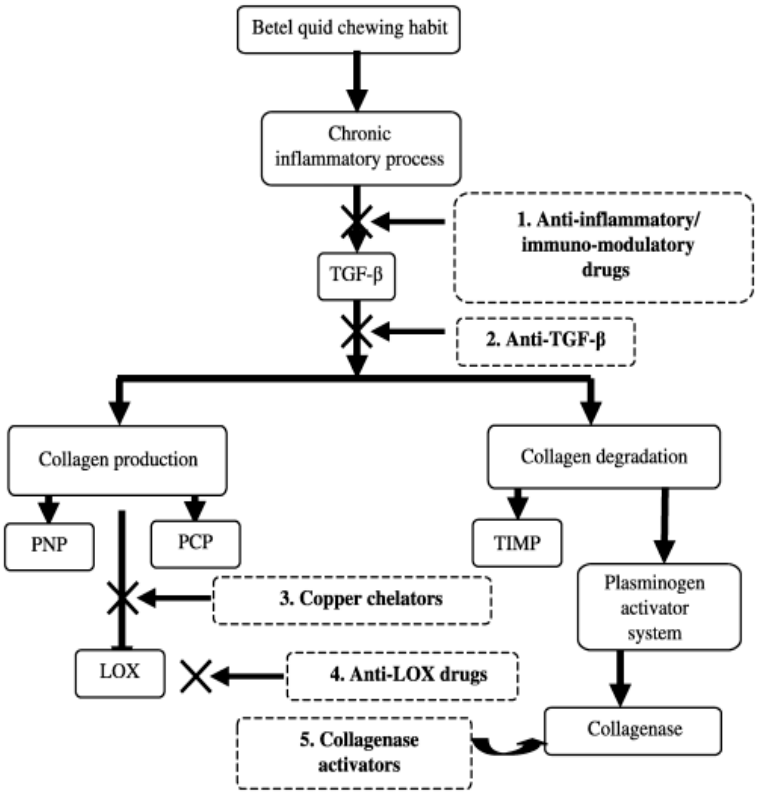
• Grade 1 – Burning, depapillation, blanching or leathery mucosa (disease triad for OSF) – mouth opening - >35mm
• Grade 2 - Moderate limitation of opening 20-35mm
• Grade 3 - Severe OSF, limitation of opening <20 mm
• Grade 4A – OSF + other potentially malignant disorder
• Grade 4B - OSF with oral epithelial dysplasia

• Grade 5 - OSF + SCC

Table 6: Recommendations for Future Research

Researcher recommendation	**WWOM V Group 3 Review on the Medical Management of Oral Submucous Fibrosis**
Population/setting *(taking context/equity/social determinants of health into consideration for defining future subgroups in the study*)	• Studies in India, Sri Lanka, Nepal, Taiwan/China • Studies in immigrant populations (US/UK) • Studies in adults and children • Studies based on stage of disease
Intervention *(taking values and preferences into consideration*)	• Habit control/prevention • Targeting early-intermediate stages • Use of systemic agents (alone or in combination) eg curcumin • Anti-inflammatory agents, anti-oxidants, anti-fibrinolytics, targeted therapies, chemotherapy vs malignant transformation • Development of QOL scale
Comparison	• Compare medical agent(s) to controls • Develop "standard of care" therapy and compare other therapies to it.
Outcomes *(taking patient views into consideration*)	Primary: • Subjective o QOL scale o Pain/burning • Objective o Inter-incisal opening • Presence of Potentially Malignant Oral Disorders • Habit cessation success rates at 1 year
Timing	Variable depending on type of trial
Study Design	Double-blinded RCT
Sample Size	Variable depending on type of trial. It is essential to conduct a power calculation to ensure the sample size for each treatment arm is adequate

Figure 1: Pathogenesis of OSF



From: (Rajalalitha & Vali, 2005)