UNIVERSITAT DE BARCELONA

Oral health in long-term space missions: previous experience, prevention and treatment needs

Víctor Lloro Boada

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PhD Thesis

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Faculty of Medicine and Health Sciences
Bellvitge Health Sciences Campus
Department of Pathology and Experimental Therapy
Unit of Human Anatomy and Embryology

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Oral health in long-term space missions: previous experience, prevention and treatment needs

PhD Thesis presented by **Víctor Lloro Boada**

This doctoral thesis has been directed by
Dr. Mª Cristina Manzanares Céspedes and Dr. Laura Giovannoni

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Some say that he has achieved his goals solely on his own merits. It's not my case. Although it is true that to carry out this thesis I have had to put all my energy, it would be unfair and unrealistic to say that it is exclusively my merit.
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Abbreviations

ATP: Adenosine Triphosphate

CAD-CAM: Computer-Aided Design Computer-Aided Manufacturing

CBCT: Cone Beam Computed Tomography

CI: Confidence interval

DIFOTI: Digital Imaging Fiber-Optic Trans-Illumination instrument

ESA: European Space Agency

IgA: Immunoglobin A

HVE: High-Volume Evacuator

MMP: Metalloproteinase

NASA: National Aeronautics and Space Administration

OAC: Oroantral communication

OBF®: Oral Bio Filter

PMTC: Professional Mechanical Tooth Cleaning

RLU: Relative Light Unit

US: United States

UV: Ultraviolet

Abstract

This PhD thesis is the result of a four-year-long research project oriented to establish whether dentistry is relevant to the space race, and if, consequently, the creation of a scalable dental module capable of housing a treatment center for dental pathologies on the next manned missions to the Moon and Mars is necessary and feasible.

Aeronautical and aerospace dentistry as a scientific field have made a discrete number of investigations about the effects of microgravity on the oral cavity, most of them historically located in the past decade. Space agencies around the world consider knowledge of aerospace dentistry to be a priority, both at a preventive level and in terms of treatment needs for space missions, in which a dental emergency could represent an important risk for the success of the mission.

To establish if dentistry is relevant to space race and if, therefore, it is necessary and feasible to create a scalable dental module with several specific pieces of equipment, this PhD Thesis includes:

Chapters 1 and 2: Two systematic reviews of the literature published to date on oral health incidents related to situations of isolation and microgravity, respectively.

Chapter 3: The design and patent obtention of a device, named OralBioFilter (OBF®), aimed initially to avoid environmental contamination and cross-contamination in enclosed areas and to prevent aerosol dissemination from the mouth during dental procedures.

Chapter 4: The analysis of the efficacy of this OBF® device by means of a comparative study made in a dental practice clinical setting.

Chapter 5: The proposal of the design requirements of a module for dental treatment with the equipment, including OBF® device, specifically designed for the dental practice in microgravity conditions.

Chapter 1:

The Incidence of Dental Needs During Isolated Missions Compared to Non-isolated Missions: A Systematic Review and Implications for Future Prevention Strategies. Mil Med. 2019 Mar 1; 184(3-4):e148-e155. doi: 10.1093/milmed/usy364.

Dental emergencies in isolated groups have always been difficult to treat, especially in people or groups who need urgent dental assistance and cannot be evacuated (long-term submarine missions, long-term space missions, military or non-governmental organizations'[NGOs] deployments in conflict areas, military maneuvers, etc.). The dental and evacuation problems could put the success of the mission at risk, with relevant associated economic and strategic costs.

This study summarized current evidence about dental problems in isolated personnel (submarines and Antarctic missions) compared to other non-isolation conditions (military deployment in conflict area, military maneuvers) with the objective to assess the need for specific dental equipment in special long-term isolation conditions. To analyze this, Medline, Cochrane Library, and Dentalgate databases between 1960 and 2017 for studies reporting dental diseases in long-term isolation conditions (with a minimum of one month) versus non-isolation conditions were searched. The comparison of the incidence rate was performed by fitting a Poisson regression model to see the effect of the individual's condition on the incidence of dental event. Thirty-eight studies were included in the systematic review. Antarctic missions showed a higher dental incidence rate compared to non-isolation conditions, but submarine missions showed the lowest dental incidence rate.

In the sub-analysis of acute dental events, the incidence rates of those with great impact on unit effectiveness were higher. Caries and secondary decay events were the most prevalent dental problem in all conditions, followed by periodontal pathologies and fractures of teeth or tooth problems that aren't due to tooth decay in isolation conditions, and by molar and endodontic problems in non-isolation conditions. The most common acute dental events were third molar problems and endodontic problems in all conditions.

This systematic review shows that the incidence of dental pathology in long-term isolation conditions may seem relatively infrequent, but it exists and is relevant. Dental events are unpredictable, unrelated to trauma, and caused mainly by poor dental status. Preventive measures considerably reduce the prevalence of such events.

Chapter 2:

Lloro V, Giovannoni ML, Lozano-de Luaces V, Lloro I, Manzanares MC. Is oral health affected in long period space missions only by microgravity? A systematic review. Acta Astronautica 2020 167: 343–350. doi: 10.1016/j.actaastro.2019.11.015.

Numerous studies describe the effect of microgravity on the body health of the astronauts. Some of these studies analyzed dental diseases and were conducted in conditions of microgravity and simulated microgravity, during short or long periods. Taking into account the increase of long space missions, it was necessary to systematically review the oral health events related with short and long periods spent in space missions with all the available evidence.

To identify all relevant oral diseases attributed to the effects of microgravity, we performed a rigorous systematic review regarding the published articles regarding microgravity and dental diseases from 1969 to 2018. Databases such as PubMed, Cochrane, Scielo, Google Scholar and the NASA were consulted. Additional studies from the reference lists of the selected articles were included in order to get a better overview. Ten scientific documents (containing 12 studies) related to oral and dental health and microgravity were assessed. Five studies about short period missions (≤30 days) were included.

The studies showed increases of cortisol as well as salivary immunoglobin A (IgA) and salivary IgG. Seven studies about long period missions (>30-220 days) were included, and the most important fact retrieved was the increase of anaerobic bacteria. Future long-term missions to Mars or to space stations will require 18-24 months of exposure to microgravity, that, added to other conditions, could have potentially deleterious effects on human physiology, including oral health. Preventive measures, adequate material and training of the crew have to be applied to avoid an oral health event to jeopardize the mission.

Chapter 3:

OBF® auxiliary device for dental procedure patent (EP 3 360 508 B1). Application number: 17382070.5. Date of publication and mention of the grant of the patent: 30.10.2019 Bulletin 2019/44

This chapter describes the Oral BioFilter(OBF®) patent: an auxiliary device for dental procedures that does not obstruct a patient's buccal orifice, thereby enabling a healthcare professional to work normally during the procedure, being able to treat any accessible space or tissue through the mouth of the patient. The device is intended to be applied in or adjacent to the perioral area of a patient and comprises a flow-generating member of a gaseous fluid that exerts a barrier effect between the inner area of the patient's mouth and the outside of the mouth; and a support of said member, which keeps it arranged in an area close to said perioral area.

Chapter 4:

Lloro V, Giovannoni ML, Lozano-de Luaces V, Manzanares MC. Perioral Aerosol Sequestration Suction Device Effectively Reduces Biological Cross-Contamination in Dental Procedures. Eur J Dent. 2021 Mar 12. doi: 10.1055/s-0041-1724152. (Published)

The infection risk during dental procedures is a common concern for dental professionals which has increased due to coronavirus (SARS-CoV-2) pandemic. The development of devices to specifically mitigate cross-contamination by droplet/splatter is crucial to stop infection transmission.

This study aimed to assess the effectiveness of a perioral suction device (Oral BioFilter, OBF®) to reduce biological contamination spread during dental procedures. Forty patients were randomized 1:1 to a standard professional dental hygiene treatment with and without OBF®. An Adenosine Triphosphate (ATP) bioluminescence assay was used to evaluate the spread of potential contaminants. The total number of Relative Light Units (RLU) from key dental operatory locations: the operator's face shield, the back of the operator's surgical gloves, the patient's safety goggles, and the instrumental table were measured. Contamination reduction percentages between control and OBF® were compared. Primary outcome (total RLUs) was analyzed comparing the means of logged data, using a two-sided two-sample t-test. Secondary outcomes as RLUs of logged data for the different locations were analyzed in the same way. The proportion of patients from whom different locations reported events (clean, acceptable and failure) were analyzed using Fisher's exact test. For the whole dental environment, the percentage of RLU reduction (<150-units) achieved with OBF® was 98.4% (97.4%-99%). Separating the results from each dental operatory location, the reduction in RLUs was from 99.6%, on the operator's faceshield to 83% on the instrumental table. The control group reported a very high percentage of failures,

(>300) being 100% on the surfaces closer to the patient's mouth and decreasing to 70% on the instrumental table. In contrast, the higher failure percentage in the OBF®-group was found on the patient's goggles (40%), while the operator's face shield showed an absence of contamination. OBF® device has shown efficient reduction of biological aerosol cross-contamination during dental procedures as proved by the ATP-bioluminiscence assay. Nevertheless, for maximum safety, its use must be combined with standard protective gear such as goggles, face shield and surgical gloves.

Chapter 5:

The aim of this chapter is to describe the necessary dental equipment capable of housing dental procedures in long-term missions (2 years), and advanced dental treatments for stays that are longer than 2 years. It includes all the necessary equipment adaptations for weightless conditions, as well as an ergonomic distribution for the patient and the operator. The necessary equipment for diagnosis and for material sterilization is also supplied. This description will provide the physical basis to establish a specific and realistic dental intervention protocol in the future space long-term missions and Mars settlement.

Introduction

Dental incidence in isolated condition

Dental problems in isolated and confined groups have become a concern for the potential patients, but also to the oral health and general health workforce who must deal with the prevention, as well as the treatment of the oral problem (1). Groups that are subject to isolation or with no chance to freely access or evacuate a location are particularly sensitive (1). In view of the future expansion of the manned space program, as well as research in Antarctica, submarine missions, or for populations serving in isolated or confined environments, oral health planning is essential for long-term missions (2).

In the modern era, the first reference of dental problems in isolated conditions was reported in Antarctic expeditions from the earliest days of exploration. In this sense Cherry-Garrardwrote in 1911: “I do not know why our tongues never froze but all my teeth, the nerves of which had been killed, split to pieces” (3). In Scott’s Antarctic expedition, only one member possessed a toothbrush and he described it as “one essential portion of our equipment” (4).

Later in 1963, the memorandum report 63-14 of the United States (US) Naval Medical Research Laboratory described oral health problems of submarine personnel and suggested a program for their management (5). This report showed information of dental problems in 1471 submarine patrol reports of World War II, indicating that “oral health problems of submarine crews disrupt the schedules and reduce the operating efficiency of submarines to a greater extent than is generally realized”. In this sense, despite the rigid admission standards, the crew suffered toothaches, infections and traumatic injuries with a considerable number of sick days that interferes with duty functions and were the source of discomfort to the crew (5). After patrol, dental examinations of 2363 men from 30 submarines showed that 31% had active dental caries, 7.3% needed dental extractions, 13.4% had gingivitis, and 1.2% had necrotizing ulcerative gingivitis.

Subsequently, from June 1st 1959 to June 1st 1960 641 dental emergencies were reported in 71 US submarines (5). Some preventive measures suggested in this report included: “stricter adherence to dental standards in acceptance of submarine candidates; adequate correction of deficiencies prior to patrols, a course of training for

medical personnel in diagnosis and treatment of dental conditions, as well as certain additions to the present dental equipment carried on submarines" (5).

During the 1980sKeller et al., in a study with a large cohort of 4728 US Army personnel during the period from 1982 to1984 showed that, of the total of dental emergency attendances, the pain was the main complaint for 72% of patients, with 25% of those having experienced some level of pain for more than 1 week (6). In this period of time, Nice reported that 7% of all medical evacuations occurring in US ships were due to noninjury-related dental problems (7).

Already in this century, Deutsch showed that medical evacuations due to dental problems carried out in 240 US submarine patrols of the Atlantic and Pacific task force were 6.9% and 9.3%, respectively (2). In this study, 109 dental emergencies were attended, and 45 revisits were recorded during these patrols. Of these visits, 48.6% were for an emergency related to an endodontic or caries problem, 13.1% of which because of a dental problem during the 101-day submergence, 9.8% due to a canker sore, and 4.1% on account of a gum problem (2).

Although we considered that the above studies were realized a long time ago with different standards of self-healthcare and worse healthcare measures than currently, recent studies have shown that dental problems are a reality in confinement situations. von Wilmowsky et al. (2015) found in a study carried out in a German naval task group formed of three hips that 71 (10.92%) patients (mean age of 25.1±5.3 years) required 136 oral treatments, 17.65% due to emergencies, which was equivalent to 3.69% of all servicemen (650 soldiers) of the task group. The reasons for dental emergencies were in 95.84% caused by caries (8). The authors concluded that: 1) "The pre-screening of sailors before an overseas deployment is necessary to avoid severe dental treatments"; 2) "Caries remains the main cause for dental emergencies on board military ships"; 3) "If a dentist is not on board, medical doctors should be trained in the excavation of caries, trepanation, medical root canal treatment, temporary fillings and recementing of failed restorations, in order to handle dental emergencies"; and 4) "Soldiers with a lower rank have a higher probability of being treated for a dental emergency during overseas deployments" (8).

Another study realized outside ship conditions was carried out by Gunepin et al., in a ground deployment scenario, the Operation Serval (9). The study comprised the period of February 15thto May 15th, 2013. In this period, 54 of the 338 medical evacuations

recorded were required to treat dental emergencies, 23.9% of which were due to nonbattle injuries with an average of 10.5 days of unavailability to treat this emergency. Thus, the authors concluded that: 1) “Dental casualties requiring medical evacuation are absent from their units for almost two weeks, which could drastically decrease their operational capacity and ability to complete their mission”; and 2)“Pre-deployment dental readiness and the presence of a dental surgeon in close proximity to deployed forces may reduce the number of medical evacuations required and the time away from the unit” (9).

In terms of economic costs of dental emergencies in deployment scenarios, another study showed that the direct economic cost due to dental emergencies of US troops deployed in Iraq and Afghanistan during Operation Iraqi Freedom was estimated at $14 million to return the soldiers to service. This was twice the cost of the treatment required for these dental events (10).

Consequently, military and space health services in dentistry have as their primary aim to achieve a stable oral health status, so that personnel will be prepared to carry out assigned duties without loss of time or effectiveness attributable to an oral cause. In other words, the attainment of the objective or mission cannot be delayed or impaired by a predictable oral health problem (11, 12).

On the other hand, it is important to note that, with the previous experience in isolation condition we know the risk factors that produce these events and then act on them decreasing the likelihood of dental emergencies during these situations. In this sense, preventive medicine has been widely used in different situations: servicemen on submarine missions are known to have lower levels of vitamin C in their blood due to the unique environmental conditions aboard submarines; this is true even for patients receiving dietary supplements of vitamin C (13). Regarding space travel, unique environmental conditions result in the depletion of nutrients from the body, the main problem being calcium homeostasis (14, 15). Regarding dental medicine, the preventive measures taken are an exhaustive and effective dental screening previous to the missions in submarines (16) and in the case of deployment, several countries apply a dental classification system before the mission, in order to send personnel with adequate dental conditions (8).

As a corollary, to prevent and manage dental emergencies in long-term missions (e.g., space missions), previous data and solid knowledge about dental problems in isolation

conditions, as well as the importance of preventive measures are to be considered. For this reason, a systematic review, as part of this doctoral thesis, has been carried out to provide information of dental incidence in isolated condition.

Oral health in microgravity condition

The astronauts' health has been a subject of the utmost importance, since they are submitted to another challenge aside from oral health added to isolation condition: microgravity. As previously exposed, in long-term missions in space the evacuation of the patients will not always be possible, thus the crew has to be trained to deal with any health problems, including emergency medical conditions. New health issues not considered to date and microgravity exposure for long periods of time have to be taken into account.

The reports of dental events during space missions are scarce; only two countries (USA and Russia) have enough experience in space missions. Although there are other countries with space agencies, as China, no manned missions have been documented.

The first documented dental problem occurred in space under microgravity condition was a Russian cosmonaut that reported incapacitating dental pain during the last two weeks of his 96-day flight aboard Salyut 6 in 1978 (17) without any contingency plan in place to solve such situation (18). Other documented dental problems occurred in the Russian Space Station MIR. In this sense, several dental events were reported in the MIR station between March 1995 and June 1998, comprising 1% of the medical events reported during that period (18). Dental caries were identified and treated with a temporary filling from a dental kit (19). In addition, between February 7th, 1987 and February 9th, 1996, MIR program documented 304 medical events, one of them related to a case of dental caries, resulting in an incidence rate of 0.01% per 100 days (18). It is important to consider that the lost fillings and crowns reported by Russian cosmonauts were thought to be due to the vibrations associated with launch (20). Moreover, cosmonauts have reported cases of dental pain during space missions (21).

In the case of US space experience, no written documentation about dental emergencies experienced by astronauts has been found (18). However in December 2011, Hatcher described an in-flight crown displacement that was temporarily repaired by the crewmember with on-board supplies, with no mention of complications (18).

Other cases of dental problems (pulpitis) that required emergent attention have been reported during the periods of pre-flight and post-flight in the US Apollo program (22). If these cases occurred during the space mission, the crewmember might not have been able to accomplish critical tasks because of the resulting pain (18, 22). Other three minor dental events (displaced crowns and tooth fractures) that required treatment in a pre-space mission phase have been also documented (18).

More recently, in the shuttle program, similar preflight dental events (periapical abscesses) were identified and treated immediately two weeks before the space mission (18). And as it was reported in the Apollo program, if these events would have occurred during the space mission, the severe pain experienced by the crewmembers would have caused a significant difficulty to attain their operational objectives (18).

It is important to note that the events described in space increase its magnitude and may thus interfere with both physical and psychological performance or increase the likelihood of injury because of higher error rates (19).

NASA's Space Medicine Division identified the medical conditions of concern for exploration missions and elaborated a list called *The Space Medicine Exploration Medical Condition List* (23, 24) based on the inability to adequately recognize or treat an ill or injured crewmember. Among the list of priority medical conditions that are most likely to occur during exploration space flight missions, there is a group whose diagnostic and treatment capability must be provided. This list includes dental health conditions related to: cavity and temporary filling, crown replacement, exposed pulp/pulpitis/periapical abscess, total avulsion or complete tooth loss and toothache (23, 24).

Among the possible dental events, the most probable are pulpitis in a tooth which had previously been restored or severe, localized gingival inflammation with or without a periodontal abscess, added to their incapacitating associated pain (25). Another dental problem to be prevented is dental caries, although it was not considered a problem in missions of up to 3 months because of the high level of oral health of all crewmen and

the frequent dental evaluations they received (25). However, dental caries could constitute a problem in long-term space missions.

To prevent health problems and, in particular, oral events, astronauts candidates, including those destined to the International Space Station (ISS), are submitted to medical tests and are required to meet minimum medical standards. The standards were settled by NASA in 1977, and included an oral clinical examination and imaging (panorex), as well as complete periapical dental X-rays within the previous 2 years (26). Moreover, according to the integrated mathematical medical model that simulates medical events to estimate the impact of these medical events for a given design reference mission (as near-Earth asteroid and Mars missions), dental emergencies have to be one of the top five conditions to predict to avoid its impact on mission objectives (27).

Despite this, it is known that the long exposition to microgravity and radiation during long-term space missions produce an increase of oral diseases (28). In this sense, it has been documented that periodontitis, dental caries, bone loss, jaw fracture, salivary duct stones, and oral cancer are more prevalent after simulated microgravity exposition compared to Earth gravity (28-33). Moreover, it has been published that bone mineral density and bone mineral content were significantly lower, with higher levels of proteolytic enzymes as metalloproteinases 8 and 9 (MMP-8 and MMP-9), in addition to cathepsin and osteocalcin, under simulated microgravity conditions (32).

Another important issue related to oral health is the fact that the oral region constitutes the portal of entry for pathogenic agents and acts as a reservoir for infectious micro-organisms, consequently playing a role in cross-contamination and disease transmission (25).To prevent infections caused by dental problems that must be treated in reduced, isolated spaces, and to avoid cross-contamination due to the expansion of saliva droplets is mandatory. This is the rationale for the development of a suction device named OralBioFilter (OBF®) aimed to reduce cross-contamination by way of aerosols (34) that could be difficult to eliminate in microgravity conditions.

OBF® role in biological cross-contamination in dental procedures

Maintaining a healthy and pathogen-free working environment is essential for the health of workers and, therefore, for work productivity. In space missions this principle is even more important as it has an impact on the success of the mission. It is therefore necessary to take measures to avoid contamination. The recent pandemics caused by coronavirus (SARS-CoV-2) which, on 11th February 2020, World Health Organization (WHO) named as “Corona Virus Disease” (35), has caused this concern to increase.

In isolated conditions and in reference to dental clinics, it has been reported that the probability of pathogen transmission is increased due to high patient infectiousness, the absence of respiratory protection, and poor indoor air quality (36, 37). A sensitivity analysis has shown that the transmission probability is strongly driven by indoor air quality, followed by patient infectiousness, and by respiratory protection from medical face mask use (37). This work concluded that improving indoor air quality through ventilation and reducing carbon dioxide emissions is the most important factor for decreasing the probability of pathogen transmission (37).

Effective protective measures must be adopted to prevent pathogen transmission (38). It has been described that cross-transmission of micro-organisms can be prevented by blocking the air contamination (39). At a macro level, increasing ventilation is required, but impossible when it comes to space missions, so the only option is to apply filters to purify the air in the facility (25).

In the context of oral health professionals treating an oral problem, the cross-contamination and dissemination of pathogens in a dental operatory environment is a concern during most dental procedures. Dental professionals must be aware that droplet and splatter (aerosols) have proven to be the main spread routes of oral pathogens (35).

Oral droplet and splatter are biological substances (made of a combination of particles, gases, vapors, biological fragments or micro-organisms that are or have become airborne) with a diameter between 0.5 and 10 µm that have the potential to penetrate and lodge in the smaller passages of the lungs (40, 41). These particles are

disseminated during standard dental treatments (e.g., ultrasonic scaling, professional mechanical tooth cleaning, etc.) and are potential sources of cross-transmission of microorganisms (40, 42, 43).

In this regard, dental operatories are high-risk zones due to the infectious bioaerosols produced by ultrasonic and high-speed rotary tools used in dental procedures which remain airborne for hours, most especially within 4.5 meters of the bioaerosol generating source (this is, high-speed tools used at the patient's oral cavity) (42). Bacteria (such as streptococcus and staphylococcus) and viruses are common contaminants located in the mouth. Therefore, instruments that work with turbines, compressed air or water polishers are potential propagators of supra or subgingival microorganisms into the space around the patient and the professionals performing teeth cleaning or oral surgery procedures (42, 44). Dental procedures constitute a professional risk since they can become potential carriers of the disease due to their unique nature, which involves aerosol generation added to handling of sharp instruments, and close proximity to the highly contaminated oropharyngeal region of symptomatic and asymptomatic patients (45).

Regarding space missions, cross-contamination is a significant risk factor for astronauts because, in the absence of gravity, particles of saliva or blood containing pathogens are released into the environment (34, 46). In this sense, the facility filters are not enough to avoid cross-contamination. For this reason, an aerosol suction device to reduce the dissemination of aerosol into the environment in absence of gravity during dental procedures was developed and patented with the OBF® brand (34, 46).

OBF® is a perioral suction device that consists of an ergonomic lip retractor that supports an extraoral suction device which connects to the dental chair's High-Volume Evacuator (HVE) suction system. It acts as a filter that prevents airborne micro-particles from expanding beyond the work area, thus preventing the dentist or personnel in charge of this task from contamination, as well as the rest of the crew. Consequently, OBF® improves everyone's safety by maintaining the dental workplace's hygiene and cleanliness (46, 47).

To assess the effectiveness of the OBF® device to reduce cross-transmission of microorganisms as a part of this doctoral thesis, a comparative study was carried out analyzing the contamination patterns produced by droplet and splatter during

professional dental hygiene with ultrasonic scaling followed by Professional Mechanical Tooth Cleaning (PMTC) with high-speed contra-angle handpiece measured with Adenosine triphosphate (ATP) by bioluminescence assay, a technique routinely used in hospitals and the food industry (48-51) for fast and accurate quantification of biological contamination on surfaces.

Dental equipment for long-term missions

Human nature has always led to exceed all limits, so we are destined to live beyond our planet, hence man has been developing a space program since the 1960s. The next set of goals in the conquest of space begin in our solar system and have as their nearest objective to build permanent inhabited colonies on the Moon and Mars. With the current technology, the trips to Mars and the Moon require long periods of time, and it is to be expected that permanence in these places will also be relatively long. Given the characteristics of these voyages and of the future colonies, these astronauts will live in a situation of isolation and confinement. Then, they will be subject to difficult travelling conditions and no possibility to receive external help or being evacuated from a location, thus being forced to deal with any emergency situation as for example a sudden disease or health problem.

Dental problems in isolated and confinement situations will then be of concern, not only for the patients but also for the health workforce in charge. For this reason, with the expansion of the manned space program, a dental planning for populations serving in an isolated or confinement environment is essential (2).

It is known that weightlessness and/or microgravity in space have a direct impact on human physiology (52-54) and oral health is also affected (33). The European Space Agency (ESA) and other agencies consider aerospace dentistry knowledge a priority, both at a preventive level and as a treatment in long-term missions, taking into account that dental pathologies are potentially incapacitating. In this sense, given the previous episodes of dental problems in space missions, a dental set and training initiatives for preventing dental pathologies was introduced in the next space programs (55).

However, few dental research projects have been executed in microgravity conditions (28, 56, 57).

The next projects to Mars will require a bigger exposure to microgravity and isolation conditions, estimated between 18 and 24 months, which will have important effects on human physiology, including the oral cavity. It has been reported that several diseases, periodontitis, caries, loss of bone mass and fractures in the jaws, pain and numbness of teeth and tissue of the oral cavity, stones in salivary ducts and oral cancer, are more prevalent in microgravity (28), along with problems in immunity of the oral mucosa and the delay in the healing of wounds due to stress (58). On the other hand, in long-term missions, it will be necessary to include in the crew a health professional or to provide a staff member with enough healthcare training to make him or her 100% autonomous, since telemedicine options will be compromised by the delay in the communications (59).

Although dental emergencies are the main cause of evacuation in isolated and confinement conditions (60), dental events have been uncommon in spaceships thanks to the health tests realized before the flight and the preventive measures applied during the crew training (28). It is expected that the increase period of the flights~~,~~ will raise the possibility of dental emergencies. For this reason the crew receives a preparatory training for treating dental emergencies (28), but it has not evolved practically.

The description of the necessary dental equipment capable of housing expected and unexpected dental procedures in long-term missions will therefore be mandatory in the future space voyagerships and inhabited colonies. This equipment will probably have to be included in health facilities in order to maximize the available space, since these places are expected to be small.

Because of the costs and the logistic, the health facility must be dimensioned according to the mission's duration (until two years or more), the number of crew members and the probability of certain oral health events in this specific period of time. This health facility with must include the necessary dental equipment in function of the mission's characteristics.

The health facility must contain equipment for diagnosis and for material sterilization. 3D technology will facilitate the on-site manufacturing of pieces required for diverse

surgical procedures. The health facility walls must be painted with light tones of reflective paint, which is commonly used in dental operating rooms.

The proposed equipment and materials that must be available in the health facility to take care of oral health foreseeable events include telemedicine equipment, such as Google Glass® or a similar device, material for preventing temporomandibular joint disorders, material and equipment for caries and endodontic treatment, periodontics treatment and for surgery emergences. In regard to advanced dental treatments, material and equipment for prosthesis for dental implants and for orthodontics also have to be included.

The present work, as part of this doctoral thesis, tries to contribute to the space race by establishing ergonomic and safe spaces to optimize the emergency and rehabilitation of dental treatments, designing modifications with the current technology for the weightlessness and/or microgravity conditions to avoid problems that affect the success of the space mission. Moreover, a dentist or a crew member specialist in dental procedures that should prevent in-flight hazards when they treat members will be essential (61).

Hypothesis and Objectives

Hypothesis:

Dental events that occur in isolation can compromise space missions even if they are not caused by trauma. Its prevalence and relevance must be assessed, since it requires prevention, diagnosis and treatment by the crew. Causal factors for oral health events in long missions need to be known in order to establish the priority of preventive measures and requirements for treatments. Consequently, the use of preventive measures and the inclusion of a dental module designed for the treatment in situ will reduce dental events in long-term missions. Among preventive measures, the OralBioFilter (OBF®) device could be a useful tool to prevent the spread of microorganisms from the oral cavity during the use of rotary or ultrasonic devices, thus avoiding cross-contamination in isolation and microgravity conditions.

Moreover, the design of a scalable healthcare module, capable of housing a treatment center for dental and general pathologies with adapted equipment would be a requirement for future missions to the Moon and Mars.

Objectives:

1 To assess the incidence and prevalence of dental and orofacial health problems reported to date in situations similar to that of space mission crew isolation in order to establish the most probable dental and oral health events that a space crew could be confronted with.

2 To determine the most probable causal factors of such dental and oral health events in both short and long space mission conditions.

3 Validation of the Oral BioFilter (OBF®) device for the control of cross-contamination by aerosols and microdroplets.

4 To determine the requirements to be established for the dental treatment module, in terms of equipment and materials required to respond "in situ" to the most probable situations (oral health events).

Results

The following publications report the results of the studies already carried out.

Published studies in scientific journals:

- Lloro V, Lozano-de Luaces V, Lloro I, Manzanares MC. The Incidence of Dental Needs During Isolated Missions Compared to Non-isolated Missions: A Systematic Review and Implications for Future Prevention Strategies. Mil Med. 2019 Mar 1; 184(3-4):e148-e155. doi: 10.1093/milmed/usy364.

- Lloro V, Giovannoni ML, Lozano-de Luaces V, Lloro I, Manzanares MC. Is oral health affected in long period space missions only by microgravity? A systematic review. Acta Astronautica 2020 167: 343–350. doi: 10.1016/j.actaastro.2019.11.015.

- Lloro V, Giovannoni ML, Lozano-de Luaces V, Manzanares MC. Perioral Aerosol Sequestration Suction Device Effectively Reduces Biological Cross-Contamination in Dental Procedures. Eur J Dent. 2021 Mar 12. doi: 10.1055/s-0041-1724152.

Moreover, a European patent complemented the above publications:

- OBF® auxiliary device for dental procedure patent (EP 3 360 508 B1). Application number: 17382070.5. Date of publication and mention of the grant of the patent: 30.10.2019 Bulletin 2019/44

Chapter 1: Long-term dental incidence in isolated condition

The Incidence of Dental Needs During Isolated Missions Compared to Non-isolated Missions: A Systematic Review and Implications for Future Prevention Strategies

V. Lloro; V. Lozano-de Luaces†; I. Lloro‡; M.C. Manzanares§*

ABSTRACT Introduction: Dental emergencies in isolated groups have always been difficult to treat. Especially in people or groups who cannot be evacuated and who need urgent dental assistance: long-term submarine missions, long-term spaceship trips, military or non-governmental organizations deployments in conflict areas, military maneuvers, etc. The dental and evacuation problems could put the success of the mission at risk, with relevant associated economic and strategic costs. Our study summarizes current evidence about dental problems in isolated personnel (submarines and Antarctic missions) compared to other non-isolation conditions (military deployment in conflict area, military maneuvers) with the objective to assess the need for specific dental equipment in special long-term isolation conditions. Materials and Methods: We searched Medline, Cochrane Library, and Dentalgate between 1960 and 2017 for studies reporting dental disease in long-term isolation conditions (minimum 1 month) versus non-isolation conditions. We conducted the systematic review with all studies fitting the inclusion criteria. The comparison of the incidence rate was performed fitting a Poisson regression model to see the effect of the individual's condition on the incidence of dental event. Results: Thirty-eight studies were included in the systematic review. Antarctic missions showed a higher dental incidence rate compared to non-isolation conditions, but submarine missions showed the lowest dental incidence rate. In the sub-analysis of acute dental events, those with great impact on unit effectiveness, the incidence rates were higher. Caries and secondary decay events were the most prevalent dental problem in all conditions, followed by periodontal pathology and fractures of teeth or tooth problems not due to tooth decay in isolation conditions, and then by molar problems and endodontic problems in non-isolation conditions. The most common acute dental events were third molar problems and endodontic problems in all conditions. Conclusion: This systematic review shows that the incidence of dental pathology in long-term isolation conditions may seem relatively infrequent but it exists and is relevant. Dental events are unpredictable, unrelated to trauma, and caused mainly by poor dental status. Preventive measures considerably reduce dental prevalence.

INTRODUCTION

Dental problems in isolated and confinement groups have become a concern not only for the possible patients, but also to the dentists who must deal with the prevention as well as the treatment. Groups that are subject to isolation or with no chance to freely access or evacuate a location are particularly sensitive. With the expansion of the manned space program, research in Antarctica, and submarine missions, dental planning for populations serving in isolated or confined environments is essential.[1]

Military and space health services in dentistry have as their primary endpoint to achieve a stable oral health status, so that personnel will be prepared to carry out assigned duties without loss of time or effectiveness attributable to an oral cause. In other words, the attainment of the objective or mission cannot be delayed or impaired by a predictable oral health problem.[2,3] The direct economic cost due to dental emergencies of U.S. troops deployed in Iraq and Afghanistan during Operation Iraqi Freedom was estimated at $14 million to return the soldiers to service. This was twice the cost of the treatment required for these dental events.[4]

Thus, if risk factors for an emergency can be determined, it should be possible to address those factors and decrease the risk of emergencies.[1] In this sense, the preventive medicine has been widely used in different situations, servicemen on submarine missions are known to have lower levels of vitamin C in their blood due to the unique environmental conditions aboard submarines; this is true even for patients receiving dietary supplements of vitamin C.[5] In the case of space travel, unique environmental conditions result in the depletion of nutrients from the body, the main problem being calcium homeostasis.[6,7] Regarding dental medicine, the preventive measures taken are an exhaustive and effective dental screenings in submarines previous to the missions[8] and in the case of deployment, several countries have a dental classification system, previous the mission, for send personnel with adequate dental conditions.[9]

*Odontology Hospital UB, Feixa Llarga Street, 08907, Barcelona, Spain.

†Falculty of Medicine and Health Sciences, University of Barcelona, Feixa Llarga Street, 08907, Hospitalet, Spain.

‡Institute of Space Sciences (IEEC-CSIC), Campus de la Universitat Autònoma de Barcelona (UAB) de Bellaterra, Carrer de Can Magrans, 08193 Cerdanyola del Vallès, Barcelona, Spain.

§Human Anatomy and Embryology Unit, Experimental Pathology and Therapeutics Department, University of Barcelona, Feixa Llarga Street, 08907, Hospitalet, Spain.

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Few studies, with a wide range of dental emergency rates, have addressed dental problems that occur in isolated conditions.[1,10–13] The variability in rates observed in these studies is due to differences in study design, observation periods, dental class status, and access to clinical services due to environmental and operational challenges.[14]

Although this systematic review is focused on military studies because the patients are in special conditions – including isolation and non-isolation (e.g., military deployment in conflict areas and military maneuvers) – it also has significance for prevention and treatment of dental emergencies in long-term missions (e.g., space missions). Our study summarizes current evidence of dental problems (non-acute and acute) in isolated personnel, with the objective to assess the need for specific dental equipment in special conditions, mainly in long-term isolation missions.

METHODS

Search Strategy

We searched the Medline, Cochrane, and Dentalgate databases for studies of dental disease, dental events, and dental emergencies in special long-term isolation (e.g., submarines and Antarctic missions) and other non-isolation conditions (e.g., military deployment in conflict areas and military maneuvers) published between 1960 and 2017. Search terms used were: *dental disease* OR *dental events* OR *dental emergencies* AND *isolated conditions*, *long-term period*, *space*, *submarine*, *Antarctic missions*, *military personnel*, *deployment*, *maneuver*, or *conflict* AND *dental incidence*. We also searched in the reference lists of published studies.

Selection of Studies

There are few studies about dental health in isolation conditions. Because of that, comparative studies, studies including similar populations (submarine and Antarctic personnel; with limited or no access to dental assistance) in periods of isolation, or in relative or no isolation but in special missions (military deployment in conflict areas and military maneuvers) were used. The selected studies must have had a study duration ≥1 month, been published between 1960 until 2107, been written in English or Spanish, and have the highest number of citations in journals in the first three quartiles.

Data Extraction and Quality Assessment

Data were abstracted and quality was assessed using guidelines published by the Cochrane Collaboration[15] (Table I, Supplementary Table S1). Any disagreement was resolved by discussion between the authors in consultation with a statistician. Characteristics of studies included in the systematic review are shown in Table I. Supplementary Table S1 shows excluded studies and exclusion criteria.

Dental Event Definition and Type of Event

Due to the high variability in the definition of a "dental event" in published articles, we defined "dental event" as any of the following terms: dental emergency, evacuation due to dental disease, initial emergency visit to dentist, emergency visit to dentist, traumatic injury, dental trauma, oral facial injury, and dental problem.

Additionally, a sub-analysis of acute events was made, only was selected dental events from sources in which a great impact on unit effectiveness is claimed. The selected terms and its explanation from the articles (Table I) were: dental emergency, infectious disease (health problems requiring medical care disease or a trauma [physical or psychological]), dental disease and non-battle injury (defined as any oral or craniofacial issue perceived by the soldier to be a problem that caused them to seek the help or advice of a dental officer), emergency visit, dental disease (with operational incapacity), dental condition (their effects can have a great impact on unit effectiveness, fighting strength and morale or military personnel), orofacial injuries, dental trauma (commando fighters are highly predisposed to dental trauma, resulting in the interference of their continuous daily activity). Terms excluded as non-acute events were: traumatic injury (no statistical correlation between personal weapon impact and dental injury), dental trauma (dental traumas comprise 2–8% of all military dental emergency cases), dental problem with no details, and dental event (potentially mission-impacting medical events reported among crew members that were rare).

Different dental events were classified and grouped in their respective preference term. The groups were: caries and secondary decay events, endodontic problems (which are always secondary to caries), fractures of teeth or tooth problems not due to tooth decay, fractures and problems with prosthesis, third molar problems, periodontal pathology, oral pathology, mandibular problems, joint and occlusal problems, postoperative problems, and others.

Variables

The dental incidence is defined as the number of new dental events accounted for that appear in a given period of time. In our study, the main variable was the dental event incidence rate, presented as events per person-years and calculated as number of events/number of units at risk (the number of units at risk being the number of person-year). The calculation of the units at risk was based on the number of individuals that remains constant during the observation period, and is calculated as the number of individuals multiplied by the observation period in years.

The classification variable to be compared refers to "personnel condition" such as in deployment in conflict area, in maneuvers or field exercises, submarines or Antarctic stations. In the case of deployment in a conflict area, a comparison was also performed for periods before and after 2006 in

TABLE I. Characteristics of Studies Included in the Systematic Review

Study	Population	Condition	Time	Number of Events	Time (Person-Year)
Tansey WA. 1979[32] (*)	U.S. Navy submarines Polaris	Submarine	>1 month	50	20,958.9
Thomas TL. 2000[34] (*)	U.S. Navy submarines	Submarine	>1 month	41	3,561.6
Thomas TL. 2003[33] (*)	U.S. Navy submarines	Submarine	>1 month	83	50,028
Deutsch W. 2008[1]	U.S. Navy submarines	Submarine	3 months	109	5,946.89
Nielsen AG. 1963[24]	U.S. Navy submarines	Submarine	>1 months	641	9,230
O´Shea MK. 2009[25]	U.K. submarines Vanguard Class	Submarine	2 months	121.98	928.6
Rohani B. 2016[28]	Iran submarines	Submarine	>1 month	0.00327	12
Fletcher LD. 1983[19] (*)	Australian Base Davis	Antarctica	>1 month	10	21
	Australian Base Mawson	Antarctica	>1 month	22	42.75
	Australian Base Macquarie	Antarctica	>1 month	41	69.75
SimeceK JW. 2014[31]	US Army Personnel in Afganistan/Kuwait	Deployment		1,020.6	9,018
	US Army Personnel in Irak	Deployment		3,354	20,066
von Wilmowsky C. 2014[35]	German warships	Deployment	3 months	24	162.5
Dunn WJ. 2004[18]	U.S. Soldiers in Saudi Arabia	Deployment	6 months	759	4,974
Dunn WJ. 2004b[17]	U.S. Soldiers in Oman	Deployment	6 months	135	986
Aoun O. 2014[14]	French soldiers in Afghanistan	Deployment	3–6 months	0	432
	French soldiers in Lebanon	Deployment	3–6 months	8	476
	French soldiers in Côte d'Ivoire	Deployment	3–6 months	8	450
Sauvet F. 2009[29]	French soldiers in Ivory Coast	Deployment	4 months	30	200.1
Teweles R. 1987[40]	U.S. Soldiers in Sinai Penninsula	Deployment	5 months	39	244.29
Mombiedro R. 2007[2]	Spanish soldiers in Bosnia-Herzegovina	Deployment	2 months	56	185,4
Gunepin M. 2015[20]	French soldier in Mali	Deployment	3 months	54	955
Ludwick W. 1974[23]	Vietnam War 1970	Deployment		2,398	15,057.4
	Vietnam War 1996	Deployment		3,370	16,041.5
Deutch WM. 1996[8]	US soldier in Kuwait	Deployment		4,776	31,835
Zadik Y. 2008[36]	Israeli elite commando units	Maneuver	38 months	76	889
Payne FT. 1981[26]	US Soldiers	Maneuver		360	2,500
Parker (Roberts JE)[27]	US Soldiers 1981	Maneuver		92	2,482.6
Immonen M. 2014[21] (*)	Finnish Defense Forces	Maneuver	12 months	185	28,256
Colthirst P. 2012[16]	U. S. Brigade Combat Team	Maneuver	3 months	255	1,142.6
Fairchild (Roberts JE)[27]	US Soldiers 1996	Maneuver		35	455.59
	US Soldiers 1997	Maneuver		57	697.9
	US Soldiers 1998	Maneuver		50	762.6
Becker T. 2009[15] (*)	Israeli soldiers in basic combat training	Maneuver	8 months	118	7,405.51
Sumnicht (Roberts JE)[27]	US Soldiers 1964	Maneuver		1453	9,257
King JE. 1984[22]	US Soldiers	Maneuver		355	1,367.17
Grover PS. 1983[9]	U.S. Army recruits in basic field training	Maneuver	6 months	1294	2,500
SimeceK JW. 2008[30]	U.S. Marine Corps personnel	Maneuver	4 years	262	1,999.7

Note: (*): Studies excluded in the sub-analysis of acute dental events.

order to assess the differences between studies of conflict with greater deployment of soldiers before and after the establishment of dental care measures. Moreover, a sub-analysis of acute events was made.

Statistical Analysis

All variables were analyzed descriptively by condition. Incidence rates were described by means of summary statistics and confidence intervals. The comparison of the incidence rate has been performed fitting a Poisson regression model to see the effect of the individual's condition on the incidence of dental event. As over-dispersion appeared, the final model was based on a negative binomial distribution of events, estimating the number of events and the ratios of incidence rates. For the calculation of the incidence rate in a group (condition), the sum of the events in each group was divided by the total number of individuals-year multiplied by the mean of years in that group. Proportions of types of events in each group were described by means summary statistics. STATA IC 15 ([StataCorp2015] Stata Survey Data Reference Manual – Release 15. College Station, TX, USA: Stata Press) was used for managing and analyzing all data.

RESULTS

Literature Search of Included Studies

We identified 13,783 studies according to the search criteria. Of these, 12,853 were not in compliance with the complete search criteria and were excluded based on the title and abstract, leaving 47 studies to be assessed for eligibility due to scientific proximity to the research itself. Thirty-eight studies were included in the systematic review (Table I, Fig. 1). Nine publications were excluded because the population was

different from the one included in the review's criteria and/or lack of data (Supplementary Table S1).

Events

A total of 3,412 dental events were recorded, 1,506 (44.1%) in *maneuvers*, 1,023 (29.9%) in *deployment*, 813 (23.8%) in *submarines*, and 70 (2.2%) in *Antarctic missions*.

Caries and secondary decay events ranged from 441 (43.1%) to 693 (46%) in non-isolation conditions while were present in 7 (10%) to 334 (41.1%) of long-term isolation conditions. Periodontal pathology was more prevalent with 176 events (21.6%) in *submarines*, while fractures of teeth or tooth problems not due to tooth decay appeared more frequently in *Antarctic missions* with 36 events (51.4%). Third molar problems: 183 events (17.9%) and 187 events (12.4%) and endodontic problems 119 events (11.6%) and 159 events (10.6%) in *deployment* and *maneuvers* were the second-rated dental problems in non-isolation conditions (Table II).

In the sub-analysis of acute events, those with great impact on unit effectiveness, a total of 1,474 acute dental events were recorded, 671 (45.5%) in *maneuvers*, 450 (30.5%) in *deployment*, 300 (20.4%) in *submarines*, and 53 (3.6%) in *Antarctic missions*.

Third molar problems 119 (26.5%), 183 (40.7%), and 116 (38.7%) were the event more prevalent in all situations except in *Antarctic missions* 0 (0%). Endodontic events were the second more prevalent with 187 (27.9%), 159 (23.7%) and 57 (19.0%) events in all situations except in *Antarctic missions* 0 (0 %). Fractures of teeth or tooth problems not due to tooth decay appeared more frequently in *Antarctic missions* with 36 (67.9%) events followed *deployment* 109 (24.2%) events, however this event appeared only in 33 (4.9%) in *maneuvers* and 20 (6.7%) in *submarines* (Table III).

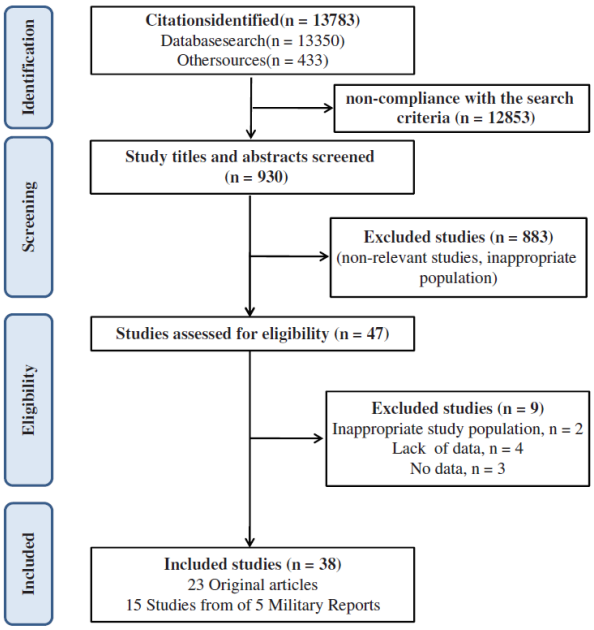

FIGURE 1. Study flow diagram following the preferred reporting items for systematic reviews. Of the 13,783 citations identified according to the search dental problems, we included finally 38 studies.

Dental Incidence

The dental incidence rate was obtained from the 38 studies from data on number of events and exposure time (Table I). There were differences in the dental incidence rate across the different conditions, which was higher in *Antarctic missions* (467/1000 person-year; 95% confidence interval [CI]: 359.7, 574.2), followed military *deployment* in conflict areas. In U.S. studies after 2006, dental incidence rate was less than half the rate before 2006 (Table IV). The lowest dental incidence rate was found in *submarine* missions (2.39/1,000 person-year; CI: 2.24, 2.53). In long-term isolation condition (*Submarines* + *Antarctic*) the dental incidence rate was 4.12/1,000 person-year, which was very lower compared with the other non-isolation conditions (Table IV).

In the sub-analysis of acute dental events, those with great impact on unit effectiveness, military *deployment* in

TABLE II. Dental Events

Type of Event	Deployment		Maneuvers		Submarines		Antarctica	
	N	%	*N*	%	*N*	%	*N*	%
Caries and secondary decay events	441	43.1	693	46.0	334	41.1	7	10.0
Endodontic problems	119	11.6	159	10.6	57	7.0	0	0.0
Fractures of teeth or tooth problems not from tooth decay	109	10.7	33	2.2	20	2.5	36	51.4
Fractures and problems with prosthesis	30	2.9	12	0.78	3	0.4	3	4.3
Third molar problems	183	17.9	187	12.4	116	14.3	0	0.0
Periodontal pathology	65	6.4	130	8.6	176	21.6	7	10.0
Oral pathology	9	0.9	109	7.2	2	0.2	0	0.0
Mandibular problems	0	0.0	14	0.9	10	1.2	0	0.0
Joint and occlusal problems	37	3.6	0	0	0	0.0	0	0.0
Postoperative problems	2	0.2	152	10.0	55	6.8	0	0.0
Others	28	2.7	17	1.1	40	4.9	17	24.3
Total	1,023	100.0	1,506	100.0	813	100.0	70	100

TABLE III. Acute Dental Events

Type of Event	Deployment		Maneuvers		Submarines		Antarctica	
	N	%	*N*	%	*N*	%	*N*	%
Endodontic problems	119	26.5	159	23.7	57	19.0	0	0.0
Fractures of teeth or tooth problems not from tooth decay	109	24.2	33	4.9	20	6.7	36	67.9
Third molar problems	183	40.7	187	27.9	116	38.7	0	0.0
Oral pathology	9	2.0	109	16.2	2	0.7	0	0.0
Mandibular problems	0	0.0	14	2.1	10	3.3	0	0.0
Postoperative problems	2	0.44	152	22.7	55	18.3	0	0.0
Others	28	6.2	17	2.5	40	13.3	17	32.1
Total	450	100.0	671	100.0	300	100.0	53	100

TABLE IV. Dental Incidence Rate by Condition

Condition	Events	Person-Year	Years (mean)	Incidence Rate by 1,000 Person-Year[a]	95% Confidence Intervals
Maneuver	4,592	59,715.7	0.707	108	104.8–111.1
Deployment	16,031.6	101,083.2	0.475	333.9	328.7–339.0
Before 2006	10,853	63,178.2	0.46	364.1	357.1–371.0
After 2006	4,374.6	29,084.0	1.2	125	121.2–128.7
Submarines	1,045.9	90,665.9	4.809	2.39	2.24–2.53
Antarctica	73	133.5	1.17	467	359.7–574.2
Submarines + Antarctica	1,118.9	90,799.4	2.99	4.12	3.87–4.36

[a]Based on mean of years.

conflict areas not showed changes. However, the acute dental incidence rate found submarine missions was 12.0/1,000 person-year (CI: 11.20, 12.80), that was five times higher regarding all submarine dental events. In *maneuvers*, the acute dental incidence rate was 260.7/1,000 person-year (CI: 252.80, 268.50), that was 2.4 times higher regarding all maneuvers dental events (Supplementary Table S2).

Estimated incidence rates calculated from the negative binomial model are presented in Table V and Supplementary Table S3. Submarine condition was used as reference group. The estimated mean of events for Antarctic station was not significant (3,492 events; 95% CI: −395–7,378). In the other conditions, the means was significant. In deployment in conflict areas, the predicted mean number of events was 855, showing a predicted incidence rate of 3.5 times the incidence rate found in submarines. In maneuver conditions, the predicted mean number of events was 918, showing an incidence rate of 3.76 times the incidence rate in submarines. With respect to Antarctic stations, the rate of incidence was 14.3 times that of submarines. When comparing deployment in conflict areas before and after 2006, the means look similar (after, 2,159 and before, 2,631). The estimated incidence rate ratio after 2006 was 0.82 (95% CI: 0.62–1.08) (Table V).

In the sub-analysis of acute dental events, Submarine condition was used as reference group. In deployment in conflict areas, the predicted mean number of acute events was 607, showing a predicted incidence rate of 1.97 times the incidence rate found in submarines. In maneuver conditions, the predicted mean number of acute events was 763, showing an incidence rate of 2.47 times the incidence rate in submarines (Supplementary Table S3).

TABLE V. Estimated Dental Incidence Rate by Condition

Condition	Estimated Mean (95% CI)	Estimated IRR (95% CI)
Deployment in conflict area	855 (437–1,272)	3.5 (1.44–8.5)
Maneuvers	918 (439–1,397)	3.76 (1.51–9.3)
Antarctic station	3,492 (−395–7,378)	14.3 (3.7–54.5)
Submarine	244 (63–426)	
Deployment in conflict area after 2006	2,159 (1677–2,641)	0.82 (0.62–1.08)
Deployment in conflict area before 2006	2,631 (2191–3,071)	

DISCUSSION

This study shows that the dental incidence in long-term isolation conditions is relevant. The dental incidence rate in Antarctic missions is the highest; however, the rate is lowered when considering all long-term isolation conditions (*Antarctic missions + submarines*). The dental incidence rate is high in the other conditions analyzed in this study; moreover, the sub-analysis of acute dental incidence rates shows higher incidence rates. Dental events were mainly related to caries and secondary decay events across all conditions, followed by periodontal pathology and fractures of teeth or tooth problems not originated in tooth decay in long-term isolation conditions, and problems related to third molar and endodontic in non-isolation conditions. Acute dental events,

those with great impact on unit effectiveness, were mainly related to third molar problems and endodontic problems in the three conditions analyzed.

Despite the fact that the information is scarce and dental problems are poorly assessed as medical emergencies, the obtained information is valuable and relevant. The main problem encountered was the different terms used to describe dental incidents and dental problems in the literature. Our systemic review builds on the results of 38 published evidence studies evaluating dental problems and their incidence.[1,2,8–11,16–36] Moreover, the information was homogenized and classified to facilitate data interpretation.

The dental incidence rate in long-term isolation conditions may seem relatively modest, but it is relevant. Moreover, it is possible that the rate is higher in part because some personnel may have experienced mild injuries that went unreported, and in part because of the relatively short time period of the missions (maximum three months). The low incidence rate found in submarines was due to the intense and effective dental screenings carried out.[8] Several military services across different countries have introduced a dental classification system to reduce the number of dental emergencies and to avoid deployment of personnel with non-adequate dental conditions.[9] Hence, the primary objective of this classification is to achieve the performance of the mission.[22] Despite this, the dental incidence is 4.12/1,000 person-year in isolation conditions, and 108–333.9/1,000 person-year in similar populations in complicated or stressed conditions. These differences could be explained in part by the above-mentioned dental screenings for submarine crew members compared to other military populations,[1] or by pre-existing dental pathologies in the case of deployment or maneuvers,[22] or by length of the mission[22] or by different diets.[22]

The lower dental incidence (less than half) found in deployment in conflict areas after 2006 can be explained because, in 2006, the U.S. House Armed Services Committee added permanent health and dental benefits to soldiers and the National Guard. These benefits were added when a large number of reservists during the Persian Gulf War mobilizations of 1990–1991 could not be deployed due to poor dental status.[37] The reduction in dental incidence after 2006 shows that preventive measures notably reduce dental events in these conditions, thus increasing the number of deployable soldiers.

It is interesting to note that the higher dental incidence found in Antarctic missions, and several arguments could explain this data. Antarctic missions are staffed mainly by scientific personnel, who are older and have a higher level of education, which aligns with the data reported by Thomas et al about the dental incidence in submarine officers being half of the enlisted personnel.[34] Although level of education is important in health status, dental screenings prior to the mission likely have greater weight; dental exams are therefore likely to be less intense and effective for military personnel.[1] Another factor that affects the dental health of individuals in the Antarctic is repeated cold exposure, which has been described as a serious contributive factor, affecting fracture damage, new carious lesions, and dentinal erosion.[21] The main dental event found in our analysis of Antarctic missions was tooth fractures.

When analyzed the acute dental incidence, there are an increase (12/1,000 person-year in submarines, and 260.7–333.9/1,000 person-year in similar populations in complicated or stressed conditions). This acute incidence represents the dental incidence in the operational theater, which means on the one hand, a strategic costs in form of effectiveness of the mission decrease and reduction in the morale of the deployed personnel, due to the average time lost of the affected personnel is 3 days per unit and entails other non-quantifiable costs as overload the duties of the other unit members, replace the affected personnel, etc.[4,38] And regarding the economic costs as the evacuation or transportation to a dental facility, treatment costs, specialized dental personnel costs, etc.[38] This economic costs are variable and depend mainly of the incidence of acute dental events and level of activity of the dental services.[39] In this sense, Colthirst showed that these variable costs were twice the fixed costs.[4]

Dental problems are sometimes unpredictable and can require an evacuation to a dental treatment facility, assuming the loss of the soldier to their mission joint to the personnel to translate him/her.[32] In this sense, Deutsch et al found that non-injury-related dental problems accounted for 6.9–9.3% of all medical evacuations from submarines between 1991 and 1999,[1] and Gunepin et al found that 15.7% of the medical evacuations recorded in soldiers deployed in Mali were to treat non-battle dental emergencies.[22] Although the conditions are different, the evacuation percentages are similar, showing that dental evacuations are independent of the mission condition. These data demonstrate the need for dental equipment and trained dental personnel to address dental conditions.[9,22]

The data obtained show that the most common dental problems that occur both in long-term isolation (except in Antarctic missions) and non-isolation conditions are caries and secondary decay events. Periodontal pathology and fractures of teeth or tooth problems not from tooth decay in isolation conditions, and third molar problems and endodontic problems in non-isolation conditions, were the next most-frequent events. In the case of acute dental problems, the most common were mainly related to third molar problems and endodontic problems. All these events occurred despite previous dental screenings being carried out. In this sense, York et al found that more than 50% of recruits began their military service with the worst dental classification and, after 4 years, only 57.4% of them achieved the best dental classification.[40] On the other hand, Mahoney reported that a well-prepared dentally force experiment 150–200 dental emergencies per year and in contrast this incidence is the triple in soldiers with less dental health status.[41] Moreover, other studies showed that the monotony of diet, lack of variety of fresh foods,[22] and poor dental hygiene[21] make it difficult to maintain good dental status. On the other hand, tooth fractures observed in isolation conditions, mainly in Antarctic missions, were minor and occurred during

mastication in teeth that had been previously treated (i.e., affected by an underlying dental problem).[21]

Finally, the dental events studied were largely unrelated to traumatic causes across all conditions. Our results align with a non-included manuscript that reported that 11% of unscheduled absences on British warships are due to trauma.[42] Hence, these data corroborate the idea that unpredictable dental problems should be considered in future long-term isolation conditions, like spaceflights or Mars missions.

Plausible solutions to the observed dental events exist. For example, caries and endodontic problems can only be solved by placing on-site dental services with qualified personnel (dentist or trained crew). Third molar problems (second most common problem in deployment and maneuvers and third in submarines, but the first acute event in all situations) could be solved by extraction during the previous dental screening, thus eliminating the inherent risk. On the other hand, the fact that periodontal problems are the second most common dental problem in long-term isolation conditions suggests that this prolonged period affects dental hygiene and is probably aggravated by diet. That situation would be easily solved by training the on-board medical officer in dental hygiene with a Cavitron, and requiring the crew to receive routine professional hygiene. The use of discharge splints in a routine way would diminish the bruxism secondary to the stress in different conditions, thereby diminishing the incidence of dental fractures not secondary to caries as well as the incidence of joint and occlusal problems. We believe that with these measures could diminish 29.9% of dental events observed in deployment in conflict conditions, 44.1% in maneuvers, and 23.8% in submarines.

CONCLUSIONS

This systematic review shows that dental incidence in long-term isolation conditions may seem relatively low compared with non-isolation conditions (deployment and maneuvers) but is a fact and is relevant. The use of preventive measures and previous screenings considerably reduce dental incidence rates. The dental events are mainly related to caries and secondary decay events in all conditions, followed by periodontal pathology and problems related to the third molar. These events are unpredictable and caused mainly by previous poor dental status, lack of fresh and varied food, and poor dental hygiene, and are unrelated to traumatic causes. These results reflect the need to implement specific dental personnel and equipment in special conditions, mainly in future long-term space missions.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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Chapter 2: Oral health in microgravity condition

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Research paper

Is oral health affected in long period space missions only by microgravity? A systematic review

V. Lloro[a,*], L.M. Giovannoni[a], V. Lozano-de Luaces[b], I. Lloro[c], M.C. Manzanares[d]

[a] Odontology Hospital UB; Feixa Llarga Street, 08907, L'Hospitalet, Barcelona, Spain
[b] Faculty of Medicine and Health Sciences, Health University of Barcelona Campus, L'Hospitalet, 08907, Barcelona, Spain
[c] Institute of Space Sciences (IEEC-CSIC), Campus de La UniversitatAutònoma de Barcelona (UAB) de Bellaterra, Carrer de Can Magrans, Zipcode 08193, Cerdanyola Del Vallès, Barcelona, Spain
[d] Human Anatomy and Embryology Unit, Experimental Pathology and Therapeutics Department, Faculty of Medicine and Health Sciences, Health University of Barcelona Campus, L'Hospitalet, 08907, Barcelona, Spain

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ABSTRACT

Background: Since the starting of Space Age astronaut's health has been a subject of the utmost importance. To date, numerous studies describe the effect of microgravity on the body health of the astronauts. Some of these studies analyzed dental diseases and were conducted in conditions of microgravity and simulated microgravity, during short or long periods. Taking into account the increase of long space missions, it is necessary to systematically review the oral health events related with short and long periods spent in space missions with all the available evidence.

Methods: To identify all relevant oral diseases attributed to the effects of microgravity, we performed a rigorous systematic review regarding the published articles regarding microgravity and dental diseases from 1969 to 2018. Databases such as Pubmed, Cochrane, Scielo, Google Scholar and the NASA were consulted. Additional studies from the reference lists of the selected articles were included in order to get a greater complete overview. Ten scientific documents (containing 12 studies) with a direct relation with oral/dental health and microgravity were assessed.

Results: Five studies about short period missions ($\leq$30 days) were included. The studies showed increases of cortisol as well as salivary immunoglobulin A (IgA) and salivary IgG. Seven studies about long period missions ($>$ 30–220 days) were included, and the more important fact retrieved was the increase of anaerobic bacteriae.

Conclusion: Future long-term missions to Mars or to space stations will require 18–24 months of exposure to microgravity, that, added to other conditions, could have potentially deleterious effects on human physiology, including oral health. Preventive measures, adequate material and training of the crew have to be applied to avoid an oral health event to jeopardize the mission.

1. Introduction

Since the starting of Space Age the health of the astronauts has been a subject of the utmost importance. As the space exploration missions are increasing in time and distance, new health issues not considered to date could arise. Moreover, in long missions in space the evacuation of the patients will not always be possible, thus the crew has to be trained to deal with any health problem including emergency medical conditions.

The NASA's Space Medicine Division identified the medical conditions of concern for exploration missions and elaborated a condition list called The Space Medicine Exploration Medical Condition List [1] based on the inability to adequately recognize or treat an ill or injured crewmember. Among the list of priority medical conditions that are most likely to occur during exploration space flight missions, there are a group for which diagnostic and treatment capability must be provided. In this list are included dental health conditions related to: cavity/temporary filling, crown replacement, exposed pulp/pulpitis/periapical abscess, total avulsion or complete tooth loss and toothache [1].

It is known that the long exposition to microgravity and radiation during long-term space missions produce an increase of oral diseases, including oral cancer [2]. However, further research is necessary on the long-term effects of space flights.

Astronaut's candidates including those destined to the International

* Corresponding author. 5305, P Govern, Health University of Barcelona campus, Feixa Llarga street, L'Hospitalet, 08907, Barcelona, Spain.
E-mail address: victor.lloro@astradentium.com (V. Lloro).

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Space Station (ISS) are submitted to medical tests and are required to meet minimum medical standards. The standards were settled by NASA in 1977, and included an oral clinical examination and imaging, panorex as well as complete periapical dental X-rays within the previous 2 years [3].

Some NASA flight surgeons have reported dental emergencies requiring root canal treatment happening as close as 2 weeks before a launch [4]. A dental emergency in a long time mission could impact mission objectives. According with the Integrated Mathematical Medical Model that simulates medical events to estimate the impact of these medical events for a given design reference mission (as near-Earth asteroid and Mars missions) dental emergencies have to be one of the top five conditions to predict to avoid its impact on mission objectives [4].

We have a moral obligation to establish maximum security levels for future astronauts stepping into untested Mars spacecraft. Space is intrinsically dangerous. Therefore we need advance slow pace with more risk avoidance [5].

It is necessary to compare with all the available evidence to current date the effects of space and simulated microgravity in oral health to prevent a dental event in short- and long-term period space missions.

2. Methods

2.1. Search strategy

A rigorous literature search was conducted in the following databases: Pubmed, Cochrane, Scielo, NASA and Google Scholar. Additional studies from the reference lists of the selected articles were included in order to get a complete overview of the state of the art. Search terms used were: *"spaceflight dental health" "space medicine," "microgravity," "aeronautic dentistry," "health spaceflight," "spaceflight oral medicine," "mars", "space missions", "space stations"*. For a better searching strategy the terms were combined using "AND" and "OR".

2.2. Selection of studies

To be included in the study, the studies had to have a direct relation with Oral and Dental Health and microgravity in the following scenarios: Space conditions, Spaceship and studies with simulated microgravity. The selected studies must have been published between 1969 and 2018 (the reason to consider 1969 as start date is because this was the year in which human landed at the Moon and it supposed to be the time for the human in space), been written in English/French/Spanish/Portuguese and must describe and evaluate oral health events in situations of simulated microgravity or space environment, as well as the incidence of this kind of health problems. The study was then divided in long term and short term space flights or research in Earth stations with simulated microgravity conditions to evaluate the effects of the microgravity in the oral health.

Short period mission is defined as a mission with less than 30 days of duration. A long period mission is defined as a mission with duration between 30 and 220 days, according with the Multilateral Space Medicine Board (MSMB). The MSMB is the ISS (International Space Station) medical certification body for ISS crew members, that has substantial experience in the management of medical risks in space crewmembers [6]. Therefore, studies outside of the above mentioned scope were excluded from the study (Fig. 1).

2.3. Data extraction and quality assessment

Data were abstracted and quality was assessed using the guidelines published by the Cochrane Collaboration [7]. Characteristics of the studies included in the systematic review are shown in Table 1.

2.4. "Relevant dental event" definition

Due to the limited number of dental events reported on space missions [8] and in order to get a comprehensive evaluation of the oral health events due to the exposure of space microgravity or simulated microgravity, the term "relevant dental event", includes not only any dental disease, but also any physiological changes due to the effects of the microgravity that may lead to a dental disease. In other words oral event or oral incidence addressed in this paper is defined as those that affect the dental health of the subject or may lead to an oral disease, because various oral anatomical structures apart of teeth, as well as saliva and oral microbiota, are involved.

3. Results

228,000 articles were identified in the initial search. A total of 215,147 articles were excluded due to the time window 1969–2018. Of these a number of 12,853 articles and abstracts were screened. Despite the presence of related words in the title or the abstract, a number of 12,772 were excluded because the articles did not report a relationship between oral health and microgravity. The remaining 81 studies were assessed with the inclusion and exclusion criteria. Thus, 12 studies: 6 original articles, 2 reviews, 1 book and 1 report with 3 original studies, were included in the systematic review (Fig. 1).

Table 1 includes the relevant events of the studies included as well as the exposure to space microgravity or simulated microgravity, and the time mission divided in short or long period. In Table 2 the relevant oral events have been grouped to study the global incidence of all the oral events found in the review. The limited documented and reported oral events precluded the statistical analysis of the data.

The following events were identified in the included articles: incapacitating dental pain, dental caries, crown displacement, increase of anaerobic and streptococcal components (*S. mutans*) in saliva and dental plaque microflora, increase of salivary IgA, increase of pain scores in teeth, mandibular angle regions, sublingual and submandibular opening duct regions, increase of *Mycoplasma* in saliva, increase of salivary IgM and IgG, increase of salivary alfa amylase, increase in average time of wound healing, increase of salivary cortisol, and increase of MM-P8 and MM-P9 in crevicular fluid (Tables 1 and 2).

3.1. Long period missions and space microgravity

The higher incidence corresponds to Increase of IgA in saliva (also reported in short periods), followed by increase of anaerobic and streptococcal components (*S. mutans*) in saliva and dental plaque microflora. Dental caries and incapacitating dental pain showed lower incidence.

3.2. Short period missions and microgravity

The increase of metalloproteinases (MM-P) MM-P8 and MM-P9, cortisol and alfa amylase in saliva were found to be more frequent in short period missions and in simulated microgravity. The increase of teeth pain while articulation of teeth, pain in mandibular angle regions while closing or opening the mouth, pain in sublingual and submandibular opening duct regions was also seen in short period missions and in simulated microgravity. A crown displacement incidence was observed in a short period mission. Wound healing delay, increase in IgM and IgG and increase of Mycoplasma in saliva were the lowest incidence events reported in short period on simulated microgravity.

Regarding the incidence of dental events grouped without considering either the period of the mission or the microgravity being space or simulated, the higher percentages found were of increases of salivary alfa amylase, increases in salivary cortisol and increases of MM-P8, MM-P. The increase of anaerobics was higher when it was observed in the long period studies with space or in simulated microgravity.

Table 1
Characteristics of studies included in the systematic review.

Articles	Relevant Event	Number of Cases	Microgravity	Exposed time
Ball JR. 2001 [49].	Incapaciting Dental Pain	1	Space	Long period 96-day flight aboard/In the last 2 weeks
Gontcharov IB et al., 2005 [22].	Caries Dental	1	Space	Long period 115 days–188 days (Total days: 977)
Brown LR et al., 1976. Skylab 2 [15].	Increase of Salivary IgA	3	Space	Long Period
	Increase of anaerobic and streptococcal components (S. Mutans) in saliva and dental plaque microflora	3		30 days
Brown LR et al., 1976. Skylab 3 [15].	Increase of Salivary IgA	3	Space	Long Period
	Increase of anaerobic and streptococcal components (S. Mutans) in saliva and dental plaque microflora	3		59 days
Brown LR et al., 1976. Skylab 4 [15].	Increase of Salivary IgA	2	Space	Long Period
	Increase of anaerobic and streptococcal components (S.Mutans) in saliva and dental plaque microflora	3		84 days
Brown LR et al., 1974 [25].	Increases in Saliva of Mycoplasma, increase of IgA	3	Simulated	Long period
	Increase of S. Mutants (cariogenic Streptococc) in dental plaque.	3		50 days
Rai B et al., 2011 [27].	Increase of pain scores in teeth, mandibular angle regions, sublingual and submandibular opening duct regions	10	Simulated	Long period 6 weeks
Rai B et al., 2010 [30].	Increase of MM-P8, MM-P9	20	Simulated	Short period 3 weeks
Rai B, 2012 [38]	Increases of Salivary alfa amylase	6	Simulated	Short Period
	Increases in Salivary cortisol	6		2 weeks
Rai B et al., 2011 [32].	Increases of Salivary alfa amylase	12	Simulated	Short Period
	Increases in Salivary cortisol	12		21 days
Rai B et al., 2012 [42].	Increase in average time of wound healing	2	Simulated	Short Period
	Increases in salivary IgA, IgM, IgG and cortisol levels			14 days
Menon A. 2012 [29].	Crown displacement	1	Space	Short period

4. Discussion

Conditions during space flight, such as microgravity, radiation and the interaction between them during various cellular-responses [9], lack of load-bearing, stress, acceleration forces, present unique physiological problems [10]. Dental and oral health are included in this physiological problems [2]. In this sense, this systematic review has revealed several oral health changes related to different microgravity and simulated microgravity exposition periods.

The oral events found in long-term and microgravity missions were the following: increase of anaerobic and streptococcal components (*Streptococcus mutans* [*S. mutans*]) in saliva and dental plaque microflora; increase of IgA in saliva (also showing high incidence in short periods); dental caries and incapacitating dental pain showed lower incidence. And in simulated microgravity the more frequent events reported were the increase of pain scores when moving or operating teeth, mandibular angle regions, sublingual and submandibular opening duct regions, and the increase of Mycoplasma in Saliva.

When the species of microorganisms that reside in the oral cavity or in other body surfaces are kept in balance (*symbiosis*), we speak of a healthy state. On the contrary, the rupture of this balance (*dysbiosis*) is associated with disease and is characterized by the alteration of the diversity and the relative proportions of the microbiota species [11].The alteration of the microbiome has been linked to: 1) exposure to disturbing molecules (food ingredients such as sugars, gluten, chlorinated water, antibiotics, and a multitude of chemical products); 2) lack of nutrients that encourage healthy colonies of bacteria (diets deficient in vegetables with fiber or with an excess of saturated fat), and 3) situations that cause and maintain stress, such as the astronaut's stress during missions, confirmed by the increase in cortisol in saliva. As a consequence, the altered microbiome contributes to a state of chronic inflammation that predisposes to diseases as varied as asthma, various allergies, obesity, diabetes, cancer, depression, autism, arthritis, ischemic heart disease, multiple sclerosis, Parkinson's disease and Alzheimer's disease [12]. The alteration of the microbiome and the chronic inflammatory processes derived favor the permeability of the mucosa of the different affected tracts (eyes, nose, mouth, throat, respiratory tract, gastrointestinal tract, urogenital tracts), which constitute broad entry routes for potential pathogens [13,14].

The increase of anaerobic microbiota in dental plaque as well as the increase of Mycoplasma in saliva is relevant. These anaerobics have been described, both in studies within long period missions with simulated gravity in earth and in studies with astronauts in Space Station from Skylab missions in space microgravity [15]. One of the problems associated with the increase of the anaerobics, is the increment of dental calculus and gingival inflammation postflight as compared with the preflight values for all Skylab missions and was observed for all missions and in all crewmembers [15].

The anaerobics presented and increased in the three Skylab missions were: *Bacteriodes* sp, *Veillonella* sp, *Fusobacterium* sp, *Neisseria* sp and *S. mutans*. *S. mutans* was already discussed as one of the main causes of dental caries [16] while *Veillonella* sp, *Fusobacterium* sp and *Bacterioides* sp are related to caries progression [17]. *Veillonella* sp in plaque would represent up to 45% in the initial stages of gingivitis or associated periodontitis [18]. *Fusobacterium* sp is a direct bacterial pathogen involved in the genesis of periodontitis and other periodontal diseases such as gingivitis, added to various associated factors [18]. *S. mutans, S. wiggsiae, P. denticolens*, and *L. salivarius*, were found almost exclusively in plaques collected from dentin carious lesions. But *S. sanguinis* and certain species of *Neisseria* and *Leptotrichia* have been frequently found in plaques collected from healthy tooth surfaces in children [19]. The relevance of the periodontitis problem is evident when considering that, in a patient with moderate periodontitis the surface of the periodontal bag in direct contact with the bacterial plaque is about 72 cm^2, approximately the size of the palm of the hand [20].

As in the previously mentioned Skylab mission, *S mutans* was observed in long period mission conditions. Caries progresses from initial demineralized lesions, visible as white spots on the enamel, to deep cavitated lesions. *S mutans* may initiate the caries first stages, since in recent studies high levels of the bacteria are often observed in the white spots but it is also present in lower levels in healthy subjects [21]. In this sense, in Space Station MIR during March 1995 and June 1998, one

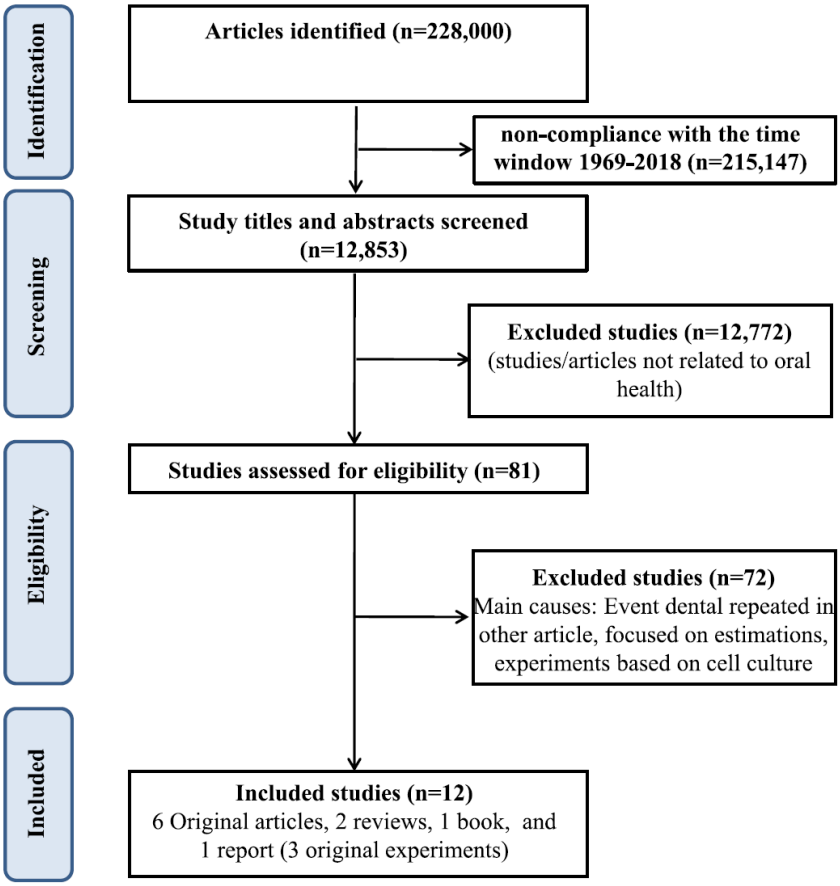

Fig. 1. Study flow diagram following the preferred reporting items for systematic review. Of the 228,00 citations identified according to the search dental problems, we included finally 12 studies.

dental caries (cavity) was identified and treated with a temporary filling from a dental kit, in what was described as a long period mission [22]; this caries could be associated with the increases of anaerobics but unfortunately the origin of this caries was not explained. According Skylab experience, the period in which the anaerobics increase was 56 days in space microgravity. So, in periods of more than 56 days in space, it would be essential to design a contingency plan and prepare the required dental equipment to prevent a dental urgency due to these bacteriae.

Saliva and crevicular fluid provide nutrients for microbial growth and contain components with antimicrobial activities [23,24]. Acute infections of the oral mucosa are rare, despite the dense microbial colonization. It can be attributed to host-microbe interactions, which importance is highlighted when observing immunosuppressed patients, who may experience life-threatening bacterial, viral and fungal infections [12]. Salivary proteins include secretory IgA (glycoproteins) and other substances like agglutinin, mucins and proline-rich proteins that affect the oral biofilm formation. These proteins can promote microbial adhesion because the salivary film and its constituent proteins bind to the teeth and mucosal membranes [16]. On the other hand, Secretory IgA antibody from parotid gland or serum IgG derived from the gingival crevicular fluid may influence the accumulation of cariogenic

Table 2
Number of cases of Oral Events.

Relevant Event	Number of Cases	Microgravity	Exposed time
Incapaciting Dental Pain	1	Space	Long period
Caries Dental	1	Space	Long period
Increase of anaerobic and streptococcal components (S. Mutans) in saliva and dental plaque microflora	12	Space & Simulated	Long period
Increase of IgA in Saliva	13	Space & Simulated	Long & Short period
Crown displacement	1	Space	Short period
Increase of pain scores in teeth, mandibular angle regions, sublingual and submandibular opening duct regions	10	Simulated	Long period
Increase of Mycoplasma in Saliva	3	Simulated	Long period
Increase of salivary IgM and Ig G	2	Simulated	Short period
Increase in average time of wound healing	2	Simulated	Short period
Increase of Salivary alfa amylase	18	Simulated	Short period
Increases in Salivary cortisol	20	Simulated	Short period
Increase of MM-P8, MM-P9	20	Simulated	Short period
Total	103		

microbiota at various stages of infection [16].

Regarding saliva, in a simulation study of a Skylab mission, Secretory IgA increased persistently during chamber confinement and reached a maximum level at the 55th day of sampling [25]. In the same study, although the changes of mycoplasma and enteric bacilli were statistically significant, no increase of *S. mutans* was found in saliva. However, there was an increase of *S. mutans* in dental plaque, that was related with a high sucrose diet [25]. In addition to the simulation of Skylab mission, experiments were carried out under space microgravity within the biomedical Skylab Program. In Long period Skylab missions 2, 3 and 4, consistent with the long period simulated microgravity studies already described, increases in Ig A were observed [26]. In Skylab 2 the secretory IgA levels were increased for the three crewmen during the flight. These changes were attributed to responses to a subclinical viral infection [26]. In Skylab 3 the three crewmen communicated an increase of the secretory IgA concurrently with saliva flow rate increment and salivary protein decrement. The decrease of the salivary protein and its reasons were not explained [26]. In Skylab 4 secretory IgA levels were increased and levels of protein and lysozyme as well as saliva flow rates were similar to the ones reported in Skylab 3 flight. In the Skylab 4 the increase in secretory IgA occurred in only two of the three crewmen. The IgA levels of the third crewman remained relatively constant [26].

Another salivary change in long periods in simulated microgravity was the increase of salivary glucosyltranferase (n = 10). Salivary glucosyltransferase B levels were increased in simulated microgravity condition of −6 head-down-tilt (HDT) as compared to normal in 10 healthy volunteers, and indicated that caries prevalence is higher during microgravity [27]. Glucosyltranferase enzymes are essential for the expression of virulence by *S mutans* in the pathogenesis of dental caries because of their ability to synthesize glucans from sucrose. The bacterial cell surface protein antigen with glucosyltransferase (Gtf) enzymes could mediate the binding of micro-organisms to tooth surfaces [28].

A Russian cosmonaut reported an incapacitating dental pain during the last 2 weeks of his 96-day flight aboard in Salut 6 mission in 1978, what means that the dental event was reported in a long period mission. But, unfortunately the origin of this pain was not explained. According to the report, no contingency plan was in place [29].

The relevant events described in short-term and simulated microgravity are changes of MMP-8 and MMP-9, increases in salivary cortisol, salivary alfa-amylase, increases in IgM and IgG, and increase in average time of wound healing. Only one case of crown displacement was found in space microgravity.

In short period the relevant events described are changes of MMP-8 and MMP-9, the most frequent proteinases, which function is to remodel tissues, as well as to degrade extracellular matrix and collagen. The increase of MM-P8 and MM-P9 is attributed to the reported increase of the metalloproteinases in the onset of collagen destruction in periodontitis [30]. Moreover the onset of collagen destruction in periodontitis is caused by the action of collagenases. Decrease of bone mineral density and bone mineral content is greater in women than in men, but not significant, due to the activity of hormones. In the study under microgravity stimulated conditions MMP 8 and MMP 9 are higher because of the increased virulence of bacteria. This was reported in an experiment with *S. typhimurium* that resulted in a higher increase in the level of invasion/phagocytosis, compared to normal gravity-grown bacteria [30,31]. The effects of simulated microgravity on host cell signaling, that could lead to a possibly immune suppression are not well clarified and require more detailed studies.

Salivary cortisol increment may be caused by the stress and the activation of the sympathetic adrenomedullary system [32]. The intense relationship between stress and oral pathology, as with other systemic pathologies, encourages us to think that in situations of special isolation such as microgravity conditions, it is necessary to control stress with regular controls of cortisol in saliva and others more instant like the facial recognition systems by computer to monitor facially the stress [33]. In a systematic review the effect of periodontal status on salivary cortisol levels proof that the increase of this salivary biomarker is in concordance with the progress and severity of periodontitis [34]. Cortisol as oxidative damage mediator may contribute to those differences since in aggressive periodontitis oxidative stress seems to highly contribute to periodontal pathology [35,36]. In this line of evidence, a study showed that the growth rate of *P. gingivalis* was significantly increased after addition of cortisol in the culture medium at12 h and 24 h in a dose-independent manner. This finding suggests that stress-induced hormone cortisol may have a specific effect on the growth of *P. gingivalis* [37].

In a study including six crewmembers, 3 men and 3 women, at the Mars Desert Research Station (MDRS) during two weeks-short period, salivary cortisol, alpha-amylase levels, and current stress scores were shown to be significantly higher after the end of the mission compared to before the start of the mission. Plaque levels and bleeding gums were increased during the mission. The investigators hypothesized that these outcomes were related to stress and improper oral hygiene [38].

Another study, carried out in a similar short period in simulated microgravity conditions, where 12 men with a mean age 24.75 (SD 2.2) were in 6° head-down tilt during 21 days, the outcomes were very similar to the ones described above. In the 12 men the salivary alpha-amylase and cortisol were significantly higher at 1 week after initiation of HDT. These findings are similar to those of previous studies [32]. Stress due to microgravity activates the hypothalamus-pituitary-adrenocortical (HPA) system and induces significant changes in salivary cortisol and beta-endorphin levels [32]. In this study the authors pointed out that the increase of salivary alpha-amylase in microgravity conditions depended of the activation of the sympathetic adrenomedullary system [32].

Given that changes in the physiology of astronauts affect the periodontal status, it is important to highlight the biological relationship it has with systemic diseases such as diabetes, cardiovascular diseases, cancer, chronic respiratory diseases and obstetric complications [37]. The significant association between periodontitis and chronic non-communicable diseases and ageing is widely reported in the literature. Such data provided the impetus for an international workshop in 2012 [39], where consensus statements for periodontitis and atherogenic cardiovascular disease, periodontitis and diabetes, and periodontitis and adverse pregnancy outcomes were developed, based upon 10 systematic reviews addressing epidemiology, mechanisms of association and periodontal intervention studies. A common theme that emerged was the impact of periodontal bacteraemia/endotoxaemia following daily activities such as eating and tooth brushing upon low grade systemic inflammation, via acute-phase (C-reactive protein, CRP) and neutrophil oxidative stress responses. The evidence base for independent associations between periodontitis and type-2 diabetes is long established, with a dual directionality of influence reported. In the diabetes–periodontitis direction, hyperglycaemia is associated with an increased risk and severity of periodontitis and poorer periodontal outcomes following periodontal therapy [39]. In the periodontitis–diabetes direction, the 2012 workshop concluded that severe periodontitis was associated with significantly elevated serum levels of HbA1C in people without diabetes (glycaemia) and in those with diabetes (hyperglycaemia), and there appeared to be a direct relationship between the severity of the periodontitis and cardio-renal complications of diabetes [39].

Also several studies report the relationship between periodontitis and osteoporosis, which is a major concern to astronauts' health. During space flight, it has been documented that astronauts suffer from progressive bone loss. The bone mass of astronauts has revealed a reduction in their bone mineral density with a loss of 1–2% per month under microgravity conditions. Numerous studies have demonstrated that microgravity can directly stimulate osteoclastogenesis and increase bone resorption in space or in a simulated microgravity environment.

These findings indicate that osteoclasts end their precursors are the direct targets of mechanical forces. However, the underlying mechanism remains unclear [40]. In this sense, there are results that determine moderate and severe periodontitis were found to have 1.56, 2.09 and 2.08 times the risk of osteoporosis respectively compared to patients without periodontitis. Log-rank analysis revealed that patients with periodontitis had significantly higher cumulative incidence rates of osteoporosis than the control group [41].

In another short study period two crewmembers were evaluated to heal an induced wound in microgravity simulated conditions. Each crew member was case and control, it was compared the complete healing period of the wound, during vacation and during the mission. It took crewmembers an average of 15.78 days for the wound to heal completely during their resting period, compared with 21.23 days during the mission [42]. The sample was of only two subjects so more studies with more subjects exposed to microgravity are needed to ascertain the causes and mechanisms for this event.

Interestingly, other factors that could make fail the missions to Mars, such as psychological changes, have been studied extensively [43], but even if there are indications of risk of oral pathology under long-term microgravity conditions, no prospective studies have stablished a risk assessment or proposed the curative or palliative treatments that will ensure the success of the mission.

There is a lack of knowledge about oral health risks for long-distance missions such as Moon missions and, to a greater extent, Mars, as shown by the fact that in the “Russian Program crews health state monitoring in spaceflights” [44], they monitor practically all aspects of astronaut physiology, from cardiac activity, through analysis of urea and blood and even audiometry, but does not include any type of oral or saliva control. Similarly one of the most important studies on changes in human physiology performed with twins, does not evaluate changes in the oral environment, even if the materials and methods of the article report that saliva was collected [45]. Despite of the fact that the oral health aspects were not analyzed, the comparative study between the twins Scott (in the ISS) and Mark Kelly (on Earth) is interesting because it shows that there were behavioral and physiological alterations in Scott, symptoms very similar to those that usually are caused by stress, but in a much more accentuated way. If this is the result of the stress of living 340 days in space, sleeping without gravity, eating freeze-dried food or if it is a direct effect only of microgravity remains uncertain. The changes in the intestinal microbiota observed by the NASA in this project have to be considered as well.

On the other hand, the chromatomass-spectrometry method tests confirmed that on the seventh day of flight there is an increase in the pathogenicity potential, that is, a quantitative increase of conventional microbiota pathogens and a decrease in the protective groups. Therefore, it is surprising that the most complete models of medical supply and astronaut health as the one proposed by Assad [46] do not contemplate oral pathology or its treatment.

Given that the amount and type of oral microbiota as well as different markers in saliva such as cortisol suffer modifications especially in long stays in microgravity it is necessary to use an autonomous control system as the one showed by Viacheslav et al. [47], that can serve as well as a control for numerous oral and systemic health risk factors. That is why we must emphasize the need to design a space and machinery, such as the use of ultrasound and imaging support system by Dulchavsky that will allow to replace the consultant expert [48], for space missions that can solve, in the hands of astronauts non-physicians or non-specialist physicians, crew oral health problems, thus going from the “dental event” limited concept to a broader “oral health status” consideration.

From our point of view the current protocols do not cover all the possible oral health incidents that may be due to the different conditions influencing long-range space missions. The need for a revision is necessary, taking into account the different pathogenic mechanisms and the relation between the oral and the systemic health status. Moreover, other possible pathogenic factors than microgravity have been reported [49] when dealing with the health of the crew in space missions: chemical and bacterial contamination, as well as water recycling [50] and vibration are part of the challenges that affect the crew in such a confined habitat and could lead to oral health alterations. External factors such as the radiation could add to the causes for the compromise of the astronaut's oral and systemic health. In addition, as we have already studied [51], different types and levels of isolation favor different oral pathologies, and therefore they will require specific treatment and prevention protocols.

5. Limitations of the study

The first limitation is the short number of articles published about the long period effects of the microgravity in the oral health. The review is focused on the reported relevant oral events and the microgravity, but the effect of other factors such as space radiation was not considered in most reports.

6. Conclusions

Future long-term missions to Mars or to space stations will require 18–24 months of exposure to microgravity conditions, which could have potentially deleterious effects on human physiology, including oral health. Microgravity is one of the various conditions that affect the oral and systemic health status during space missions.

This systematic review shows that in short missions in microgravity physiologic changes such as the increase of IgA and of salivary α-amylase due to the activation of the hypothalamus-pituitary-adrenocortical system have been observed. In combination with the changes of the microflora also observed in space missions, oral health alterations could jeopardize the success of long period missions by causing oral and systemic pathologies. Consequently, it will be necessary to adopt specific preventive measures, to train the personnel to deal with oral health events and to employ special equipment in long term missions.

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Declaration of competing interest

The authors declare no conflict of interest.

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Giovannoni M. L., Graduated from the University of Barcelona, with a degree in Odontology. Prof. In Odontology at the University of Barcelona.Doctor in Odontology (PhD Degree) from the University of Barcelona. Author of publications of scientifics articles. Member of Sepa (Spain society of Periodontology). Speaker at International Conferences. Peer reviewer.Active Collaboration of Vicente Ferrer Foundation in India.

Lloro Boada, Ivan. MEng MSc Ivan Lloro has contributed instrumentation to major space missions such as LISA PathFinder (Data and Diagnostics Subsystem) and Euclid (Near Infrared Spectrometer and Photometer Filter Wheel Assembly). In the meantime, his space engineering knowledge has been applied to the development of several medical devices, mainly focused in the oral healthcare sector.

Lloro Boada, Victor. DDS, PhD Candidate UB and private practitioner Víctor LLoro is a dentist at the University of Barcelona. Specialist in oral surgery by the University of Toulusse III. Doing the doctorate in medicine at the University of Barcelona. International speaker in several conventions of the Aerospace Medical Association (ASMA) and meetings of the International Association of Aerospace Dentistry (IAAD). Member of ASMA, IAAD, Spanish Society of Oral Surgery and other scientific associations.

Lozano-de Luaces, Vicente. Doctor in Medicine and Surgery and Stomatology. Prof in Barcelona Dental School, Barcelona University and NYU. Member of different Medicals and Dental Associations. Member of International Association of Aerospace Dentistry (IAAD). Master in Dental Environment and Master in Endodontics. Director of 12 Doctoral Thesis. Approximately 55 National and Internationals Publications in Dentistry. Approximately 160 dictates courses in all the World. In this moment Advisor of Rector in Barcelona University Prof Invitation for Courses and Conferences in: Edinburgh, NYU, Paris, London, Rome, Caracas, Bogotá, Miami.

Maria-Cristina Manzanares-Céspedes. Born the 28th November 1960 in Barcelona, Spain. M.D. (Faculty of Medicine, Autonomous University of Barcelona [UAB], Spain, 1985), PhD (Faculty of Medicine, Catholic University of Louvain, Belgium, 1988). Associated Professor of Human Anatomy and Embryology (Faculty of Dentistry, UB, 1989–1992). Ordinary professor since 1992 (Faculty of Dentistry, presently School of Dentistry, Faculty of Medicine and Health Sciences, UB, Spain). Invited professor in the *Instituto Universitàrio de Ciències da Saùde*, (CESPU, Gandra, Portugal); and the Faculty of Dentistry of the University of Brescia (Italy). Secretary General ADEE (Association for Dental Education in Europe). Secretary General IFDEA (International Federation of Dental Educators and Associations). Associated Editor of "European Journal of Dental Education" and "European Journal of Anatomy". ORCID: https://orcid.org/0000-0002-4585-4953, https://www.researchgate.net/profile/Maria-Cristina_Manzanares_Cespedes

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(54) **AUXILIARY DEVICE FOR DENTAL PROCEDURE**

HILFSVORRICHTUNG FÜR ZAHNÄRZTLICHES VERFAHREN

DISPOSITIF AUXILIAIRE POUR PROCÉDURE DENTAIRE

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(73) Proprietor: **Astradentium Health Technologies, S.L.**
08003 Barcelona (ES)

(72) Inventors:
- **LLORO BOADA, Victor Alejandro**
  08860 Castelldefels (ES)
- **LLORO BOADA, Ivan**
  08860 Castelldefels (ES)

(74) Representative: **Gallego Jiménez, José Fernando**
Ingenias Creaciones, Signos e Invenciones S.L.P.
Avda. Diagonal 421, 2
08008 Barcelona (ES)

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Description

Technical field

[0001] The present invention generally relates to the field of dental devices. In particular, the invention relates to an auxiliary device for dental procedure that does not obstruct a patient's buccal orifice, thereby enabling a healthcare professional to work normally during the dental procedure, being able to treat any accessible space or tissue through the mouth of the patient.

Background of the Invention

[0002] US-B2-7300401 discloses a device for dental use that is placed in the mouth of a patient during the dental procedure for retraction of the mouth and expulsion of saliva. Said device includes a frontal suction part, a right cheek retraction part, a left cheek retraction portion, and an aspiration portion. Furthermore, the device consists of a rigid single piece of elastic and tubular material, having a cylindrical shape or another cross-sectional shape.

[0003] US-B2-7785105 discloses a device for keeping the operating field dry during a dental procedure. The device includes a U-shaped member for securing the patient's tongue during the dental procedure. In addition, it includes lip retractors that extend in an arched disposition around the cheeks. In some embodiments the device also includes a saliva ejector.

[0004] According to Chinese utility model CN-Y-201115660, a device with lateral retractors for opening the mouth of a patient during a dental procedure is known, such device including a saliva aspiration function by means of two tubular mechanisms for filtration /evacuation of the saliva, which rest positioned in the back of the patient's mouth during the procedure. With the aforementioned aspiration function contamination can be reduced due to the air present in the room or due to an inhaler.

[0005] EP-B1-1131015 also discloses an intraoral lighting dental device which enables the interior of the buccal cavity of a patient to be lighted during a dental procedure and thereby avoiding lighting issues. The lighting device comprises an occlusion apparatus designed to fit into the patient's dentition so that during the dental procedure the patient can rest his jaws and the device is fixed in his mouth. Moreover, the dental device has a retractor for the tongue and cheeks that allows isolation and protection of the tongue and tissue from the patient's cheeks during the medical procedure. The device may also include fluid extraction channels for extracting the fluids present in the interior of the patient's buccal cavity during the dental procedure.

[0006] US-A-3396468 discloses a device applicable in the buccal cavity for dental procedures, said device eliminates the fluids and can be easily and quickly inserted into the patient's mouth.

[0007] US-A-4053984 discloses a removable dental device, which allows the patient's mouth to be opened for dental work while maintaining a dry and wide operation field.

[0008] US-A-4967320 discloses an air emitting light and shielding apparatus for dental treatment. The apparatus is comprised of a pressurized air source connected to an adjustably positionable air emitting light formed so as to develop an air envelope substantially surrounding the face and oral cavity or other body parts of a patient residing in a selected position in the dental chair or other operating table including positions in which the patient may be tilted such that vapors, blood, saliva splash, dental particles, or other foreign matter propelled from the patient's oral cavity during drilling, air-water syringing, or the like, are deflected by the inner boundary of the air envelope and are transported downstream of the patient's oral cavity for collection on a disposable patient drape thereby preventing the same from reaching the face and respiratory tract of a dental team member operating on the patient.

[0009] US3537447, JP2004033474 and JPH1028696 also disclose devices for dental procedures forming a protective shield between a dentist and a patient.

[0010] US-A-5127411 discloses an apparatus to aid in isolating a medical practitioner from infectious materials found in a patient. The apparatus includes a collector for providing a vacuum barrier around the mouth of a patient to trap aerosols and the like emanating from the patient during a dental procedure. The collector is flow connected to a vacuum source for drawing a vacuum, and gases drawn in by the source are passed through a filter. The collector is ring-shaped to surround the mouth and to allow the practitioner to see into the site of the procedure and is disposable after each operation.

[0011] However, there is at present no known device for dental procedure which is held inside or in the mouth of a patient during the dental procedure and which includes a barrier mechanism between the inside and the outside of the patient's mouth formed by one or more ducts including an opening at one of its ends which, by generating a gaseous fluid flow or air curtain, provides greater protection by allowing the filtration of pathogens during the dental procedure.

Disclosure of the invention

[0012] The present invention provides an auxiliary device for dental procedure as defined in claim 1. Preferred embodiments are defined in the dependent claims 1. The auxiliary device is intended to be applied to or adjacent to a patient's perioral area, i.e. the space comprised by the volume of 3 cm around the entire length of the lip vermilion, including commissure. The proposed auxiliary device does not obstruct the buccal orifice so that a healthcare professional can work normally by treating any space or tissue accessible through the patient's mouth (such as the oral cavity, nasal cavity, larynx, pharynx, esophagus or maxillary sinus).

[0013] The proposed auxiliary device characteristically comprises a gaseous fluid flow-generating member, or air curtain, which exerts a barrier effect between an interior area of the patient's mouth and the outside of the mouth, and a support of said gaseous flow generating member which maintains it placed in an area proximate to said perioral area. Said generating member is formed by at least one duct including at one of its ends an opening which is placed in the exterior of the perioral area, in front of said support. Herein, the proposed auxiliary device prevents or minimizes the passage of sprays, micro-droplets, drops, or other particles, as well as pathogens (such as viruses, fungi, bacteria, prions, etc.) from the interior of the buccal cavity to the exterior, and vice versa, thus avoiding direct cross-contamination between the patient and the healthcare professional, and vice versa, as well as indirect contamination (that is to say, through the environmental contamination of a dental clinic or work area of a healthcare professional or tooling, etc. in such a way that the infection of the patient or healthcare professional can originate due to a previous patient). Likewise, the proposed auxiliary device allows the healthcare professional to work normally and unobstructed throughout the entire buccal cavity, and can be used autonomously or in conjunction with a rubber dam.

[0014] The proposed auxiliary device also prevents particles resulting from the removal of potentially hazardous dental restorative materials (for example, dental amalgams) from leaving the patient's mouth, which up to date is solved using elaborate methods based on a combination of suction hoods, rubber dams and specialized masks.

[0015] Preferably, the gaseous flow is a laminar flow.

[0016] Preferably, said aperture has an elongate shape with a central portion of greater width. Further, the generating member may be attached to the holder in a central portion, or, alternatively, in a lateral portion.

[0017] In one exemplary embodiment, another end of said duct is connectable to an aspiration or pressure-blowing pump of a gaseous fluid selected from air or other neutral gas.

[0018] Optionally, the aspiration or pressure-blowing pump may also be associated with a circuit in which an anti-pathogen agent will be provided.

[0019] In one exemplary embodiment said generating member comprises two ducts, each including at one of its ends said aperture, and being connected at the other end thereof to a single tubular section which is connectable to an aspiration or pressure- blowing pump of a gaseous fluid selected from air or other neutral gas. According to this embodiment, optionally, the aspiration or pressure-blowing pump may also be associated with a circuit in which an anti-pathogen agent will be provided.

[0020] In one exemplary embodiment, the support further includes one or more supports for cannulas or saliva aspiration ejectors.

[0021] In one exemplary embodiment, the cited support includes a buccal expansion element comprising at least a portion providing props in distal areas of the mouth for cheek separation (buccal mucosa expansion) during the dental procedure. Alternatively, in another embodiment, the support includes a buccal expansion member comprising at least a portion which provides lip-shaped props for lip retraction during the dental procedure.

[0022] Said mouth expansion element may be formed of two identical, arcuate portions or parts which engage in distal, lateral, or alternatively, labial or lateral areas of the patient's mouth.

[0023] Moreover, the aspiration or pressure-blowing pump may be associated with flow control means.

[0024] In still yet another embodiment, the device includes or has a support part for a lighting unit, for example a LED or a light wave guide such as an optical fiber, to light up the interior of the oral cavity of the mouth of the patient during the dental procedure.

[0025] The proposed auxiliary device can be used for protection between the patient and a healthcare professional, and vice versa, due to cross-contamination of biological type by direct contagion including Flügge micro-droplets or micro-droplets produced by a cooling spray, or indirect via contamination of surfaces, wardrobe or instrumental of a dental box.

[0026] Likewise, the auxiliary device may also be used for protection between the patient and the healthcare professional, and vice versa, due to cross-contamination of the chemical type through direct contact or intoxication including suspended particles of dental powder or dental reconstruction material such as resins, amalgams, composites or gases produced by gutta-percha incineration, or indirect contamination of surfaces, clothing or instruments of a dental box.

[0027] The auxiliary device may also be used to prevent water soaking or wetting of a dental instrument into the patient's oral cavity including materials, surfaces, tissues and instruments, or even to protect the healthcare professional from the patient's halitosis.

Brief description of the drawings

[0028] The above and other features and advantages of the present invention will become more apparent from the following detailed description of exemplary embodiments, which are merely illustrative and not limitative, with reference to the accompanying drawings, in which:

Figs. 1 and 2 show different views of the proposed auxiliary device for dental procedure according to a preferred embodiment of the present invention;

Fig. 3 shows an alternative example of an auxiliary device for dental procedures, in which the support includes supports for saliva aspirating cannulas or ejectors.

Detailed description of exemplary embodiments

[0029] The present invention will be described in more detail by reference to the following embodiments which are presented for purpose of illustration and should not be constructed to limit the scope of the invention thereto.

[0030] The present invention provides an auxiliary device for dental procedures, referenced as 1 in the figures, which allows the filtering of pathogens or other particles by generation, when the auxiliary device is positioned inside the mouth of a patient during said dental procedure, of a gaseous fluid flow, for example laminar, thereby exerting a barrier effect between the inside and the outside of the patient's mouth.

[0031] Figs. 1 and 2 show a first exemplary embodiment of the proposed auxiliary device 1 constructed in accordance with the present invention. As can be seen, the auxiliary device 1 includes a generating member 10 of said gaseous fluid flow and a support 11 for holding the generating member 10 placed in an area proximate to the perioral area. According to this first embodiment, the generating member 10 is attached to the support 11 in a central portion, although this is not limiting since, in other examples, in this case not shown, the generating member 10 may be attached to the support 11 in a lateral portion. Also according to this exemplary embodiment, the generating member 10 is formed by a duct including at one of its ends an opening 12 which is placed in the exterior of the perioral area in front of said support. The aperture 12 may be of different dimensions, but preferably, it is elongated with a central portion of greater width as shown in the figures.

[0032] The support 11 comprises a buccal expansion element, formed by two identical or arcuate portions or parts 16A, 16B, which provide supports in distal areas of the patient's mouth to allow separation of the cheeks and lips (lip retraction) during the dental procedure. Also, the auxiliary device 1 includes a tubular section 15 connectable to one or more aspiration or blow-off air intakes available in a dental chair (not illustrated) or, alternatively, to an aspiration or pressure-blowing pump of a gaseous fluid (not illustrated), for example air or, alternatively, another neutral gas.

[0033] Said aspiration or pressure-blowing pump of a gaseous fluid is preferably associated with flow control means. Optionally, the aspiration or pressure-blowing pump may also be associated with a circuit (not illustrated) which provides an anti-pathogenic agent.

[0034] Referring to Fig. 3, a second exemplary embodiment of the proposed auxiliary device 1 is shown. The auxiliary device 1 of this exemplary embodiment is the same as described above with the particularity that the support 11 includes two supports or props 13 for supporting saliva aspiration cannulas or ejectors. Alternatively, instead of including two props 13, a single support 13 could be included.

[0035] According to another exemplary embodiment, in this case not illustrated, the generating member 10 comprises two ducts, each one including at one of its ends said aperture 12, and being connected by the other of its ends to the tubular section 15, by forming a 'Y'.

[0036] Said aspiration or pressure-blowing pump of a gaseous fluid is preferably associated with flow control means, and a circuit for supplying said anti-pathogen chemical.

[0037] In still other alternative embodiments of the proposed auxiliary device 1, also not illustrated by the simplicity of the figures, further includes a lighting unit to light up the interior of the oral cavity of the patient's mouth during the dental procedure. In one exemplary embodiment, said lighting unit comprises lighting elements for example of LED type (light-emitting diode) and is supplied by a source of electrical energy (such as batteries or a generator) included in the auxiliary device itself or externally thereto. Alternatively, said lighting unit comprises a light waveguide such as an optical fiber.

[0038] The proposed auxiliary device 1 can come in different sizes and accommodate different shapes and sizes of the mouth.

[0039] The scope of the present invention is defined in the appended claims.

Claims

1. Auxiliary device for dental procedure, said device (1) comprising a support (11) intended to be placed in a perioral area of a patient, **characterized in that** the device further comprises a generating member (10) of a gaseous fluid flow exerting a barrier effect between an inner area of the patient's mouth and the outside of the mouth, said generating member (10) of a gaseous fluid flow being formed by at least one duct including at one of its ends an aperture (12) that is placed in the exterior of the perioral area of the patient in front of said support (11), and the generating member (10) being attached to the support (11) in a central portion.

2. The device according to claim 1, wherein said aperture (12) is elongated and has a central portion of greater width.

3. The device according to claims 1 or 2, wherein another end of said duct is connectable to an aspiration or pressure-blowing pump of a gaseous fluid selected from air or other neutral gas.

4. The device according to claims 1 or 2, wherein said generating member (10) comprises two ducts, each one including at one of its ends said aperture (12), and being connected at the other end to a single tubular section (15) which is connectable to an aspiration or pressure-blowing pump of a gaseous fluid selected from air or other neutral gas.

5. The device of any one of the preceding claims, wherein said support (11) includes a buccal expansion element comprising at least a portion which provides props in distal areas of the patient's mouth for separation of the cheeks during said dental procedure.

6. The device of any of the preceding claims 1 to 4, wherein said support (11) includes a buccal expansion element comprising at least a portion which provides props in labial areas of the patient's mouth for lip retraction during said dental procedure.

7. The device of claim 1, wherein the gaseous fluid flow is a laminar flow.

8. The device of claims 5 or 6, wherein said support (11) further includes at least one support (13) for saliva aspiration cannulas or ejectors.

9. The device of claim 5, wherein the buccal expansion element is formed by two identical, arcuate portions or pieces which engage in distal, lateral areas of the patient's mouth.

10. The device of claim 6, wherein the buccal expansion element is formed by two identical, arcuate portions or pieces which engage in labial, lateral areas of the patient's mouth.

11. The device of claims 3 or 4, wherein said aspiration or pressure-blowing pump is associated with flow control means.

12. The device of claims 3, 4 or 11, wherein said aspiration or pressure-blowing pump is associated with a circuit providing an anti-pathogenic agent.

13. The device of any one of the preceding claims, further comprising a lighting unit to light up the interior of the oral cavity of the patient's mouth during the dental procedure.

14. The device of claim 13, wherein said lighting unit comprises LED-type lighting elements or a light-waveguide.

Patentansprüche

1. Hilfsvorrichtung für zahnärztliche Eingriffe, wobei die Vorrichtung (1) eine Stütze (11) umfasst, die dazu bestimmt ist, in einem perioralen Bereich eines Patienten platziert zu werden, **dadurch gekennzeichnet, dass** die Vorrichtung ferner ein Erzeugungselement (10) eines gasförmigen Fluidstroms umfasst, das eine Barrierewirkung zwischen einem inneren Bereich des Mundes des Patienten und der Außenseite des Mundes ausübt, wobei das Erzeugungselement (10) eines gasförmigen Fluidstroms durch mindestens einen Kanal gebildet wird, der an einem seiner Enden eine Öffnung (12) aufweist, die außerhalb des perioralen Bereichs des Patienten vor der Stütze (11) platziert ist, und wobei das Erzeugungselement (10) an dem Träger (11) in einem zentralen Abschnitt angebracht ist.

2. Vorrichtung nach Anspruch 1, wobei die Öffnung (12) länglich ist und einen zentralen Abschnitt größerer Breite aufweist.

3. Vorrichtung nach Anspruch 1 oder 2, wobei ein anderes Ende des Kanals mit einer Ansaug- oder Druckblaspumpe eines gasförmigen Fluids verbunden werden kann, das aus Luft oder einem anderen neutralen Gas ausgewählt ist.

4. Vorrichtung nach Anspruch 1 oder 2, wobei das Erzeugungselement (10) zwei Kanäle aufweist, von denen jeder an einem seiner Enden die Öffnung (12) aufweist und am anderen Ende mit einem einzelnen rohrförmigen Abschnitt (15) verbunden ist, der mit einer Ansaug- oder Druckblaspumpe eines gasförmigen Fluids verbunden werden kann, das aus Luft oder einem anderen neutralen Gas ausgewählt ist.

5. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei die Stütze (11) ein bukkales Expansionselement aufweist, das mindestens einen Abschnitt umfasst, der in distalen Bereichen des Patientenmundes Abstützungen zum Trennen der Wangen während des zahnärztlichen Eingriffs bereitstellt.

6. Vorrichtung nach einem der Ansprüche 1 bis 4, wobei die Stütze (11) ein bukkales Expansionselement umfasst, das mindestens einen Abschnitt umfasst, der in labialen Bereichen des Patientenmundes Abstützungen zum Zurückziehen der Lippen während des zahnärztlichen Eingriffs bereitstellt.

7. Vorrichtung nach Anspruch 1, wobei das gasförmige Fluid ein Laminarfluss ist.

8. Vorrichtung nach einem der Ansprüche 5 oder 6, wobei die Stütze (11) ferner mindestens eine Stütze (13) für Speichelabsaugskanülen oder -ejektoren aufweist.

9. Vorrichtung nach Anspruch 5, wobei das bukkale Expansionselement durch zwei identische bogenförmige Abschnitte oder Stücke gebildet ist, die in distale laterale Bereiche des Patientenmundes eingreifen.

10. Vorrichtung nach Anspruch 6, wobei das bukkale Expansionselement durch zwei identische bogenförmi-

ge Abschnitte oder Stücke gebildet ist, die laterale innere Lippenbereiche des Patientenmundes eingreifen.

11. Vorrichtung nach Anspruch 3 oder 4, wobei die Ansaug- oder Druckblaspumpe mit Flusssteuermitteln verknüpft ist.

12. Vorrichtung nach Anspruch 3, 4 oder 11, wobei die Ansaug- oder Druckblaspumpe mit einer Schaltung verknüpft ist, die einen antipathogenen Wirkstoff bereitstellt.

13. Vorrichtung nach einem der vorhergehenden Ansprüche, ferner umfassend eine Beleuchtungseinheit zum Beleuchten des Innenraums der Mundhöhle des Patienten während des zahnärztlichen Eingriffs.

14. Vorrichtung nach Anspruch 13, wobei die Beleuchtungseinheit LEDartige Beleuchtungselemente oder einen Lichtwellenleiter umfasst.

Revendications

1. Dispositif auxiliaire pour procédure dentaire, ledit dispositif (1) comprenant un support (11) destiné à être placé dans une zone péri-orale d'un patient, **caractérisé en ce que** le dispositif comprend en outre un élément générateur (10) d'un flux de fluide gazeux exerçant un effet de barrière entre une zone interne de la bouche du patient et l'extérieur de la bouche, ledit élément générateur (10) d'un flux de fluide gazeux étant constitué d'au moins un conduit comportant à l'une de ses extrémités une ouverture (12) qui est placée à l'extérieur de la zone péri-orale du patient en face dudit support (11), et l'élément générateur (10) étant fixé au support (11) dans une partie centrale.

2. Dispositif selon la revendication 1, dans lequel ladite ouverture (12) est allongée et a une partie centrale de plus grande largeur.

3. Dispositif selon les revendications 1 ou 2, dans lequel une autre extrémité dudit conduit peut être raccordée à une pompe d'aspiration ou de soufflage sous pression d'un fluide gazeux choisi parmi l'air ou un autre gaz neutre.

4. Dispositif selon les revendications 1 ou 2, dans lequel ledit élément générateur (10) comprend deux conduits, chacun comportant à l'une de ses extrémités ladite ouverture (12), et étant raccordé à l'autre extrémité à une section tubulaire unique (15) qui peut être raccordée à une pompe d'aspiration ou de soufflage sous pression d'un fluide gazeux choisi parmi l'air ou un autre neutre gaz.

5. Dispositif de l'une quelconque des revendications précédentes, dans lequel ledit support (11) comporte un élément d'expansion buccale comprenant au moins une partie qui fournit des cales dans les zones distales de la bouche du patient pour la séparation des joues pendant ladite procédure dentaire.

6. Dispositif de l'une quelconque des revendications précédentes 1 à 4, dans lequel ledit support (11) comporte un élément d'expansion buccale comprenant au moins une partie qui fournit des cales dans les zones labiales de la bouche du patient pour la rétraction de la lèvre pendant ladite procédure dentaire.

7. Dispositif de la revendication 1, dans lequel le flux de fluide gazeux est un flux laminaire.

8. Dispositif des revendications 5 ou 6, dans lequel ledit support (11) comporte en outre au moins un support (13) pour des canules d'aspiration ou extracteurs de salive.

9. Dispositif de la revendication 5, dans lequel l'élément d'expansion buccale est constitué de deux parties ou pièces identiques, arquées qui sont introduites dans les zones distales, latérales de la bouche du patient.

10. Dispositif de la revendication 6, dans lequel l'élément d'expansion buccale est constitué de deux parties ou pièces identiques, arquées qui sont introduites dans les zones labiales, latérales de la bouche du patient.

11. Dispositif des revendications 3 ou 4, dans lequel ladite pompe d'aspiration ou de soufflage sous pression est associée à des moyens de régulation de flux.

12. Dispositif des revendications 3, 4 ou 11, dans lequel ladite pompe d'aspiration ou de soufflage sous pression est associée à un circuit fournissant un agent anti-pathogène.

13. Dispositif de l'une quelconque des revendications précédentes, comprenant en outre une unité d'éclairage pour éclairer l'intérieur de la cavité buccale de la bouche du patient pendant la procédure dentaire.

14. Dispositif de la revendication 13, dans lequel ladite unité d'éclairage comprend des éléments d'éclairage du type à LED ou un guide d'ondes lumineuses.

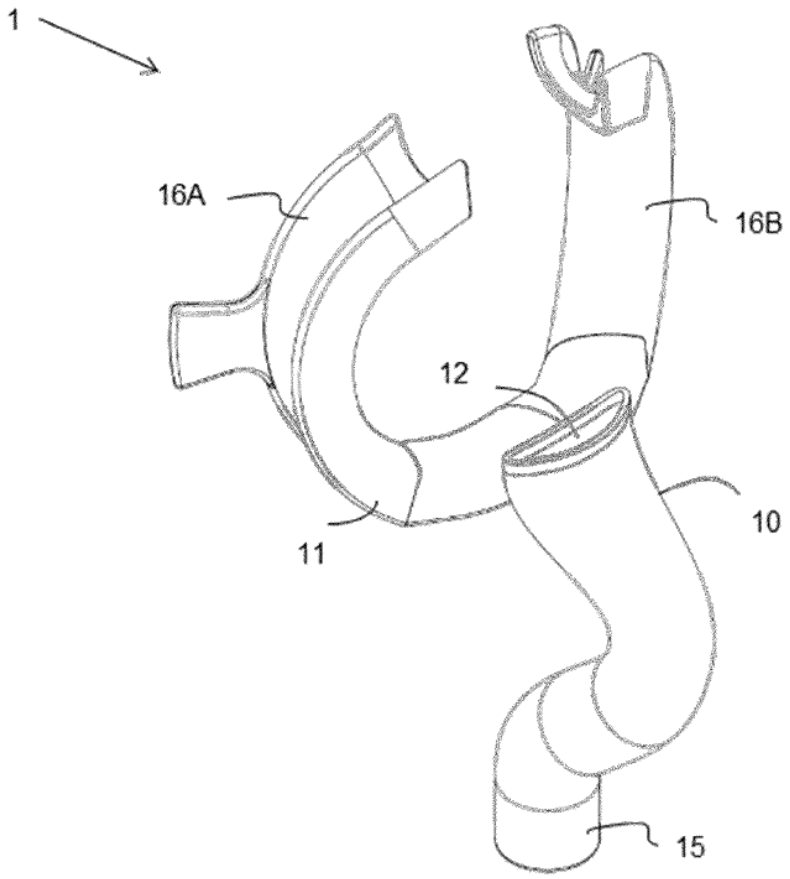

Fig. 1

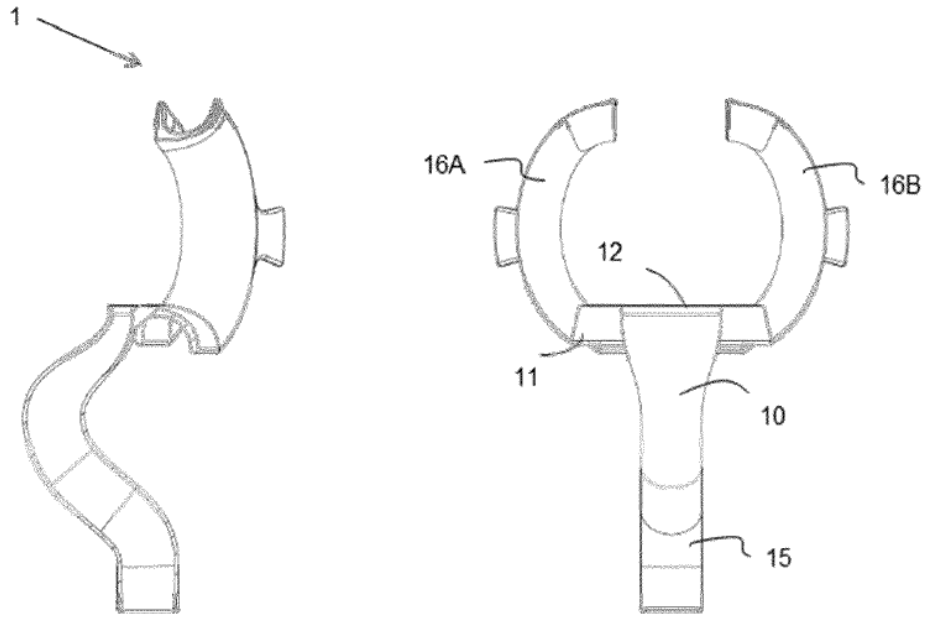

Fig. 2

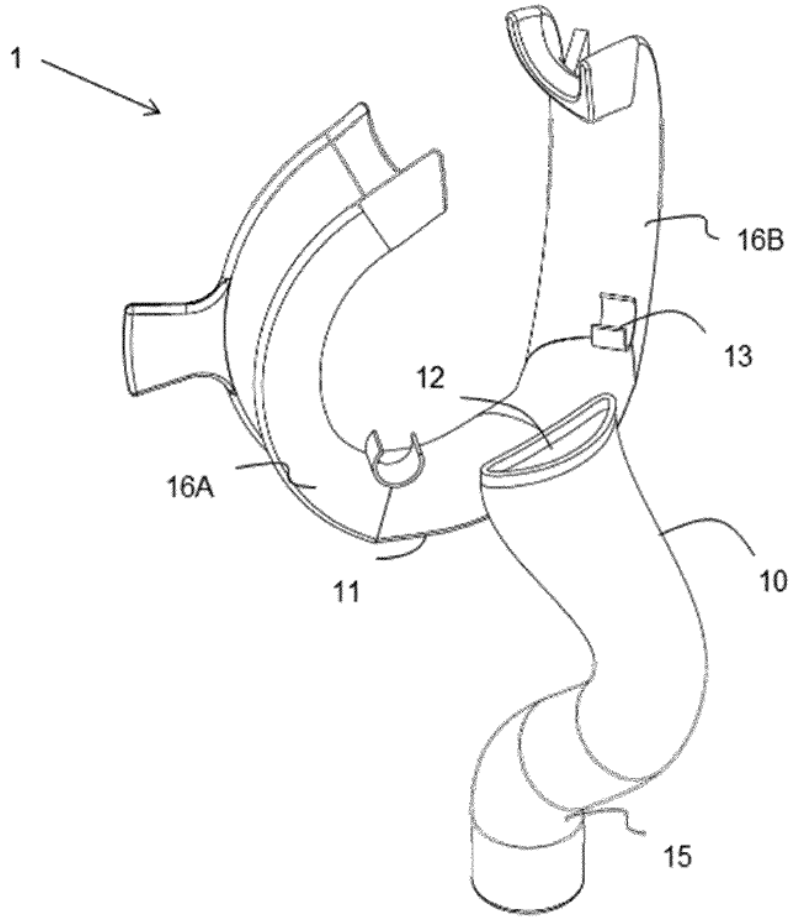

Fig. 3

REFERENCES CITED IN THE DESCRIPTION

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Chapter 4: OBF reduces biological cross-contamination in dental procedures

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Perioral Aerosol Sequestration Suction Device Effectively Reduces Biological Cross-Contamination in Dental Procedures

Víctor Lloro[1] Maria Laura Giovannoni[2] Vicente Lozano-de Luaces[3] Maria Cristina Manzanares[1]

[1]Human Anatomy and Embryology Unit, Experimental Pathology and Therapeutics Department, Faculty of Medicine and Health Sciences, Health University of Barcelona, Barcelona, Spain
[2]Odontology Hospital UB, Odontostomatology Department, Faculty of Medicine and Health Sciences, Health University of Barcelona, Barcelona, Spain
[3]Faculty of Medicine and Health Sciences, Health University of Barcelona, Barcelona, Spain

Address for correspondence Víctor Lloro, DDS, MSc, 5305, P Govern, Health University of Barcelona campus, Feixa Llarga Street, L'Hospitalet, 08907 Barcelona, Spain (e-mail: vllorobo7@alumnes.ub.edu).

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Abstract

Objective The infection risk during dental procedures is a common concern for dental professionals which has increased due to coronavirus (severe acute respiratory syndrome coronavirus 2) pandemic. The development of devices to specifically mitigate cross-contamination by droplet/splatter is crucial to stop infection transmission. The objective of this study is to assess the effectiveness of a perioral suction device (Oral BioFilter, OBF) to reduce biological contamination spread during dental procedures.

Materials and Methods Forty patients were randomized 1:1 to a standard professional dental hygiene treatment with OBF and without. Adenosine triphosphate (ATP) bioluminescence assay was used to evaluate the spread of potential contaminants. The total number of relative light units (RLU) from key dental operatory locations: operator's face-shield, back of the surgical operator's-gloves, patient's safety-goggles, and instrumental table were measured. Percentage contamination reductions between control and OBF were compared.

Statistical Analysis Primary outcome, total RLU, was analyzed by comparing the means of logged data, using a two-sided two-sample *t*-test. Secondary outcomes as RLU of logged data for the different locations were analyzed in the same way. Proportion of patients from whom different locations reported events (clean, acceptable, and failure) were analyzed by using Fisher's exact test.

Results For the whole dental environment, RLUs reduction (<150 units) achieved with OBF was 98.4% (97.4–99%). By dental operatory location the reduction in RLUs

Keywords
- aerosol
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was from 99.6%, on the operator face-shield, to 83% on instrumental table. The control group reported a very high percentage of failures, (>300) being 100% on the surfaces closer to the patient's mouth and decreasing to 70% on instrumental table. In contrast, the higher failure percentage in the OBF group was found on the patient's goggles (40%), while the operator face-shield showed an absence of contamination.

Conclusion OBF device has shown efficient reduction of biological aerosol cross-contamination during dental procedures as proved by ATP-bioluminescence assay. Nevertheless, for maximum safety, its use must be combined with standard protective gear such as goggles, face shield, and surgical gloves.

Introduction

The cross-contamination and dissemination of pathogens in a dental operatory environment is a concern during dental procedures. The recent pandemic caused by coronavirus (SARS-CoV-2) that on February 11, 2020, World Health Organization named as "coronavirus disease"[1] has increased this concern. Dental professionals must be aware that droplet and splatter have proven to be the main spread routes of oral pathogens and, among them, SARS-CoV-2.[1]

Oral droplet and splatter are biological substances (made of a combination of particles, gases, vapors, biological fragments, or microorganisms that are or become airborne) with a diameter between 0.5 and 10 µm that have the potential to penetrate and lodge in the smaller passages of the lungs.[2,3] These particles are disseminated during standard dental treatments (e.g., ultrasonic scaling, professional mechanical tooth cleaning, etc.) and are potential sources of cross-transmission of microorganisms.[4] In this regard, a recent study has shown that instruments, such as rotating tools, ultrasonic scalers, and piezo tools, produce a greater amount of aerosols/spray during dental procedures that can widely spread the saliva of a potentially infected patient, thereby exponentially increasing the risk of contamination/contagion.[5]

These considerations have gained relevance since SARS-CoV-2 represents a high risk for cross-transmission of microorganisms for oral health professionals (OHP), which can become potential carriers of the disease due to the unique nature of oral health procedures, that involve aerosol generation and the close proximity of the professionals to the highly contaminated oropharyngeal region of symptomatic and asymptomatic patients.[6] Besides, as reported by Zemouri et al,[7] patients could also generate droplets and splatter by coughing, sneezing, and talking; therefore, the transmission probability is driven by indoor air quality, patients infectiousness, and the masks used by OHPs. Actually, Gou et al concluded that SARS-CoV-2 has been widely distributed in the air (as an aerosol) and on object surfaces with transmission distances close to 4 m in hospital facilities such as intensive care units. This poses a high infection risk for medical staff and other close persons. Most particularly, such risk is the highest in small indoor rooms.[8]

Measuring the concentration of adenosine triphosphate (ATP) by bioluminescence assay is a technique routinely used in hospitals and the food industry[9-12] for fast and accurate quantification of biological contamination on surfaces. ATP systems are able to detect dried organic materials and dead microorganisms[9] and to determine the efficacy of environmental cleanliness procedures even with low microbial counts,[13,14] but do not detect viruses. This measurement technique has been successfully used in a recent dentistry study which showed increased biocontamination levels on operator's goggles, masks, arms, and patient's goggles after standard dental procedures, demonstrating the ability of generated droplet and splatter to spread infection among operators and patients.[4]

Cross-transmission of microorganisms can be prevented by preventing the contamination.[15] This can be achieved either at a macro level increasing ventilation or at the source of contamination by applying an aerosol suction device, like the OBF, which was initially developed for astronauts in space. In the absence of gravity, particles of saliva or blood containing pathogens are released into the environment[16,17] as also reported in patients in isolated missions[17] both probably due to reduced ventilation, as suggested by Zemouri et al,[7] which studied the analogous situation in dental clinics due to the indoor air quality. The perioral suction device named Oral BioFilter (OBF) consists in an ergonomic lip retractor that supports an extraoral suction device which connects to the dental chair's high-volume evacuator (HVE) suction system. This device acts as a filter that prevents airborne microparticles from expanding beyond the work area, thus harming the OHP as well as the patients. As a consequence, OBF improves everyone's safety by keeping the dental workplace hygiene and cleanliness.[16,18]

The aim of the present study is to assess the effectiveness of the OBF device to reduce cross-transmission of microorganisms by analyzing the contamination patterns produced by droplet and splatter during professional dental hygiene with ultrasonic scaling, followed by professional mechanical tooth cleaning (PMTC) with high-speed contra-angle handpiece.

Materials and Methods

Study Design

The study was performed during the routine clinical practice in patients undergoing a programmed professional dental hygiene with ultrasonic scaler followed by a PMTC. All participants gave written informed consent to the procedure, which was approved by the University of Barcelona Bioethics Committee, as a part of the first author PhD Thesis project, and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

The standard professional dental hygiene procedure was performed by a single right-handed hygienist at a height of 1.55 m with no assistant, using an ultrasonic scaler (Satelec Acteon group, Merignac, France) during 10 minutes, followed by polishing with polishing paste and NSK contra-angle (M 25 S-MAX, NSK, Nakanishi, Tochigi-ken, Japan). As a pretreatment standard procedure, patients' oral cavity was rinsed with 0.2% povidone iodine for 1 minute to reduce pathogen load stemming from droplet and splatter forming procedures in dental settings.[19,20] The instrumental table was located 1 m from the patient's mouth, on the right of the patient and in front of the hygienist. Patients were lying down in the dentist' chair (FEDESA JS 500, FEDESA, Madrid, Spain), with a distance between the operator's face shield and the patient's mouth of 30 cm (►**Fig. 1**). The procedure was carried out with a dental chair's HVE suction system, which provided at the HVE hose while saliva ejector was also active a relative negative pressure of 143 mbar measured by a vacuum meter (Thyracont VD81, Thyracont, Passau, Germany) and an air flow of 240 liters per minute (DURR ROTA 84.4000 SW N4 10× flowmeter, Dürr systems, Bietigheim-Bissingen, Germany). The sole difference between the control and the OBF group was the static device connecting the HVE system with the patient's mouth, during a dental hygiene two hands procedure, with the OHP keeping the intraoral mirror in the left hand while scaling with the right hand.

Patients were randomized 1:1 to use or not the OBF device. The study primary outcome was the total number of RLU from every location of dental environment: operator's face shield, operator's back of the surgical glove, patient's safety goggles, and instrumental table. Secondary outcomes were percentage contamination differences at the different locations between control and OBF groups.

Fig. 1 (**A**) Image of Oral BioFilter device. (**B**) Representative image of professional hygienic procedure.

Sample Collection and Illuminometer Assay

The analyzed surfaces were the instrumental table, the operator's right hand protection (long cuff sterile latex surgical gloves), the patient's safety goggles, and the operator's face shield. They were cleaned with 70% alcohol disposable gauze just before the dental procedure and after taking the samples. Operator's gloves were changed and discarded between patients.

Samples were obtained immediately after dental procedure finalization from the aforementioned surfaces from the patient as well as the operator using a chemically impregnated reagent cotton swab (ATP Test Swab UXL100, 3M, Minnesota, United States) for ATP assay. Areas measured consisted in 100 cm^2 on the surface of the face shield, patient dental goggles, OHP back of right-hand glove, and instrumental table.

All samples were obtained by a second operator, also provided with the adequate protective equipment. The ATP bioluminescence assessment was performed as described by Sanna et al.,[11] by using a Lumitester (3M Clean-Trace LM1, 3M, Minnesota, United States) according to the manufacturer's instructions.

Biocontamination levels, expressed in relative light units (RLUs) which in turn are a function of ATP concentration, were recorded. An RLU level <150 units was considered as clean; RLU levels ranging from 151 to 300 were considered as acceptable, and an RLU level >300 was considered as a failure of the cleaning protocol, a threshold based on the report by Ho et al[21] as well as the manufacturer's recommendations.

Statistical Analysis

Variables were described by using summary statistics as median, minimum, and maximum values and splatted by group (OBF and control). The Shapiro–Wilk test was used to check normality of transformed data.

The potentially contaminated areas (100 cm^2) were measured on the surface of the operator's face shield and back of the right-hand glove, the patient's goggles, and the instrumental table. After the natural logarithm transformation, a centered distribution was reached (Shapiro–Wilk $p = 0.5447$ for OBF and $p = 0.8553$ for control groups).

Primary outcome, total RLU, was analyzed by comparing the means of logged data, using a two-sided two-sample *t*-test. Conclusions were drawn in terms of percentage of reduction as ratio of $(GM - 1) \times 100$, where GM was the geometric mean and their confidence intervals.

Power calculation was performed taking into account a previous pilot study (data not shown), in which a coefficient of variation on the original scale of 12 was obtained, then a two-sided two-sample *t*-test with 20 subjects per group and significance level of 0.05 achieved 94% power to detect a ratio of geometric means of 0.08 or reduction of 92% when using OBF.

Secondary outcomes as RLU of logged data for the different locations were analyzed in the same way. Proportion of patients from whom different locations reported events (clean, acceptable, and failure) were analyzed by using

Fisher's exact test. A natural logarithm transformation was applied for total RLUs and for every location due to the extremely asymmetrical distribution of data.

Randomization list and power calculation were performed with PASS 2020 (PASS 2020 Power Analysis and Sample Size Software (2020). NCSS, LLC. Kaysville, Utah, USA css.com/software/pass) and data management and statistical analysis with STATA 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, Texas, United States: StataCorp LLC).

Results

The study was carried out on May and June 2020. In total, 40 patients were included 16 males and 24 females, with a mean age (standard deviation) of 45.6 (16.4) years and 40.6 (13.7) years, respectively.

The mean RLU values and the difference between groups (total and by each location) are shown in ►**Table 1**, indicating the percentage of reduction using OBF with respect to control. For the whole dental environment, the percentage of reduction in RLUs achieved with OBF was 98.4%; this reduction ranged from 97.4 to 99% in the 95% of the cases (►**Table 1**). Regarding the analysis by locations, the use of OBF showed different percentages of reduction in RLUs ranging from the maximum, a 99.6%, in the OHP face shield, to a minimum (83%) in the instrumental table (►**Table 1**).

Regarding the three cleaning levels according to the RLUs values, high differences were also found favoring OBF group in all measured locations (►**Table 2**). The control group reported a very high percentage of failures, being the 100% in the surfaces nearer to the patient's mouth and decreasing to 70% in the instrumental table. In contrast, the higher percentage of failures in the OBF group was found in the patient's goggles (40%), while the OHP face shield showed a complete absence of particles as revealed by RLU counts.

The results of the present study are consistent in proving that the use OBF device reduces the bioluminescent droplet and splatter particles and splatter produced by dental procedures. The grouped results showed a 98.4% of whole dental environment contaminant reduction.

Discussion

In general dental practice, the use of face seal masks was recommended to reduce the exposure to aerosolized microorganisms such as *Mycobacterium tuberculosis*.[22] Influenza or SARS-CoV virus may be also shed into the environment and environmental surfaces and transferred to hands of patients and health care providers[23] as well as form airborne particles.[3,7] The pandemic has made more evident the need for masks since SARS-CoV-2 has been consistently detected in the saliva of COVID-19 patients.[4,24,25] In two recent reports, Zemouri et al[7,12] have reported that the highest transmission possibilities estimated in a dental clinic were for measles virus (100%), followed by coronaviruses (99.4%), influenza virus (89.4%), and *M. tuberculosis* (84%).

The detection of biological contamination in dental clinics provides useful information to promote directed hygienic measures and avoid biohazard transmission. The ATP levels (ATP bioluminescence assay) detected on surfaces and equipment showed a positive correlation with bacterial contamination in dental practice.[12] Bioluminescence has not proven to date a direct correlation between viable microbial counts and detected ATP levels.[9,13] However, ATP-bioluminescence is a valuable tool for determining the efficiency of cleanliness procedures as well as to distinguish between live and dead

Table 1 Comparison between groups for total relative light unit and by locations for logged data

Location	Mean	Difference	Reduction (%)[a]	95% CI	*p*-Value
All					
OBF	6.62	−4.15	98.4	97.4–99.0	<0.001
Control	10.77				
Face shield					
OBF	4.33	−5.46	99.6	99.2–99.8	<0.001
Control	9.79				
Surgical glove					
OBF	5.31	−3.69	97.5	94.7–98.8	<0.001
Control	9.00				
Patient safety goggles					
OBF	5.63	−2.76	93.7	86.3–97.1	<0.001
Control	8.39				
Instrumental table					
OBF	4.42	−1.77	83.0	66.1–91.6	<0.001
Control	6.19				

Abbreviations: CI, confidence interval; GM, geometric means; OBF, oral biofilter.
[a]Reduction: (ratio of GM − 1) × 100.

Table 2 Counts of occasions with clean, acceptable, and failure events by locations

Location	Clean (RLU < 150)	Acceptable (RLU = 150–300)	Failure (RLU > 300)	*p*-Value
Face shield				
OBF	15 (75)	5 (25)	0	<0.001
Control	0	0	20 (100)	
Surgical glove				
OBF	8 (40)	5 (25)	7 (35)	<0.001
Control	0	0	20 (100)	
Patient safety goggles				
OBF	6 (30)	6 (30)	8 (40)	<0.001
Control	1 (5)	0	19 (95)	
Instrumental table				
OBF	15 (75)	4 (20)	1 (5)	<0.001
Control	4 (20)	2 (10)	14 (70)	

Abbreviations: OBF, oral biofilter; RLU, relative light unit.
Note: Data are expressed as counts (%).

cells,[13] but it is not efficient in detection environmental, not cell-bound ATP and viruses.

Using ATP bioluminescence, Watanabe et al reported significant higher values of contamination and splatters in surfaces produced by droplet and splatter in operator masks, goggles, chest, and gowned right arm after dental procedures.[4] Zemouri et al[7,12] estimated that, even if the contamination due to droplet and splatter may be low in a dental clinic, the highest level of contaminated particles is to be found within 80 cm around the head of the patient because the droplet and splatter produced by oral health treatments may contain a similar number of pathogens as compared with coughing and sneezing. Although the exact numbers of viral pathogens in droplet and splatter are not known to date, Zemouri et al[7] as well as Prather et al[26] suggest that SARS-CoV-2 is spreading in droplet and splatter exhaled by highly contagious, nonsymptomatic individuals.

It is important to remark that although our study has focused in assessing the novel OBF device efficacy for cross-contamination reduction; personal protective equipment such as face shield, mask, goggles, and surgical gloves; and protective measures are still fundamental elements to mitigate infectious risks. Several studies have shown how such protective gear coupled with a reasonable dental equipment use are important to prevent infections.[27,28]

In our study, the impact of using a OBF device was assessed by using the same biological detection assay used by Watanabe et al,[4] in patients after a standard dental hygiene procedure. Since patients both groups of patients were submitted to the same standard procedure that includes a 0.2% povidone iodine mouthwash for 1 minute, the ATP bioluminescence measurement was aimed to detect and localize the biological cross-contamination, be that constituted by living or dead cells and particles. We observed a significant decrease, around 98.4%, in whole dental environment contamination with the use of OBF. Our results corroborate the risk of biological cross-contamination by droplet and splatter described by Watanabe et al[4] and Zemouri et al[7,12] in operator's and patient's protective gear, thus demonstrating the utility of bioluminescence to assess the reduction of droplet and splatter spreading by using OBF. The limitation of our study is that bioluminescence, despite being able to identify living microorganisms, such as bacteria, dinoflagellates, and fungi, does not detect the presence of viruses.[13]

Despite reports of measurable droplet and splatter reduction have encouraged the HVE use in routine dental practice while working with four hands,[29] other authors did not find neither significant droplet and splatter counts decrease nor environmental contamination reductions unless the HVE aspirator was subject to modifications.[30] In our study, the OBF device as provided by the manufacturer was attached to the standard HVE hose while permitting the OHP to operate with two hands without assistant. A much improved reduction of droplet and splatter dissemination was evidenced, when compared with the control group, that do not used the HVE device because is incompatible with the use of an intraoral mirror in two hands work. Moreover, we wanted to corroborate the dispersion distance of particles Watanabe et al found in their study[4] and to analyze the effectiveness of the OBF device against the total spread of droplet and splatter particles. For this reason, further analysis of the droplet and splatter reduction in four hands work, where the operator's dental assistant will handle the HVE and the saliva ejector, while the operator will continue to use ultrasound and the intraoral mirror are planned.

Watanabe et al reported that the surface with the highest contamination levels was in the patient's safety goggles,[4] while Zemouri et al found the highest bacterial contamination on the patient's chest area.[12] Previous studies highlighted that eye infections are common among dentists,[31] which risk being also signaled for SARS-CoV-2 both for general population[32] and for dentists. Moreover, blood

or saliva contained in the splatters could produce infection and corneal epithelial exfoliation, conjunctivitis, and keratitis.[33] With the use of OBF, the droplet and splatter reduction achieved 97.3% in patient's goggles and 99.6% in OHP's face shield, thus providing an extra protective measure against ocular cross-contamination.

The OHP's hand is the surface closest to patient's mouth; therefore, a contamination of this surface is common in clinical practice. The use of OBF promotes a reduction of contamination on the surgical gloves of 97.5% versus control group (without OBF). This result demonstrates that OBF could also enhance the prevention of biological cross-contamination in high-risk airway management procedures[34] as well as in orofacial aerosol-generating procedures also usual in head and neck surgery,[35] otolaryngology,[36] and anesthesia.[37] Although this noticeable decrease represents an improvement of the cross-contamination control, for safety purposes, adopting updated guidelines on infection prevention[7,12,38,39] is still mandatory.

It is interesting to note that the lowest percentage of the contamination reduction achieved with the OBF device was found in the instrumental table (83% reduction of biological contamination) located at a distance of 1 m from the patient which agrees with the 80 cm distance reported by Zemouri et al.[7] At first glance, despite being statistically significant, such reduction highlights the difference between 70% unacceptably contaminated surface cases (control group) down and just 1% (OBF group; $p < 0.001$). On the other hand, particles sized between 1 and 4 microns expelled by patients just by breathing have the potential of lingering in the air[7,26] and may be displaced by airflows and deposited on equipment.[40] This result is relevant as the material placed on the instrument table should be preserved in the cleanest possible condition after being unpacked, so further measures have to be taken to avoid cross contamination on this area.

The significant difference among RLU measures between both groups (OBF vs. control; 6.62 vs. 10.77 [difference = −4.15]; $p < 0.001$) confirms that the major effect of OBF is for the OHPs. When proper infection control measures are used, the chance for the patient to become contaminated by microorganisms from the previous patient is substantially limited. Therefore, only in the event that these standard measures failed due to human error, we can consider that the device adds extra protection to the next patient. The device does not remove the infection risk but reduces the cross-contamination risk by limiting the droplet and splatters.

Taken together, these first results show a significant reduction of cross-contamination on oral health operatory surfaces by using the OBF device as well as relevant information about which specific surfaces require additional hygienic measures to ensure patient's and OHPs protection.

In conclusion, to our knowledge, this is the first study that uses a specific device designed to reduce the biological cross-contamination in routine oral health practice. It is important to remark that OBF device provides a much improved protection, but it is no substitute to other protective measures such as face shield and mask, goggles, and surgical gloves which must still be considered mandatory.

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Conflict of Interest
None declared.

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Chapter 5: Dental equipment for long-term missions

This chapter should serve as the germ of a future healthcare facility that includes a dental module to provide the physical basis to establish a specific and realistic dental intervention protocol in future space long-term missions and the Mars settlement.

Plausible solutions to the observed dental events exist. For example, caries and endodontic problems can only be solved by placing on-site dental services with qualified personnel, either a dentist or specifically trained crewmember. Third molar problems could be solved by extraction during the previous dental screening, thus eliminating the inherent risk. On the other hand, the fact that periodontal problems are the second most common dental problem in long-term isolation conditions suggests that such a prolonged period of time affects dental hygiene and is probably aggravated by the astronauts' diet. That situation would be easily solved by training the on-board medical officer in oral hygiene procedures to care for the crew. The use of discharge splints in a routine way would diminish the bruxism secondary to the stress in different conditions, thereby diminishing the incidence of dental fractures not secondary to caries as well as the incidence of joint and occlusal problems. We believe that with these measures the incidence of dental events observed in isolation and confinement conditions could diminish between 23.8% and 44.1% (36).

The healthcare facility must contain the necessary equipment capable of housing oral as well as general health procedures in long-term missions. Among the requirements, an adequate multi-purpose equipment for diagnosis and for material sterilization is essential, added to an especially equipped laboratory for manufacturing dental treatment and other 3D printed devices. The healthcare module walls must be painted with light tones of reflective paint made with inorganic oxides that are 65% UV reflective, which constitutes the standard for dental operating rooms.

In addition, it must be equipped with OBF® to limit the dispersion of saliva and blood drops out of the oral cavity and a ventilation and air filter system designed to purify the environment inside the module to prevent the dissemination of oral pathogens, thereby avoiding cross-contamination. For obvious safety reasons, this ventilation system must be separated from the one serving the rest of the spacecraft.

Despite of the low number of dental problems reported in previous manned space missions, (i. e., none in Apollo missions), 5 of the 33 Apollo astronauts needed dental treatment during the 3 month pre-flight period (62). In the same manner, in Salyut and MIR missions, loss of fillings and crowns and dental caries were reported (55, 63). This

low incidence is by virtue of the previous exhaustive dental examination (55). Nevertheless, the probability of a dental problem increases with the mission's duration and with the growing number of crew members, especially in future missions aimed to colonize the Moon or Mars (57, 64). Also, bone deficits in mandible and changes in teeth morphology and composition observed in some studies, may act to increase the risks of fractures and caries progression. Therefore, a healthcare module ready to treat oral pathologies will be needed to treat caries and fractures (65).

The necessary equipment for diagnosis and for sterilization is based on routine clinical practice. Because of the lack of space dental modules and dental equipment to treat people in air due to the short durations of conventional airflights, the module is based in the dental equipment of military ships (8) and on what Häuplik-Meusburgeret al. exposed about dental treatment during a human Mars mission with remote support and advanced technology (63).

The mission to Mars, with the current technology, will require between 18 and 24 months. It will be the longest voyage in isolation conditions to date. The missions of more than two years of duration will correspond to colonies to be established on the Moon or Mars, although probably the personnel will be replaced along the mission duration. However, with time, these personnel will stay at least two years, since orbit missions in the space agencies of the ISS have lasted more than 300 days. Consequently, the present study proposes to divide the dental treatment requirements into two levels, corresponding to missions lasting until two years and missions planned for more than two years.

Dental treatment requirements for two-year missions

Equipment for sterilization

An autoclave for hot steam sterilization under pressure could be a good option for the sterilization of surgical material in the pressurized conditions of a spacecraft, since it only needs water -that can be provided by the recycled water system- and electrical energy produced by solar panels and the spacecraft generation systems.

Another option could be the ozone-based sterilization technology system Microgravity Science Glovebox (MSG) developed for the ESA to be installed on board at the ISS. MSG is a hermetically sealed incubator where experiments in the field of material

science, biotechnology, fluid science, combustion science and crystal growth research can be conducted in a close and protected environment. In order to avoid cross-contamination the Glovebox needs to be sterilized between the experiment runs. The classical approach of hot pressurized steam cannot be applied inside MSG due to technical reasons and safety considerations. Therefore, another technical solution to sterilization was required. The advantage of ozone is that it decays into pure oxygen after 20 minutes at room temperature and leaves no moisture behind (66, 67). Portable ozone sterilization devices developed for cleaning small-sized delicate dental instrumental, demonstrate total elimination of *Pseudomonas aeruginosa* within 10 min, inactivation of *Escherichia coli* after 20 min of treatment, and *Staphylococcus aureus* after 30 min of treatment (67).

Equipment for diagnosis:

The basic and necessary diagnosis equipment must include: Google Glass® with a camera, for visual exploration of fractures and caries in order to transmit Earth, a situation observed in case of a dentist is absent; intraoral scanner and intraoral cameras to confirm diagnosis from Earth; dental pulpovitalometer and cold test to determine pulp vitality; articulating paper; periodontal probe; Digital Imaging Fiber-Optic Trans-Illumination (DIFOTI) instrument; ultrasound; portable X-ray and Cone Beam Computed Tomography (CBCT) only for cases of extreme need

The use of radiation-based technology should be avoided as much as possible given that one of the great problems of space exploration is the management of the ionizing radiation received by astronauts.

Ultrasonography (US), a noninvasive, non ionizing, inexpensive, and painless imaging tool could be an alternative. US has been investigated for its capability to identify carious lesions, tooth fractures or cracks, periodontal bony defects, maxillofacial fractures. It has been used as a diagnostic aid in temporomandibular disorders, implant dentistry, and to measure muscle and soft tissue thickness (68). It constitutes a very useful diagnostic tool for many other medical situations to be cared for in space condition.

The use of Google Glass or a similar device in surgical settings is of particular interest due to the potential of the hands-free device to streamline workflow in an operating room environment (69). This device will serve as a head-mounted wearable with

several “apps”. It will provide information on the steps to be followed in each treatment or information to transmit to Earth what you observe on real time to obtain a second opinion about the diagnosis or procedures to be followed, although sometimes the delay in communications could be a limitation in urgent procedures (70).

A recent systematic review showed that Google Glass, despite their technical limitations, are well received in surgical settings due to its potential for training, consultation, patient monitoring, and audiovisual recording (69).

Preventing temporomandibular joint disorders:

Although there is not enough information on dental prevention in space, it has been reported that fractures and other joint disorders in the jawbone are more prevalent in simulated microgravity compared to Earth’s gravity (28). Hence, the use of splints could be an option to prevent jaw and dental movement. In this sense Häuplik-Meusburger, et al., reported that it is more likely that trauma and stress-induced bruxism will become the main causes for dental problems due to the previous screening and the exhaustive dental hygiene during the mission (63). Moreover, it has been recently described that splints are an efficient tool for decreasing the pain commonly associated to intra-articular temporomandibular disorders (71).

Periodontics

Prevention strategies such as personal hygiene are the best armamentarium against periodontal problems. However, according to Wolffe's law, bone demineralization in microgravity is to be expected, with the demineralization rate showing losses of 1-2% of bone mass per month in flight (72). The demineralization of the skullbones and teeth that occurs in microgravity could explain the higher prevalence of periodontitis (57).

Surgery (emergency)

Oral emergency surgery is limited to extractions, since pain could be managed with medication. The most common reasons for teeth extractions are non-restorable caries, periapical lesions, periodontal diseases, or trauma; sometimes third molars causing recurrent infections are also to be removed (73). Preventive extraction of third molars is

thus to be considered as one of the mandatory preventive measures to be applied prior to launching the mission (74).

Moreover, several studies have found that the intraoral pressure changes during flight adversely impact the healing process in the early post-extraction period (75, 76). Additionally, after a posterior maxillary tooth extraction, the site should be explored for oroantral communication (OAC); if it is present, an oral health specialist is required to solve it. In this sense, it is relevant to consider that OAC can produce sinusitis and other adverse outcomes (61, 73, 77).

The procedure in case of jaw or teeth fractures is too limited given the risk of maxillary necrosis because of the preventive prescription of bisphosphonates to astronauts. In this regard a recent study concluded that combining exercise with the bisphosphonate prescription may be useful for protecting bone health during long-duration spaceflight (78). However, bisphosphonates predispose the maxillary and mandibular bone to develop osteonecrosis (79). Another study concluded that the prevention of the bisphosphonate-related osteonecrosis of the jaw represents the best method of treatment (80).

Caries and endodontic treatment

First-hand experience

As occurs with joint disorders, it has been reported that dental caries are more prevalent in simulated microgravity compared with Earth's gravity (28). However, only one case of dental caries was reported from the MIR space station which was treated with a temporary filling from an available dental kit (81). Nevertheless, the mission duration increases the probability of event occurrence. Regarding the use of dental composite resins to filling and repairing caries one experiment entitled "*Composite Photopolymerisation for Teeth Repairing"* (56) in the 7th ESA Student Parabolic Flight Campaign 2004 project in microgravity conditions was realized. The investigators were dentistry students with no previous experience in microgravity. Moreover, the material and equipment supplied for the study were the same used in routine dental practice. The results of the polymerization procedure carried out in microgravity were not satisfactory, mainly due to the flight conditions that are different to stable microgravity of international space station. Consequently, we concluded that the filling and repair caries materials have to be adapted to be applied in space conditions.

The injectable composite resin technique is an indirect/direct method that uses a transparent silicone index for an accurate and predictable translation of a diagnostic wax-up into composite restorations without the need for tooth preparation. In this case the material necessary for dental reconstruction are splints flow composite and the usual UV lamp for simple indirect reconstructions, as described by David Geštakovski (82, 83). The 3D model transparent splints of the crewmembers could either be provided before the mission or printed in situ to carry out the restoration, even if the medical officer serving the crew is not a dentist.

Endodontic treatment

The novel concept of guided endodontics has been reported as an effective and easy method to obtain safe and reliable results in root canal treatment (84). The guided approach allows predictable, efficient endodontic treatment with minimal removal of sound dentine and less risk of root perforations (85). Thus, the CBCT and 3D scans of the crewmember's dentition must be included in their respective medical documentation, to be used by the Earth dental team to design an endodontic splint guide if required. Then, the medical crewmember will print the device that provides insertional angle, root canal localization and working length to carry out the endodontic procedure.

Advanced dental treatments for missions longer than two years

Prosthesis and dental implant

Regarding long-term missions, it would be mandatory to obtain all dental models of the crew members for their eventual substitution by means of dental implants. Although there is no experience in space missions, dental implant rehabilitation, for example, is mandatory for German Air Force pilots due to the resultant improvement in phonation, nutrition, and well-being, thus avoiding causes for incapacitation in crew members (73, 86).

The equipment necessary to carry out would be a 3D intraoral scanner, as well as a 3D printer or Computer-Aided Design Computer-Aided Manufacturing (CAD-CAM). However, since the dental product has to be adapted to the patient's needs and, in normal conditions, it is usually inserted by the dentist (63), it is necessary that a crew

medical member is trained to solve this situation. As previously described, the procedures for treatment could also be simplified. However, in missions with more members the inclusion of a dentist in the health team is mandatory.

In clinical practice, the quality criteria that must be assessed after implants are placed included: fixation, radiographic examinations, mucous membrane–gingival harmony, occlusion, and articulation (87); thus, these quality criteria must be also adapted to space conditions in order to facilitate the treatment and avoid incapacitation in crew members.

Orthodontics

This dental procedure is thought for the colonizers' descendants. This procedure deals with correcting defects and irregularities of the position of the teeth, and it must be carried out according to routine clinical practice taking into account the space and microgravity limitations. Since systems providing 3D printed splints adapted to the patient's dentition and to the advance of the orthodontic treatment are alredy in use in clinical practice, these could be equally applied in space conditions.

As a conclusion, this dental module design provides the physical basis to establish a specific and realistic dental intervention protocol in future space long-term missions and the Mars settlement. The necessary equipment presented here is the one used in usual clinical practices that in most cases do not need especial adaptations to microgravity conditions. The recent patent device (OBF®) has been demonstrated to avoid the material and salivary dispersion, allowing maintain the aseptic conditions in the module.

It is important to emphasize that dental hygiene and diet are the main preventive measures. Despite this, a routine professional control is necessary to achieve dental health status. Taken together, a dental module must be a reality for the success of future long-term missions and for future human settlements on other planets.

Corollary

Oral prevention through oral hygiene and certain dental treatments, together with the ability to solve unpredictable events in situ, is relevant to achieve success in isolation conditions. There are dental events, a high percentage of which are periodontal problems, secondary to problems with wisdom teeth and secondary to bruxism, which force the evacuation of mission members in isolation or semi-isolation situations.

These events can be avoided or modulated either by standardizing basic periodontal treatment to reduce the level of dental plaque and therefore reduce the chances of periodontal problems requiring advanced treatment, or by preventively extracting wisdom teeth before such missions, or by introducing an unloading splint in the basic sanitary kit of the members of these groups to reduce the pernicious effects at oral level (dental fractures not related to caries, joint pain, pain due to muscular contractures, etc.) of the logically expected increase in the level of stress during long-term isolation missions.

The effects of microgravity in the deterioration of oral health have been proven, but we have also determined that oral problems in people who have been in microgravity conditions can be found in an environment of multiple factors where microgravity, changes in diet, isolation, exposure to ionizing radiation, relative lack of hygiene, among others, converge.

A study was conducted during the COVID-19 pandemic with the OBF® device in which we first determined that the airway, via aerosols, is a critical contamination pathway not only in a medical module in space in isolation conditions but also as we would expect in normal clinical practices in dental clinics on Earth (supported by all post-pandemic studies).

We determined that after 15 minutes of professional ultrasonic dental prophylaxis treatment, all surfaces tested within a 1.5 meter radius indicated a level of contamination deemed intolerable in healthcare facilities. In addition, we found that there is a simple, efficient and cheap procedure to assess the spread of aerosol particles in the surgical area, which proved that the use of the OBF® suction system, specifically designed to prevent the spread of aerosols, is highly effective in minimizing this pathway of cross-contamination.

Discussion

Although beforehand it may seem that the researching aerospace dentistry may be related to a small niche, the reality is that the results of these investigations affect global problems (in this case, those related to oral and dental health), as shown by the diversity of nationalities and institutions that have referred to the results reported by this thesis. Indeed, many of the advances of the space race have served to improve oral health clinical practices. In our case, the development and patent of a suction device (OBF®BioFilter), specifically designed to prevent the spread of aerosols in space, has served to demonstrate its efficacy avoiding aerosol dissemination during the COVID-19 pandemic in routine dental practices.

The main issues of oral health affecting personnel in isolated conditions, as reviewed by Ngan et al. (88) reveal the relationship between oral status and cardiovascular risk in Cameroonian military population. The study concludes that there is a high level of correlation between these two diseases. Four articles of this systematic review report oral pathologies in military population, from which three refer to specific populations from their respective armies (Croatian, Japanese and Serbian) (88). The authors conclude that the higher prevalence of periodontitis in all the analyzed military personnel is to be attributed to the isolation conditions, in agreement with our study. Moreover, they relate the periodontal status with the prevalence of cardiac events in these specific populations, as suggested initially by Cardoso et al. (89).

Moreover, recently, Bárcena García M et al. (90) reported that most of the periodontal health studies carried out in military populations from the 1920s were conducted mainly through cross-sectional observational studies. Their reviewed results show that the assessment of the patients' periodontal status was made using the WHO probe and three indexes: the CPITN periodontal index and the gingival and plaque indexes, both developed by Silness and Löe. They found limitations related to the epidemiological design and/or implementation of such analysis, which may reduce the representativeness of the results and their comparability (90).These results confirm our use of the definition "dental events", which was based on the poor assessment of oral health problems as medical emergencies, despite of the eventual effects of a dental incidence in long-term space missions (36).

The expected incidence in these missions will be even higher than the one described in deployments, mainly because of its extended duration. Moreover, diet monotony, the lack of variety of fresh foods (9), and poor dental hygiene (91), added to microgravity and the limitations of air renewal make maintaining a good dental status difficult. These

added conditions could facilitate the progress of mild dental events to events of greater severity (64) and consequently require an evacuation to a dental treatment facility (92). Such facts explain the need for oral health preventive measures, and the prevision of dental equipment and trained dental personnel to address dental conditions (8, 9) in future manned missions, as described by Thirsk RB (70).

Added to isolation condition, microgravity has been proven to be an important factor in human physiology (64). Although their effects are still unclear and mainly derived from simulated microgravity studies (93), the exposure to microgravity, added to a radiation environment during short and long-duration space missions, has been proven to cause serious effects, mainly to the cardiovascular, musculoskeletal, nervous and stomatognathic systems, among others (64, 70, 94).

Microgravity has been recently proven as the responsible for biological modifications: indirectly, by altering stress biomarkers (95, 96), alterations in the adaptative immune system (reductions in T-cell proliferation and cytokine production, as well as NK-cell function impairment) during long-term spaceflights (97, 98), and directly, by generating metabolic cell stress through the increase of reactive oxygen species (ROS) (99). Moreover, the radiation has a role in the induction of ROS modifying the equilibrium between reduction and oxidation, promoting oxidative damage in biological physiology (100) (Figure 1).

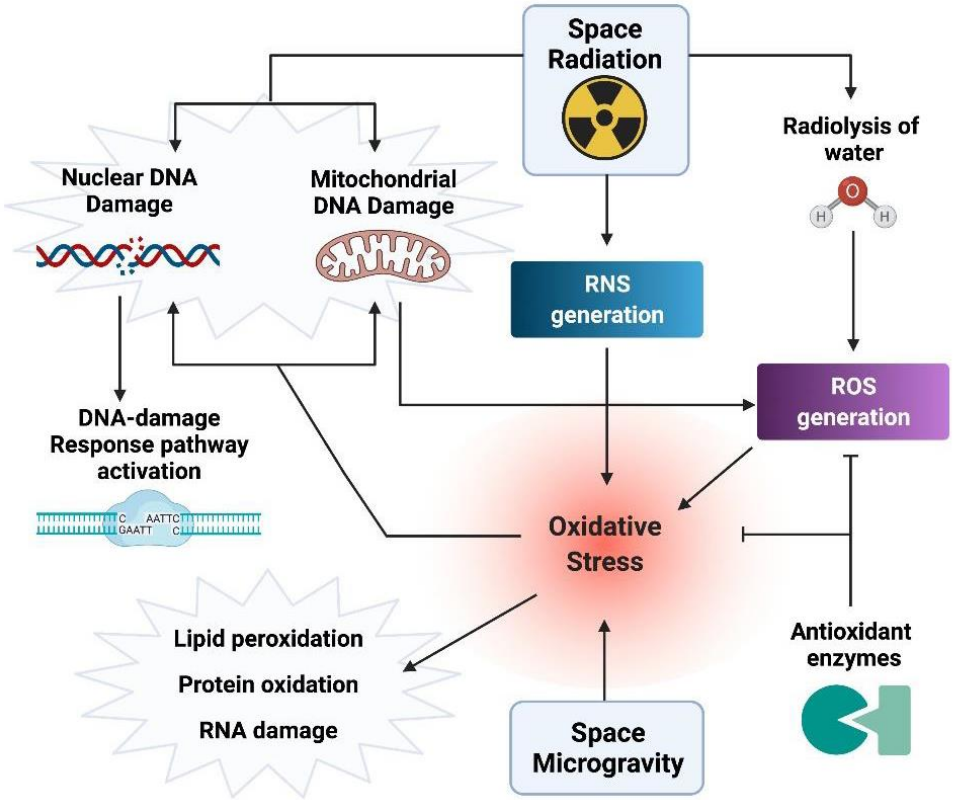

Figure 1. Scheme of the oxidative damage response in the space environment. The space environment is created by a mixture of ionizing radiation of a different quality and by reduced gravity (microgravity). Under these conditions, reactive oxygen species (ROS) are generated by radiation-induced radiolysis and by microgravity, causing oxidative stress leading to cellular damage in the oxidative DNA/RNA damage, lipid peroxidation, protein oxidation, and impairment of antioxidant activity. Reactive nitrogen species (RNS) induced by radiation also participate in the increase of oxidative stress. Once activated, the oxidative damage response interfaces with the DNA-damage Response pathway to counteract the combined effects of radiation and microgravity. Extracted from (101).

To avoid the harmful effects of space radiation in the two types of danger for space exploration (firstly, the risk of not completing the mission and, secondly —but not less important—, maintaining the health of the explorers after their return to Earth), countermeasures for radiation protection should be taken as described by Hellweg CE (102).

A recent review has shown the effects of ROS on the biological processes (Figure 2), proposing antioxidant formulations to be developed for the maintenance and mitigation of the space crew members' deleterious effects (103). This review attributes the cellular damage to the combined effects of microgravity and radiation.

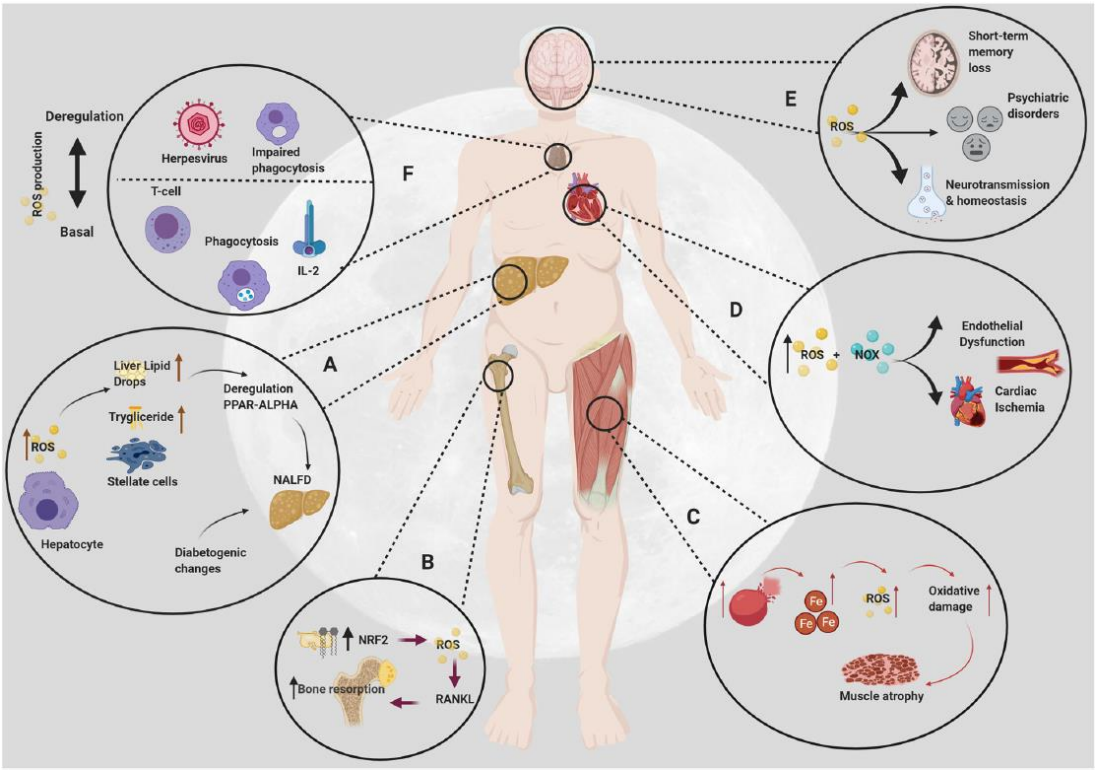

Figure 2. Effects of space missions and ROS on general physiology. **A** high level of ROS can damage hepatocytes. The damage results in increased lipid droplets in the liver, increased triglycerides, and loss of retinoids from lipid droplets in stellate cells, PPAR-α dysregulation, and diabetic changes that can cause NAFLD. **B** Space radiation damages skeletal lipids and increases the activity of NRF2. ROS acts as a second messenger during RANKL activation and differentiation. This increases bone resorption and osteoclastogenesis. **C** Microgravity and radiation can cause red blood cell destruction, which releases iron. The iron then acts as a cofactor in excess ROS production to accelerate oxidative damage and ultimately cause muscle atrophy. **D** Increased production of ROS and NOX leads to endothelial dysfunction and promotes myocardial necrosis. **E** Oxidative damage causes neurodegeneration that can alter neurotransmitters, induce psychiatric disorders, and dementia. **F** The innate immune system requires the production of ROS in the defense of microorganisms within the phagocytic process and the inflammatory response. However, a dysregulation in the production of ROS induces a lower lymphocyte response, impairing phagocytosis and increasing susceptibility to latent infections such as HSV. Extracted from (103).

The space environment is hazardous: psychological stressors (loss of privacy, reduced comforts of living, and distant relationships with family members and friends) interact with biological stressors (microgravity, radiation, alteration of biological process, microbial modifications, etc.) to influence the success of future space human missions (70).

Numerous studies have demonstrated that microgravity can directly stimulate osteoclastogenesis and increase bone resorption in space (25) or in a simulated microgravity environment (72). These findings indicate that osteoclasts and their precursors are the direct targets of mechanical forces. Consequently, the proposed measures to ameliorate bone loss in space missions are resistance exercises, together

with an adequate energy intake (104). However, the underlying mechanism remains unclear (105). In this sense, it is interesting to remark that moderate and severe periodontitis patients were found to have 1.56 to 2.09 times the risk of osteoporosis respectively, compared to patients without periodontitis (106), thus suggesting a potential role of inflammation (periodontitis) in the systemic onset of osteoporosis (89).

There is a lack of knowledge about oral health risks for long-term missions such as Moon missions. This is because in the "Russian program crews health state monitoring in spaceflights" (107) as well as in the NASA program (108), practically, despite all aspects of astronaut physiology: cardiac activity, urea and blood analysis, and even audiometry were monitored, no oral or saliva controls were carried out. The chromato-mass spectrometry method tests confirmed that on the seventh day of flight there is an increase in the microbiota pathogenicity potential; that is, a quantitative increase of conventional pathogens and a decrease in the protective groups (109). Microbiome perturbations during long-term spaceflights should be prevented by prophylactic strategies, such as the reduction of pathogen load in the spacecraft's microbiome and the crew, the latter by microbiome remodelling (110).Therefore, it is surprising that the most complete models of medical supply and astronaut health as the one proposed by Assad A (111) do not contemplate oral pathology or its treatment.

Regarding the above mentioned biological stressors and focusing on oral and dental health status, we found the information about dental events under microgravity for long-term periods to be scarce (112). However, it has revealed several oral health changes related to different microgravity exposition periods, as well as simulated microgravity exposition periods (113, 114), which have common aspects with other confined habitats (115).

A systematic review of Ghasemi S. et al (116) analyzed the potential changes in oral health by secreting specific salivary proteins (salivary biomarkers) during space travel, reaching conclusions similar to ours in which we determined that there is an oral health affectation given the number of dental events described, including the modification of salivary protein secretions, which could significantly worsen oral health.

In fact, Ghasemi S. et al.'s (116) achievements agree with our conclusions: further studies should be conducted in groups of astronauts participating in space missions longer than six months since the existing data are very limited, and refer to short-term

physiological changes under the circumstances of living in a spacecraft and its adverse effects on oral health, which cannot be extrapolated to long-term missions.

Currently, the main line of research in microgravity conditions is focused on its effect on the alteration of the microorganisms present in the human body (microbiome) and in the habitable sites of space environments. In this sense, in 2020 Ávila-Herrera et al. described the microbial profile in the mouth, nose, ear, skin and saliva of crewmembers, as well as eight localizations of the International Space Station (ISS) at different time points (pre-, during, and post-flight) (117). These results showed that skin, nostril, and ear samples are more similar in microbial composition to the ISS surfaces than mouth and saliva samples. Moreover, the microbiome of the surfaces inside the ISS resembles that of the crew's skin, with differences in microbial composition between spaceflights due to different crews (117).

Another study focused on habitable environment of ISS, has isolated and identified four strains belonging to the family *Methylobacteriaceae*, collected from different locations, that were considered novel species belonging to the genus *Methylobacterium* (118). This result suggests that the microgravity and radiation could play a role on the generation of novel species.

Regarding the oral microbiome, the increase in anaerobic microbiota in dental plaque, as well as the increase in *Mycoplasma* in saliva, which produces an increment of dental calculus and a state of gingival inflammation, have been described in studies within long-term missions with simulated gravity in Earth and in studies with astronauts in space stations from Skylab missions in space microgravity (119). The anaerobic microbiota (*Bacteriodessp, Veillonellasp, Fusobacterium sp, Neisseria sp* and *S. mutans*) was already discussed as one of the main causes of dental caries (120) while *Veillonellasp, Fusobacterium sp*and *Bacterioidessp* are related to caries progression (121). *Veillonellasp* in plaque would represent up to 45% in the initial stages of gingivitis or associated periodontitis (122). *Fusobacterium sp* is a direct bacterial pathogen involved in the genesis of periodontitis and other periodontal diseases such as gingivitis, added to various associated factors (122). *S. mutans, S. wiggsiae, P. denticolens*, and *L. salivarius*, were found almost exclusively in plaques collected from dentin carious lesions. But *S. sanguinis* and certain species of *Neisseria* and *Leptotrichia*have been frequently found in plaques collected from healthy tooth surfaces in children (123).

According to Skylab experience, the anaerobic species increase at 56 days in space microgravity (18, 25). On the other hand, later studies in ISS have shown that the microbiome diversity applicable to a single sample (alpha diversity) measure in saliva samples appears to decrease during 120-day flights and rebound after returning to Earth (117). In another study carried out in the same environment to assess the changes in microbial diversity and abundance, this decrease in alpha species was not found (124). Globally, no significant changes in the number or relative abundance of taxa were observed between collection time points, but the individualized analysis of the saliva samples of some astronauts showed significant changes in the relative abundance of taxa during and after space flight. For example, the relative abundance of *Prevotella* in saliva samples increased in two astronauts during time onboard in ISS while the relative abundance of other commensal taxa such as *Neisseria, Rothia,* and*Haemophilus* decreased (124).

Other interesting finding in ISS was the significant increment of several antimicrobial resistance genes within the crew's saliva as an elfamycin resistance gene and a CfxA6 beta-lactamase marker, although the last one returned to normal levels post-flight (124). This suggests that spaceflight conditions could have a role in the growing number of antimicrobial resistance genes, so alternate antibiotics should be included for any treatment as periodontal diseases (124, 125).

On the other hand, antibiotics should be used only if it's absolutely necessary. The crew predicted to show a loss of microbiome species diversity over time, which should be monitored and, if observed, counteracted by long-term regular microbial input (i.e., by food) and reconstitution strategies (i.e., by autologous fecal microbiome transplants [aFMT] and others) (110).

So, despite the results not being conclusive, microbial changes have been observed, and these changes returned to normal after the astronaut returns to Earth, but the information about long-term periods in space suggest a change in the microbiome (124, 125) and the habitable environment with the creation of novel species (118). Other causes related to oral microbiome alterations have been linked to: exposure to disturbing molecules (food ingredients such as sugars, gluten, chlorinated water, antibiotics, and a multitude of chemical products), lack of nutrients that encourage healthy colonies of bacteria (diets deficient in vegetables with fibre or with an excess of saturated fat) and situations that cause and maintain stress, such as the astronaut's stress during missions, confirmed by the increase in cortisol in saliva (126).

Other oral components affected by microgravity are saliva and crevicular fluid that provide nutrients for microbial growth and contain components with antimicrobial activities (127, 128).Salivary proteins include agglutinin, mucins, proline-rich proteins, secretory immunoglobulin A (IgA) (glycoprotein), glucosyltransferase and other substances like salivary cortisol, and salivary alfa-amylase (31). Agglutinin, mucins, and proline-rich proteins affect the oral biofilm formation (120). They can promote microbial adhesion because the salivary film and its constituent proteins bind to the teeth and mucosal membranes (120).

Secretory IgA antibodies from parotid glands or serum IgG derived from the gingival crevicular fluid may influence the accumulation of cariogenic microbiota at various stages of infection (120). In a simulation study of a Skylab mission and in Skylab missions 2, 3 and 4, secretory IgA increased persistently during chamber confinement and reached a maximum level by day 55 of sampling; moreover, there was an increase of *S. mutans* in dental plaque that was related with a high sucrose diet (25, 129). Salivary glucosyltranferase enzymes increase during long-term periods in simulated microgravity. These enzymes are essential for the expression of virulence by *S.mutans* in the pathogenesis of dental caries because of their ability to synthesize glucans from sucrose. The bacterial cell surface protein antigen with glucosyltransferase enzymes could mediate the binding of microorganisms to tooth surfaces (130). Recently, salivary secretory IgA, together with lysozyme, antimicrobial peptide LL-37, and the cortisol-to-dehydroepiandrosterone ratio increased in ISS crew by day 180 before the launch, during the 90 days of the mission and until 66 days after returning to Earth (131). LL-37 has an important role in oral health maintenance; low salivary LL-37 levels in patients with periodontal disease which were associated with the increase of pro-inflammatory cytokine as TNF-α and IL6 expressions have been documented (132), suggesting that space long-term periods increase the probability of presenting oral problems.

The salivary cortisol increment and salivary alfa-amylase may be caused by stress and the activation of the sympathetic adrenomedullary system (31). This increase is in concordance with the progress and severity of periodontitis (133, 134). The intense relationship between stress and oral pathology, as with other systemic pathologies, encourages us to think that, in situations of special isolation such as microgravity conditions, it is necessary to manage stress with regular controls of cortisol in saliva and other, more instant controls, like the facial recognition systems by computer to monitor stress using facial signs (135). Cortisol as an oxidative damage mediator may

contribute to aggressive periodontitis due to the oxidative stress that seems to highly contribute to periodontal pathology (136, 137). In this line of evidence, a study showed that the growth rate of *P. gingivalis* was significantly enlarged after addition of cortisol (138). In a study with six crewmembers (three men and three women) at the Mars Desert Research Station (MDRS) during a short two-weeks period, salivary cortisol, alpha-amylase levels, and current stress scores were shown to be significantly higher after the end of the mission compared to before the start. Plaque levels and incidence of bleeding gums were increased during the mission. The investigators hypothesized that these outcomes were related to stress and improper oral hygiene (139). Similar results were obtained with salivary alpha-amylase in microgravity conditions (31).

Taking into account that the human microbiome plays a significant role in maintaining human health, and that disruptions in the microbiome have been linked to various diseases (124), together with the alteration of the microorganisms presented in habitable locations in long-term missions (118), it would be essential to design a contingency plan and prepare the required dental equipment to prevent a dental urgency caused by these microorganisms.

The recent pandemic caused by SARS-CoV-2 (COVID-19) has brought into focus one of the initial bases of our research: the previously neglected aerosol transmission pathway, which has been a determining factor in the explosive expansion of this pandemic. Suwandi T et al (140) analyzed the efficacy of high-volume evacuators (HVE) and extraoral vacuum aspirators(EOVA) during the COVID-19 pandemic, in reference to the reduction of aerosols and microdroplets created during the professional dental hygiene procedure based on ultrasound.

This study compared different procedures: a saliva ejector was used alone as the control, to be compared with the same device in combination with HVE, and in combination with HVE and EOVA. The study included cross-contamination received by the operator and the assistant (Figure 3).

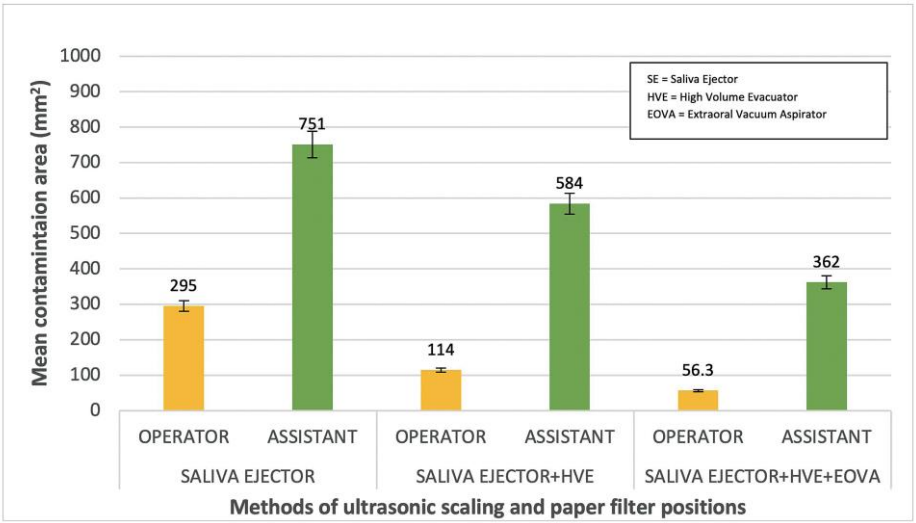

Figure3. Means of the contamination area according to scaling groups and paper filter positions. EOVA, extraoral vacuum aspirator; HVE, high volumen evacuator; SE, saliva ejector.

The study concluded that the usage of HVE and EOVA significantly reduced aerosols and droplets compared with solely using the saliva ejector. These techniques together could prevent the transmission of airborne diseases during dental cleanings, especially COVID-19 (140).However, the results for all the groups studied are substantially worse (140) than those found by us with the use of the OBF® device (141). At the same time, it is interesting that the contamination data on the assistant are significantly worse than on the operator (140). These divergences in the results are fully understandable by the fact that the OBF® device generates an air curtain and a negative intraoral pressure that pushes the particles created inside the mouth into the suction section of the device or, failing that, sends them back into the oral cavity, thus separating the inside and the outside of the mouth, while using simple aspiration has very different effects on the aerosols and microdroplets produced inside the mouth.

Chemical and bacterial contamination could lead to oral health alterations in a confined and isolated habitat, and therefore will require specific treatment and prevention protocols. In the case of dental problems that require surgery treatment, the dissemination of pathogen microbiota is a real risk. For this reason, the development of the OBF® device to specifically mitigate cross-contamination by droplets and splatter (aerosols) is aimed to effectively stop transmitting infections. In general dental practice, the use of protective measures is mandatory to prevent infections (142). The transmission of virus and bacteria in environment is mediated by contact surfaces (143) as well as from airborne particles (37, 144). The use of bioluminescence to detect biological contamination in different surfaces of the dental facility provides useful information to promote hygienic measures and avoid biohazard transmissions, and

then to detect a pattern of contamination to be applied in future health and dental space facilities, despite the possibility of the dissemination being altered due to microgravity conditions. Our results (141) confirmed those of a previous study that reported significant higher values of contamination and splatters after dental procedures in operator masks, goggles, chest, and gowned right arm, produced by droplet and splatter (43), also by means of a bioluminescence system, which is thus proven as a good method to detect cross-contamination due to aerosols.

Conclusions

This thesis aimed to stablish the basement to develop a scalable healthcare module, capable of housing a treatment center for dental and general pathologies with adapted equipment, for future manned missions to the Moon, Mars and other long-term space missions. The hypothesis and the proposed objectives have been confirmed and achieved, respectively. The main conclusions can be summarized as follows:

- Dental incidence in long-term isolation conditions may seem relatively low, but it is factual and it is relevant. Oral health events are mainly unpredictable and related to caries and secondary decay events, followed by periodontal pathologies and third molar pathologies. Most are due to a poor dental status, and dental hygiene as well as to the lack of fresh and varied food, added to specific conditions from space missions.

- Microgravity affects the oral and systemic health status during space missions. In short-term space missions in microgravity condition, physiologic changes such as the increase of IgA and salivary α-amylase and changes of the microflora have been observed.

- Oral health alterations could jeopardize the success of long-term space missions by causing oral and systemic pathologies. In long-term space missions, it is mandatory to adopt specific preventive measures, train personnel to treat oral health events and employ special equipment. The use of preventive measures and previous screenings considerably reduce dental incidence rates. The self-dental hygiene and the diet are the main preventive measures, but routine professional control is necessary to achieve an optimal dental health status.

- The aerosol cross-contamination is a risk of infection in isolated conditions as long-term space missions. In case of dental event or procedure, OBF® devices have shown a significantly efficient reduction of biological aerosol cross-contamination during routine dental procedures. OBF® devices provide a much improved protection but it is no substitute to other protective measures such as a face shield and mask, goggles and surgical gloves, which must still be considered mandatory.

- The dental module design provides the physical basis to establish a specific and realistic dental intervention protocol in future space long-term missions and the

Mars settlement. Implementing the space dental module must be a multidisciplinary project involving engineers, physicians, pharmacists, chemists, biologists, astronauts, cosmonauts, etc., based on the expertise and experience of dentists and on the evidence shown in documents such as this thesis.

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Annexes

UNIVERSITAT DE BARCELONA

Oficina de Gestió de la Recerca
Pavelló Rosa (recinte Maternitat) primer pis
Travessera de les Corts, 131-159 93-4035398
08028 Barcelona

COMISSIÓ DE BIOÈTICA

En Albert Royes i Qui, Secretari de la Comissió de Bioètica de la Universitat de Barcelona

CERTIFICA

Que analitzada la sol·licitud presentada pel Sr. Victor Lloro Boadas, doctorand en el departament de Patologia i Terapèutica Experimental , de la Facultat de Medicina, i referent a la Tesi intitulada **"Salud oral en misiones espaciales de larga duración: experiencia previa, necesidades de prevención y tratamiento. Propuestas de diseño de un equipamiento dental aeroespacial"**, dirigida per la Dra. **Maria Cristina Manzanares Céspedes,** aquesta Comissió, per acord de data 8 de juny de 2020, va aprovar informar favorablement des del punt de vista bioètic, la realització de l'esmentada tesi.

I perquè en quedi constància a tots els efectes, signa aquest document, amb el vist i plau del President de la Comissió, a Barcelona el 9 de juny de 2020.

Universitat de Barcelona
Comissió de Bioètica

Vist i Plau
El president de la Comissió de Bioètica de la Universitat de Barcelona

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UNIVERSITAT DE BARCELONA

Odontologia
Facultat de Medicina i
Ciències de la Salut

Resolució del Vicedegà d'Odontologia de la Facultat de Medicina i Ciències de la Salut, per la qual es fa pública la concessió dels ajuts de la XXIII Convocatòria per a la recerca per a estudiants de doctorat i/o postgraus i màsters de la UFR d'Odontologia-2020.

Per resolució del Vicedegà d'Odontologia de la Facultat de Medicina i Ciències de la Salut, per delegació del rector d'aquesta Universitat, s'ha convocat la XXIII Convocatòria d'ajuts per a la recerca per a estudiants de doctorat i/o postgraus i màsters de la UFR d'Odontologia 2020.

Atesa la proposta formulada en data 29 de setembre de 2020 per la Comissió Tècnica nomenada per examinar i avaluar les sol·licituds presentades.

D'acord amb la clàusula 9 de la convocatòria d'aquests ajuts

RESOLC:

Primer.- Fer pública, en annex 1 adjunt, la llista de les persones beneficiàries d'aquests ajuts amb indicació de la quantitat atorgada.

Segon.- En el termini de 10 dies des de la publicació d'aquesta resolució d'adjudicació de l'ajut, els beneficiaris hauran de lliurar a la Secretaria d'Estudiants i Docència de la Facultat de Medicina i Ciències de Salut-Campus Bellvitge, amb cita prèvia o per instància genèrica, el document d'acceptació de l'ajut, d'acord amb el model que s'adjunta com annex 2.

El Vicedegà d'Odontologia,

Dr. Josep Maria Ustrell

L'Hospitalet de Llobregat, 30 de setembre de 2020.

UNIVERSITAT DE BARCELONA
Facultat de Medicina i Ciències de la Salut
Campus Bellvitge
Secretaria d'Estudiants i Docència

D'acord amb l'establert per l'article 112 de la Llei 39/2015, d'1 d'octubre, de procediment administratiu comú de les Administracions Públiques, contra aquesta resolució, que és un acte de tràmit no qualificat, no es pot interposar cap recurs, sens perjudici de l'establert a la part dispositiva d'aquesta resolució, i que les persones interessades pugin interposar els recursos corresponents vers la resolució per la que s'aprovi la llista definitiva de persones admeses i excloses.

1

ANNEX 1

Llistat de persones beneficiàries i quantitat atorgada dels ajuts de la **XXIII Convocatòria per a la recerca per a estudiants de doctorat i/o postgraus i màsters de la UFR d'Odontologia-2020.**

Nom i cognoms	Import de l'ajut
RITA MIGUEL DUARTE CENTENO RAPOSO	2.532,00 euros
BLANCA GALLARDO BURGUET	1.570,00 euros
GUILLERMO GALVÁN LOBO	2.532,00 euros
VÍCTOR LLORO BOADA	2.532,00 euros
GEMMA PUERTA LÓPEZ-PASTOR	2.509,00 euros
MIGUEL ROMERO ALVES PESSANHA DE ANDRADE	325,00 euros

ANNEX 2

ACCEPTACIÓ DE LES OBLIGACIONS DELS BENEFICIARIS DELS AJUTS

Dr./Dra. ....., com a tutor/a de l'alumne/a sol·licitant de l'ajut .....**faig constar** que el departament en el qual estic adscrit es farà responsable de l'ajuda econòmica, en cas que l'alumne/a beneficiari/ària no compleixi les obligacions esmentades en el punt 10 de la XXIII Convocatòria d'ajuts per a la recerca per a estudiants de doctorat i/o postgraus de la UFR d'Odontologia 2020.

Vist i plau

Tutor/a responsable

Director/a del Departament

L'Hospitalet de Llobregat, ... de ..... de 2020.

Ajuntament de Barcelona

Barcelonactiva

ESA BIC Barcelona
Negotiation meeting – Minutes of the Meeting
ASTRADENTIUM

Participants	Iván Lloro Víctor Lloro Joan Bardera
ESA BIC Barcelona	Mr. Jorge Fuentes – ESA BIC Barcelona Manager Mr, Martí Foz – Business Advisor
Date	12.09.2014
Time	10:00
Location	Barcelona Activa – Glòries

INTRODUCTION

DISCUSSION/CLARIFICATION OF TECHNICAL ISSUES

- TEB RECOMMENDATIONS:

- The TEB recommends support in exploring the market, what is needed to do a test, produce samples, review the financials.

- The TEB recommends to work further and review the funding needed, especially the expenses seem to be underestimated and also the process to validate the product (clinical test, pre-production and certifications needed).

- The TEB recommends checking the scheduling of the critical tasks and their feasibility in the time allocated in the proposal.

- WORK PACKAGES AND GANTT CHART

- The work packages were properly defined in the proposal, assuming that month one starts at the moment of the signature of the incubation contract.

- Technical support from UPC. The technical support from UPC and business support from Barcelona Activa side will be established progressively according to the evolution of the company.

- The company commits to the quarterly reporting.

- The company is planning to be installed in a 30m2 office.

esa business incubation centre Barcelona

Ajuntament de Barcelona

Barcelonactiva

DISCUSSION/CLARIFICATION OF CONTRACTUAL ISSUES

- Documentation is already sent but some documentation is still missing.
- The incubation contract is still in progress and about to be signed.
- Company is already established.

DELIVERABLES AFTER INCUBATION

- Technical Deliverable: demonstrator in scale showing the product.
- Business Deliverable: Updated Business Plan.
- Marketing material (brochures, flyers, ppt, video, etc.)

SIGNATURE OF THE MINUTES OF THE MEETING

Barcelona, 12.09.2014

ESA BIC Barcelona

Mr. Jorge Fuentes

Mr. Víctor Lloro

Mr. Iván Lloro

Mr. Martí Foz

Mr. Joan Bardera

esa business incubation centre Barcelona

INCUBATION CONTRACT

Between:

Barcelona Activa SAU SPM,
Tax Code (CIF) A-58295296.
(hereinafter called "Barcelona Activa"),
located at: Llacuna, 162-164. 08018 – Barcelona. Spain

Through the ESA Business Incubation Centre at Parc Mediterrani de la Tecnologia, RDIT Building. Esteve Terrades, 1. 08860 – Castelldefels. Barcelona. Spain.
(hereinafter called "ESA BIC Barcelona"),

Represented by Mr. Jordi Joly i Lena, its Chief Executive Officer,

of the one part,

And:

ASTRADENTIUM HEALTH TECHNOLOGIES, SL
Whose Registered Office is at:
Esteve Terrades, 1 . 08860 Castelldefels (Barcelona)

Whose Trade Register Number in Spain is: B66361858

(hereinafter called the "Incubatee")

Represented by, Mr. Ivan Lloro Boada, with Passport Number 47643200B, its President.

CONTRACTE D'INCUBACIÓ

Entre:

Barcelona Activa SAU SPM
CIF A-58295296
(en endavant "Barcelona Activa"),
situada a: Llacuna, 162-164, 08018 Barcelona

A través de l'ESA Business Incubation Centre situat al Parc Mediterrani de la Tecnologia, Edifici RDIT, Esteve Terrades, 1, 08860 Castelldefels,
(en endavant "ESA BIC Barcelona"),

Representada pel senyor Jordi Joly i Lena, que n'és el Conseller Delegat,

per una part,

i

ASTRADENTIUM HEALTH TECHNOLOGIES, SL
Amb seu fiscal a:
C/Esteve Terrades, 1. 08860 Castelldefels (Barcelona)

Amb CIF espanyol: B66361858

(en endavant, l'"Empresa Incubada"),

Representada pel Sr. Ivan Lloro Boada, amb NIF 47643200B que n'és President.

Ajuntament de Barcelona
Àrea d'Economia, Empresa i Ocupació
Barcelona Activa SAU SPM

Ajuntament de Barcelona

of the other part,

(together, hereinafter referred to as the "Parties" or individually as a "Party")

Commencement Date: 1st of November 2014
Contract End Date: 31 of October 2016

the following has been agreed:

per l'altra part,

(junts, en endavant anomenats les "Parts" o individualment com a "Part")

Data d'inici: 1 de Novembre 2014
Data de finalització del contracte: 31 d'octubre 2016

Acorden el següent:

PREAMBLE

1. WHEREAS the European Space Agency (the Agency) is an intergovernmental organisation established by the Convention approved by the Conference of plenipotentiaries of its Member States on 30 May 1975 and which entered into force on 30 October 1980.

2. WHEREAS Article II of the Convention assigns to the Agency the task to promote cooperation in space research and technology and their space applications and to elaborate and implement activities and programmes in the space field.

3. WHEREAS the Agency manages a technology transfer initiative to encourage the utilisation of space technology for general non-space industrial, scientific and commercial uses.

4. WHEREAS as part of the technology transfer initiative the Agency has set up the ESA Business Incubation

PREÀMBUL

1. Que l'Agència Espacial Europea (l'Agència) és una organització intergovernamental creada per la convenció aprovada per la Conferència de Plenipotenciaris dels Estats Membres el 30 de maig de 1975 i que va entrar en vigor el 30 d'octubre de 1980.

2. Que l'article II de la Convenció assigna a l'Agència la tasca de promoure la col·laboració en la investigació i tecnologia i les seves aplicacions a l'espai, i elaborar i implementar activitats i programes en el camp de l'espai.

3. Que l'Agència gestiona una iniciativa de transferència de tecnologia per afavorir la utilització de la tecnologia espacial en general per a usos no espacials, industrials, científics i comercials.

4. Que com a part de la iniciativa de transferència de tecnologia, l'Agència ha creat els Centres

Centre's (ESA BICs) initiative to enable start-up companies (incubatees) to receive comprehensive commercial and technical assistance in order to set up their business using space technology for such general non-space industrial, scientific and commercial uses.

d'Incubació d'Empreses de l'ESA (ESA Business Incubation Centre's, ESA BICs) per tal que les empreses de nova creació (empreses incubades) rebin un ampli suport comercial i tècnic a fi d'establir aquestes empreses aplicant tecnologia espacial en general per a usos no espacials, industrials, científics i comercials.

5. WHEREAS the Agency has chosen to implement and manage the ESA BIC Barcelona through ESTEC contract.

5. Que l'Agència ha decidit implementar i gestionar l'ESA BIC Barcelona a través d'un contracte d'ESTEC.

6. WHEREAS the ESA BIC Barcelona is partly funded by the European Space Agency and Ajuntament de Barcelona, Àrea Metropolitana de Barcelona, Diputació de Barcelona and Consell Comarcal del Baix Llobregat.

6. Que ESA BIC Barcelona està finançada parcialment per l'Agència Espacial Europea i l'Ajuntament de Barcelona, l'Àrea Metropolitana de Barcelona, la Diputació de Barcelona i el Consell Comarcal del Baix Llobregat.

7. WHEREAS Caixa Capital Risc is one of the partners of Barcelona Activa and provides a convertible loan scheme to a selection of the ESA BIC Barcelona incubatees.

7. Que Caixa Capital Risc és un dels socis de Barcelona Activa i ofereix un programa de préstec participatius a una selecció de les empreses incubades de l'ESA BIC Barcelona.

8. WHEREAS the Incubatee wishes to participate in the ESA BIC Barcelona and benefit from the assistance which may be offered to it through the provisions of this Contract.

8. Que l'Empresa Incubada desitja participar a ESA BIC Barcelona i treure profit del suport que se li pot oferir tal com estipulen les clàusules d'aquest contracte.

9. WHEREAS, as part of the assistance offered to the incubatee, Barcelona Activa and the Incubatee will sign an Incubation Contract with the duties from both sides regarding

9. Que, com a part del suport que s'ofereix a l'Empresa Incubada, Barcelona Activa i l'Empresa Incubada signaran un contracte d'incubació on figuraran les

the incubation of the incubatee and associated services (Incubation Contract" attached to this document).

10. WHEREAS, as part of the assistance offered to the Incubatee, Barcelona Activa, UPC and the Incubatee will sign a Local Framework Incubation Agreement of even date with this Contract with the duties and responsibilities from all three sides regarding the incubation of the incubatee and associated services ("Local Framework Incubation Agreement" attached to this document).

ARTICLE 1 - CONTRACTUAL BASELINE

1.1. Definitions

For the purpose of this Contract the following words shall have the meanings assigned to them.

"Activity" means all the activities that the Incubatee will undertake under this Contract in relation to its participation in the ESA BIC, including the preparation of the Mid Term Report, the Executive Summary, the Annual Performance Report and the Business Plan and all other obligations and deliverables to be made by the Incubatee under this Contract.

"Annual Performance Report" shall have the meaning set out in

obligacions d'ambdues parts pel que fa a la incubació de l'Empresa Incubada i els serveis associats (Contracte d'Incubació" que s'adjunta a aquest document).

10. Que, com a part del suport que s'ofereix a l'Empresa Incubada, Barcelona Activa, la UPC i l'Empresa Incubada signaran un Acord Local Marc d'Incubació amb la mateixa data que aquest contracte, amb els deures i responsabilitats de totes tres parts en relació amb la incubació de l'Empresa Incubada i els serveis associats ("Acord Local Marc d'Incubació" que s'adjunta amb aquest document).

ARTICLE 1 – BASE CONTRACTUAL

1.1. Definicions

En aquest contracte, les paraules següents tenen els significats que se'ls assignen aquí.

"Activitat" significa totes les activitats que l'Empresa Incubada emprengui mentre duri aquest contracte en relació amb la seva participació a l'ESA BIC, inclosa la preparació de l'Informe de Mitjà Termini, el Resum Executiu, l'Informe de Rendiment Anual i el Pla de Negoci així com totes les altres obligacions i lliuraments que ha de fer l'Empresa Incubada segons aquest contracte.

"Informe de Rendiment Anual" té el significat que s'estableix a

Appendix 1, section 5.6.	l'Apèndix 1, secció 5.6.
"Business Plan" shall have the meaning set out in Appendix 1, section 5.5.	"Pla de negoci" té el significat establert a l'Apèndix 1, secció 5.5.
"Barcelona Activa" means Barcelona City Council's local development agency and an international benchmark for supporting entrepreneurship, innovation, professional improvement and job creation in its 27 years of operations with large experience in business incubation.	"Barcelona Activa" es refereix a l'agència de desenvolupament local de l'Ajuntament de Barcelona i és punt de referència internacional en el suport a l'emprenedoria, la innovació, la millora professional i la creació de llocs de treball en els seus 27 anys de funcionament, amb una gran experiència en la incubació de negocis.
"CCN" shall mean a contract change notice.	"CNN" vol dir un avís de canvi en el contracte (de l'anglès, "Contract Change Notice").
"Change Review Board" shall be a board consisting of a contractual and a technical representative of each Party established to discuss and agree upon the approval or rejection of a change proposal, and final CCN.	"Junta de Revisió de Canvis" serà una junta formada per un representant contractual i un de tècnic de cada Part reunits per comentar i acordar l'aprovació o el rebuig d'una proposta de canvi i un CCN.
"Commencement Date" shall mean the date that this Contract shall come into force, as set out in Article 5.	"Data d'inici" serà la data en que aquest contracte entri en vigor, com s'estableix a l'article 5.
"Confidential Information" shall have the meaning set out in Article 11.2.	"Informació confidencial" té el significat establert a l'article 11.2.
"Contract" shall mean an agreement between Barcelona Activa and the Incubatee regulating the Activity.	"Contracte" significa un acord entre Barcelona Activa i l'Empresa Incubada que reguli l'activitat.

"Contract End Date" shall mean the date that this Contract shall come to an end, as set out in Article 5.	"Data de fi de contracte" serà la data en que aquest contracte finalitzi, tal com s'estableix a l'article 5.
"Contract Term" shall be the period between the Commencement Date and the Contract End Date.	"Termini del contracte" serà el període entre la data d'inici i la data de fi de contracte.
"Cost report" shall mean a report detailing all costs incurred in relation to the Activity, to be submitted by the Incubatee to Barcelona Activa.	"Informe de Costos" és un informe on es detallaran totes les despeses efectuades en relació amb l'activitat, que lliurarà l'Empresa Incubada a Barcelona Activa.
"Declaration of State Aid" shall have the meaning set out in Article 8.2.	"Declaració d'Ajuts Estatals" vol dir el que s'estableix a l'article 8.2.
"Deliverables" shall have the meaning set out in Article 2.	"Lliuraments" significa el que s'explica a l'article 2.
"Disclosing Party" shall mean the Party disclosing Confidential Information.	"Part Reveladora" es refereix a la Part que reveli informació confidencial.
"Equipment" shall have the meaning set out in Article 3.2.	"Equipaments" significa el que es descriu a l'article 3.2.
"ESA BIC Barcelona" shall have the meaning set out in the Preamble.	"ESA BIC Barcelona" es refereix al que s'estipula al Preàmbul.
"Executive Summary" shall have the meaning set out in Appendix 1, section 5.4.	"Resum Executiu" significa el que descriu l'Apèndix 1, secció 5.4.
"Final Report" shall mean the complete statement of the work undertaken by the Incubatee during the Contract Term, as further defined in Appendix 1, section 5.3.	"Informe Final" significa la redacció completa de la feina portada a terme per l'Empresa Incubada durant el termini de durada del Contracte, tal com es detalla a l'Apèndix 1, secció 5.3.

"Intellectual Property Rights" shall mean all rights in copyright, patents, know-how, Confidential Information, database rights, rights in trade marks and designs (whether registered or unregistered), applications for registration of any of the foregoing and the right to apply for registration, and all other intellectual property rights and equivalent or similar forms of protection existing anywhere in the world.

"Drets de propietat intel·lectual" són tots els drets de còpia, patents, saber fer, informació confidencial, drets sobre les bases de dades, drets de marques comercials i dissenys (siguin registrats o no), sol·licituds de registre dels anteriors, i el dret de sol·licitar el registre i tots els altres drets de propietat intel·lectual i formes de protecció equivalents o similar que existeixin a qualsevol lloc del món.

"Mid Term" shall mean the midpoint date between the Commencement Date and the Contract End Date.

"Mitjà termini" significa la data de mig camí entre la d'inici i la de fi del Contracte.

"Mid Term Report" shall have the meaning set out in Article 2.1.1.

"Informe de Mitjà Termini" vol dir allò que s'estableix a l'article 2.1.1.

"Mid Term Review" shall have the meaning set out in Appendix 1, section 4.2.

"Revisió de Mitjà Termini" vol dir allò que s'estableix a l'Apèndix 1, secció 4.2.

"Receiving Party" shall mean the Party receiving Confidential Information.

"Part receptora" significa la Part que rebi informació confidencial.

"Statement of Non Co-incubation" shall mean the statement from the Incubatee that his company shall not be incubated in or receive support of any kind from any other incubator whatsoever for the duration of the Contract Term.

"Declaració de No Coincubació" significa la declaració de l'Empresa Incubada que no serà incubada ni rebrà suport de cap mena per part de qualsevol altra entitat incubadora del tipus que sigui mentre sigui vigent el termini del Contracte.

"Technical Support" shall have the meaning set out in Article 3.1.

"Suport tècnic" significa el que es descriu a l'article 3.1.

"Third Party" shall mean any person or entity other than the Agency and the Parties to this Contract or their personnel.

"Third Party Services" shall have the meaning set out in Article 4.

"Universitat Politècnica de Catalunya" or "UPC" means a university and a public institution at the service of society, conceived as an interdisciplinary hub to promote learning, scientific, technical and artistic research and social development, provide training that qualifies students to pursue professional activities, and offer scientific and technical support to advance the social, cultural and economic progress of society. UPC is a major player in research in aerospace technologies which is involved in numerous space missions for the ESA (SMOS, Galileo and ATV among others) and NASA, leading cutting-edge research into a variety of space-related fields

1.2 Contractual baseline

The Incubatee shall perform the Activity in accordance with the following applicable documents listed hereunder in order of precedence:

"Tercera part" significa qualsevol persona o entitat diferent de l'Agència i de les Parts d'aquest contracte o del seu personal.

"Serveis de terceres parts" significa el que s'estableix a l'article 4.

"Universitat Politècnica de Catalunya" o "UPC" es refereix a la universitat i a la institució pública al servei de la societat, concebuda com a punt de concentració interdisciplinari per fomentar l'aprenentatge, la investigació científica, tècnica i artística i el desenvolupament social, proporcionar formació que qualifiqui els estudiants per emprendre activitats professionals, i oferir suport científic i tècnic per avançar en el progrés social, cultural i econòmic de la societat. La UPC té un paper principal en la recerca de les tecnologies aeroespacials i està implicada en nombroses missions espacials per a l'ESA (SMOS, Galileo i ATV, entre d'altres) i la NASA, i lidera la investigació puntera en diversos camps relacionats amb l'espai.

1.2 Base contractual

L'Empresa Incubada portarà a terme l'activitat d'acord amb els documents que corresponguin dels que formen la llista següent per ordre de precedència:

1.2.1 This Incubation Contract;

1.2.2 The Agency's Standard Requirements for Management, Reporting, Meetings and Deliverables as set out in Appendix 1;

1.2.3 The Agreement for the Use of RDIT Building Facilities;

1.2.4 The Minutes of the negotiation meeting ("Kick-Off Meeting") held on the 12/09/2014, not attached hereto but known to both parties;

1.2.5 The Incubatee's Business Activity Proposal ref 119105110, dated 1st of May 2014, not attached hereto but known to both Parties.

ARTICLE 2 – ACTIVITY OF THE INCUBATEE

The Incubatee undertakes to deliver the items mentioned below (the "Deliverables"), as part of the Activity in accordance with the following provisions:

2.1 Documentation

2.1.1 Mid Term Report

At Mid Term, the Incubatee shall provide to Barcelona Activa representatives, described in Article 9.3(a) and (b), a report detailing the technical and

1.2.1 Aquest Contracte d'Incubació;

1.2.2 Els Requeriments Estàndard de l'Agència de Gestió, Informes, Reunions i Lliuraments tal com es descriuen a l'Apèndix 1;

1.2.3 El Contracte d'Ús de les Instal·lacions de l'Edifici RDIT;

1.2.4 Les actes de la reunió de negociació ("Kick-Off Meeting") duta a terme el 12/09/2014, que no s'adjunten aquí però que són conegudes per ambdues Parts;

1.2.5 La Proposta d'Activitat Empresarial de l'Empresa Incubada, amb ref. 119105110, amb data 1 de Maig 2014, que no s'adjunta aquí però que és coneguda per ambdues Parts.

ARTICLE 2 – ACTIVITAT DE L'EMPRESA INCUBADA

L'Empresa Incubada es compromet a lliurar els ítems que s'especifiquen a continuació (els "Lliuraments"), com a part de l'activitat, d'acord amb les següents disposicions:

2.1 Documentació

2.1.1 Informe de Mitjà Termini

A mitjà termini, l'Empresa Incubada proporcionarà als representants de Barcelona Activa, descrits a l'article 9.3(a) i (b), un informe on es detalli la

commercial work carried out by the Incubatee as part of the Activity during the first half of the Contract Term ("Mid Term Report"). Templates are provided in Appendix 2 herein.

feina tècnica i comercial portada a terme per l'Empresa Incubada com a part de la seva activitat durant la primera meitat del termini del Contracte ("Informe de Mitjà Termini"). Es proporcionen plantilles a l'Apèndix 2 que acompanya aquest document.

2.1.2 Business Plan

The Business Plan shall be provided to Barcelona Activa technical representative stated in Article 9.3(a) in 2 copies, not later than the Contract End Date.

2.1.2 Pla de Negoci

El Pla de Negoci es lliurarà al representant tècnic de Barcelona Activa que s'indica a l'article 9.3(a) per duplicat, no més tard de la data de fi del Contracte.

2.1.3 Final Report and Executive Summary

(a) At least two months prior to the Contract End Date, the Incubatee shall provide Barcelona Activa with draft versions of the Final Report and the Executive Summary. Barcelona Activa shall have one month to review the draft documents and provide comments on each to the Incubatee. The Incubatee shall then have the remaining month in which to produce the final version of the Final Report and the Executive Summary and submit them to Barcelona Activa. Templates are provided in Appendix 3 herein.

(b) The Final Report and the Executive Summary shall be

2.1.3 Informe Final i Resum Executiu

(a) Com a mínim dos mesos abans de la data de fi del Contracte, l'Empresa Incubada ha de proporcionar a Barcelona Activa esborranys de l'Informe Final i del Resum Executiu. Barcelona Activa disposarà d'un mes per revisar els esborranys i oferir comentaris sobre cadascun d'ells a l'Empresa Incubada. A partir de llavors, l'Empresa Incubada disposarà del mes restant per elaborar la versió final de l'Informe Final i el Resum Executiu i lliurar-los a Barcelona Activa. Es proporcionen plantilles a l'Apèndix 3 que acompanya aquest document.

(b) L'Informe Final i el Resum Executiu els lliurarà l'Empresa

delivered by the Incubatee to Barcelona Activa in 3 (2 paper copies and 1 electronic copy) and 6 copies (5 paper copies and 1 electronic copy) respectively.

2.2 Other Deliverables

As part of the Incentive Scheme, it is expected from the Incubatee to deliver proof of the developed product or service. It is to be delivered to the Agency through Barcelona Activa.

2.2.1 Software

(a) In the event that the Incubatee develops software during the Contract Term and as part of its Activity the Incubatee shall deliver such software to Barcelona Activa in a form to be agreed with Barcelona Activa.

(b) The Incubatee shall deliver such software at the end of the Contract Term or upon the cancellation of this Contract, unless otherwise agreed in writing by the Parties.

2.2.2 Hardware

(a) In the event that the Incubatee develops any hardware during the Contract Term and as part of its Activity, Barcelona Activa is entitled to request the Incubatee

Incubada a Barcelona Activa per triplicat (2 còpies en paper i 1 còpia electrònica) i per sextuplicat (5 còpies en paper i 1 còpia electrònica) respectivament.

2.2 Altres lliuraments

Com a part del Programa d'Incentius, s'espera que l'Empresa Incubada proporcioni proves del producte o servei. Les lliurarà a l'Agència a través de Barcelona Activa.

2.2.1 Programari

(a) En cas que l'Empresa Incubada desenvolupi programari durant el termini del Contracte com a part de la seva activitat, l'Empresa Incubada entregarà aquest programari a Barcelona Activa de la manera que acordi amb Barcelona Activa.

(b) L'Empresa Incubada lliurarà els programes al final del termini del Contracte o en cas de cancel·lació del Contracte, si no és que les Parts acorden altrament per escrit.

2.2.2 Maquinari

(a) En cas que l'Empresa Incubada desenvolupi maquinari durant el termini del Contracte com a part de la seva activitat, Barcelona Activa té dret a demanar a

to loan the hardware to Barcelona Activa and/or the Agency for the purposes of displaying it in an exhibition or for the Barcelona Activa and/or the Agency's promotional purposes for a period of five (5) years from the end of the Contract Term or from the cancellation of this Contract, unless otherwise agreed in writing by the Parties. ALTERNATIVELY: A dummy.

(b) Any photographs and visual presentations (i.e. an automatic slide show and/or video trailer) of any hardware developed by the Incubatee during the Contract Term and as part of its Activity shall be delivered to Barcelona Activa and/or the Agency at the end of the Contract Term or upon the cancellation of this Contract, unless otherwise agreed in writing by the Parties.

l'Empresa Incubada que presti el maquinari a Barcelona Activa i/o l'Agència amb l'objectiu d'exhibir-lo en una fira o per a propòsits promocionals de Barcelona Activa i/o l'Agència durant un període de cinc (5) anys a partir de la fi del termini del Contracte o a partir de la cancel·lació d'aquest contracte, si no és que les Parts acorden altrament per escrit. ALTERNATIVA: un model fictici.

(b) Les fotografies i presentacions visuals (és a dir, una presentació automàtica de diapositives i/o tràiler de vídeo) de qualsevol maquinari desenvolupat per l'Empresa Incubada durant el termini del Contracte com a part de la seva activitat seran lliurades a Barcelona Activa i/o l'Agència al final del termini del Contracte o quan se'n produeixi la cancel·lació, si no és que les Parts acorden altrament per escrit.

ARTICLE 3 –ESA BIC BARCELONA UNDERTAKINGS

3.1 Technical Support

(a) For the purposes of this Contract UPC will provide the Incubatee with the following technical support necessary for and directly related to the Activity of Incubatee (referred to as "Technical Support").

a maximum of 80 hrs during the contract term.

ARTICLE 3 – TASQUES D'ESA BIC BARCELONA

3.1 Suport tècnic

(a) Per satisfer els propòsits d'aquest contracte, la UPC proporcionarà a l'Empresa Incubada el següent suport tècnic necessari i relacionat directament amb l'activitat de l'Empresa Incubada (referit com a "Suport Tècnic").

Un màxim de 80 hores durant el termini del Contracte.

(b) The Technical Support shall be provided for the duration of the Contract Term, unless a shorter period is agreed between the Parties.

(c) Any information in documentary or other physical form provided to the Incubatee as part of the Technical Support shall remain the property of UPC and shall be returned to UPC at the end of the Contract Term or upon the cancellation of this Contract.

(d) For all matters relating to the technical support the responsible technical officer is nominated in Clause 9.3 a).

(b) El Suport Tècnic es proporcionarà mentre duri el Contracte, si no és que les Parts acorden un període més curt.

(c) Qualsevol informació documental o en qualsevol altre suport físic proporcionat a l'Empresa Incubada com a part del Suport Tècnic continuarà essent propietat i es retornarà a la UPC al final del termini del Contracte o en el moment que es cancel·li aquest contracte.

(d) A tots els efectes relacionats amb el suport tècnic, es nomena un oficial tècnic responsable a la clàusula 9.3 a).

3.2 Equipment

It is not foreseen the Agency, Barcelona Activa or UPC will loan the Incubatee any equipment.

3.2 Equipament

No es preveu que l'Agència, Barcelona Activa o la UPC presti a l'Empresa Incubada cap mena d'equipament.

3.3 Software

It is not foreseen the Agency, Barcelona Activa or UPC will loan the Incubatee any software.

3.3 Programari

No es preveu que l'Agència, Barcelona Activa o la UPC presti a l'Empresa Incubada cap mena de programari.

ARTICLE 4 - SERVICES TO BE PROVIDED BY THIRD PARTIES

The Incubatee shall notify Barcelona Activa when entering into agreements with Third Parties to obtain specific advice/product relevant to the Activity ("Third Party Services"). Barcelona Activa shall bear no responsibility for such

ARTICLE 4 - SERVEIS PROPORCIONATS PER TERCERES PARTS

L'Empresa Incubada notificarà Barcelona Activa quan estableixi acords amb terceres parts per obtenir-ne consell o productes relacionats amb la seva activitat ("Serveis de Terceres Parts"). Barcelona Activa no serà responsable

advice or product.

For the purposes of this Article it is hereby understood that the incentive funding shall be spent in Spain unless the product/service is not available in such territory and within the boundaries stated on Article 7.1 (Financial Contribution) hereto.

ARTICLE 5 - CONTRACT TERM

This Contract shall enter into force upon signature by the legal representatives of both Parties ("Commencement Date") and shall continue in force until ("Contract End Date"), unless it is cancelled or otherwise terminated in accordance with Article 16. In no case shall the Contract Term exceed the duration of 2 (two) years.

ARTICLE 6 – MEETINGS AND REPORTING REQUIREMENTS

Full details of reporting and meeting requirements are set out in Appendix 1 sections 3 and 4 respectively.

ARTICLE 7 – FINANCIAL CONTRIBUTION AND PAYMENT

7.1. Financial Contribution

7.1.1 The total financial contribution to the Activity **amounts up to**:

50.000 EURO (Fifty Thousand EURO) for IPR & product development.

d'aquests consells o productes.

En relació amb els objectius d'aquest article, es dóna per entès que els incentius econòmics es gastaran a Espanya si no és que el producte/servei no es trobi disponible en aquet territori i dins dels límits establerts a l'article 7.1 (Contribució Financera) d'aquest contracte.

ARTICLE 5 – TERMINI DEL CONTRACTE

Aquest contracte entrarà en vigor quan el signin els representants legals d'ambdues Parts ("Data d'inici") i seguirà vigent fins ("Data de fi de contracte"), si no és que es cancel·la o es rescindeix abans, tal com estableix l'article 16. En cap cas el termini del Contracte excedirà els 2 (dos) anys de durada.

ARTICLE 6 – REUNIONS I REQUERIMENT D'INFORMES

Tota la informació pertinent als informes i les reunions obligatoris es troba a l'Apèndix 1, seccions 3 i 4 respectivament.

ARTICLE 7 – CONTRIBUCIÓ FINANCERA I PAGAMENT

7.1. Contribució financera

7.1.1 La contribució financera total a l'activitat **es xifra en fins a**:

50.000 EURO (cinquanta mil euros) per a drets de propietat intel·lectual i desenvolupament del producte.

7.1.2 For the purpose of this Contract the above mentioned total financial contribution is stated to be a ceiling which amount shall not be exceeded and for which the Incubatee shall perform the Activity in full.	7.1.2 Dins del marc d'aquest contracte, la contribució financera total mencionada és la quantitat màxima que no es pot excedir i per la qual l'Empresa Incubada realitzarà la seva activitat completa.
7.1.2.1 At the end of the Contract Term the incubatee shall deliver a cost report detailing all costs incurred, with all invoices attached.	7.1.2.1 Al final del termini del Contracte, l'Empresa Incubada lliurarà un informe de despeses on es detallaran tots els costos que s'hagin produït, i se n'hi adjuntaran totes les factures.
7.1.2.2 The incubatee shall prove all expenses from the funding solely with third parties' invoices used for IPR and product development following the provisions on Article 4 here above. The incubatee is not authorized to use the above stated funding for reimbursement of his own hours spent in the project.	7.1.2.2 L'Empresa Incubada demostrarà les despeses cobertes amb els l'incentiu econòmic únicament amb factures de terceres parts destinades als drets de propietat intel·lectual i el desenvolupament del producte segons les disposicions de l'article 4. L'Empresa Incubada no està autoritzada a utilitzar els fons mencionats més amunt per cobrar les seves pròpies hores invertides en el projecte.
7.1.3 The above amount does not include any taxes and duties.	7.1.3 La quantitat mencionada no inclou impostos ni aranzels.
7.2 Payment Terms All payments shall be made according to the provisions of this Article 7.	7.2 Condicions de pagament Tots els pagaments es duran a terme segons les disposicions del present article 7.
7.3 Categories of Payment Relative to the financial contribution set out under Article 7.1, Barcelona Activa or Ajuntament of Barcelona shall make the following payments to	7.3 Categories de pagament En relació amb la contribució financera establerta a l'article 7.1, Barcelona Activa o l'Ajuntament de Barcelona efectuarà els pagaments següents a l'Empresa

the Incubatee:

7.3.1 Progress Payments

(a) Barcelona Activa or Ajuntament of Barcelona shall authorise progress payments in connection with this Contract.

(b) Progress payments are not final payments and shall be deducted from the sums due to the Incubatee under this Contract.

(c) Except with the specific agreement of Barcelona Activa, the Incubatee shall not divert to uses not provided for in this Contract any material or services in respect of which progress payments have been made. In the event of any violation of this provision Barcelona Activa reserves the right to require the return of the progress payments without prejudice to its rights under Article 16.

7.4 Final Settlement

7.4.1 The Incubatee shall be allowed to claim final settlement when all the Incubatee's obligations under this Contract have been fulfilled.

7.4.2 Final settlement to the Incubatee is due by Barcelona Activa or Ajuntament of Barcelona upon:

a) receipt by Barcelona Activa of the Cost Report;

Incubada:

7.3.1 Pagaments de progrés

(a) Barcelona Activa o l'Ajuntament de Barcelona autoritzaran pagaments de progrés en relació amb aquest contracte.

(b) Els pagaments de progrés no són pagaments finals i es restaran de les quantitats que pertoquin a l'Empresa Incubada per aquest contracte.

(c) Excepte per acord específic amb Barcelona Activa, l'Empresa Incubada no desviarà cap a usos no descrits en aquest contracte cap material ni servei per als quals s'hagin fet els pagaments de progrés. En cas de violació d'aquesta disposició, Barcelona Activa es reserva el dret d'exigir la devolució dels pagaments de progrés sense prejudici dels seus drets descrits a l'article 16.

7.4 Pagament final

7.4.1 L'Empresa Incubada podrà reclamar un pagament final quan totes les obligacions de l'Empresa Incubada descrites en aquest contracte s'hagin complert.

7.4.2 Barcelona Activa o l'Ajuntament de Barcelona haurà de fer efectiu el pagament final a l'Empresa Incubada quan:

a) Barcelona Activa hagi rebut l'Informe de Costos;

b) receipt by Barcelona Activa of all relevant invoice(s) from the Incubatee with a clear indication of all the invoices paid with the funding provided under this contract; and certification by Barcelona Activa of the satisfactory completion of the Activity under this Contract.

7.4.3 Unless otherwise provided for in this Contract, a period of one (1) month shall be granted for the execution of the final payment

7.4.4 Barcelona Activa or Ajuntament of Barcelona shall make the following payments:

MILESTONE DESCRIPTION	SCHEDULE DATES	AMOUNT IN EURO
PROGRESS I: Upon signature of the incubation contract by the incubatee	Expected December 2014	35.000
PROGRESS II: Upon successful MTR, acceptance by Barcelona Activa of MTR report, business plan all related deliverables	Expected December 2015	10.000
FINAL: Upon acceptance by Barcelona Activa of all Deliverables under the contract, including Final Report, business	Expected December	5.000

b) Barcelona Activa hagi rebut totes les factures pertinents de l'Empresa Incubada amb clara indicació de totes les factures pagades amb els fons proporcionats per aplicació d'aquest contracte; i Barcelona Activa certifiqui el compliment satisfactori de l'activitat que regula aquest contracte.

7.4.3 Si no es disposa altrament en aquest contracte, es donarà un període d'un (1) mes per fer efectiu el pagament final.

7.4.4 Barcelona Activa o l'Ajuntament de Barcelona realitzarà els pagaments següents:

DESCRIPCIÓ DE LA FITA	DATES PROGRAMADES	QUANTITAT EN EUROS
PROGRÉS I: En el moment que l'Empresa Incubada signi el contracte d'incubació	Previst Desembre 2014	35.000
PROGRÉS II: Després de lliurar l'Informe de Mitjà Termini i rebre l'acceptació de l'Informe, el Pla de Negoci i tots els lliuraments a Barcelona Activa	Previst Desembre 2015	10.000
FINAL: Quan Barcelona Activa hagi acceptat tots els lliuraments que marca el contracte, inclòs	Previst Desembre	

plan, the hardware and/or software and upon acceptance by Barcelona Activa of the Incubatee's Cost Report	2016	

l'Informe Final, el Pla de Negoci, el maquinari i/o el programari informàtic, i l'acceptació de l'Informe de Costos de l'Empresa Incubada per part de Barcelona Activa	2016	5.000

7.5 Invoices, place and payments

7.5.1 The incubated companies must deliver invoices justifying all payments to be made effective under this contract.

7.5.2 Payments shall be in EURO to the account specified by the Incubatee, by Article 7.1.1. hereabove. Such information shall clearly indicate the IBAN (International Bank Account Number) and BIC/SWIFT (Bank Identification Code). Payments shall be considered as effected on time if orders of payment reach its bank within the payment period stipulated in Article 7.4.3 above.

7.5.3 Any special charges related to the execution of payments will be borne by the incubatee.

ARTICLE 8 – DE MINIMIS AID

8.1 Any aid granted to the Incubatee that originates from Àrea Metropolitana de Barcelona, Diputació de Barcelona and

7.5 Factures, lloc i pagament

7.5.1 L'Empresa Incubada ha de lliurar les factures justificatives de tots els pagaments que s'hagin de fer efectius segons aquest contracte.

7.5.2 Els pagaments seran en EUROS al número de compte especificat per l'Empresa Incubada, en l'article 7.1.1. Aquesta informació indicarà clarament l'IBAN (Número Internacional de Compte Bancari) i el BIC/SWIFT (Codi d'Identificació del Banc). Els pagaments es consideraran fets a temps si el banc rep les ordres de pagament dins del període de pagament establert a l'article 7.4.3.

7.5.3 Qualsevol càrrec especial relacionat amb la realització dels pagaments anirà a càrrec de l'Empresa Incubada.

ARTICLE 8 – AJUTS DE *MINIMIS*

8.1 Qualsevol ajut que rebi l'Empresa Incubada procedent de l'Àrea Metropolitana de Barcelona, la

Consell Comarcal del Baix Llobregat that is provided under this Contract to the Incubatee by Barcelona Activa or Ajuntament of Barcelona falls under the terms of EC Regulation 1998/2006 of 15th of December 2006 on the application of Articles 87 and 88 of the EC Treaty to 'de minimis aid'.

8.2 The Incubatee shall notify Spanish authorities (i.e. Àrea Metropolitana de Barcelona, Diputació de Barcelona and Consell Comarcal del Baix Llobregat) through Barcelona Activa in writing of how much state aid it has received during the three (3) years prior to the Commencement Date from any administrative body, insofar as no approval for such state aid was previously obtained from the Commission of the European Communities ("Declaration of State Aid").

8.3 The Incubatee agrees to reimburse any state aid that the Incubatee has received under this Contract if it is later established that the payment was issued in violation of EC Regulation 1998/2006 of 15th of December 2006 on the application of Article 87 and 88 of the EC Treaty to de minimis aid.

Diputació de Barcelona i el Consell Comarcal del Baix Llobregat proporcionat dins del marc d'aquest contracte a l'Empresa Incubada per part de Barcelona Activa o l'Ajuntament de Barcelona es farà sota el que estipula el Reglament CE 1998/2006, de 15 de desembre, relatiu a l'aplicació dels articles 87 i 88 del Tractat CE referent als ajuts *de minimis*.

8.2 L'Empresa Incubada notificarà les autoritats espanyoles (és a dir, l'Àrea Metropolitana de Barcelona, la Diputació de Barcelona i el Consell Comarcal del Baix Llobregat) a través de Barcelona Activa, per escrit, de la quantitat d'ajuts estatals que hagi rebut durant els tres (3) anys previs a la data d'inici d'aquest contracte per part de qualsevol organisme de l'administració, si és que l'aprovació d'aquests ajuts no s'hagués obtingut prèviament de la Comissió de les Comunitats Europees ("Declaració d'Ajuts Estatals").

8.3 L'Empresa Incubada accepta retornar els ajuts estatals que l'Empresa Incubada hagi rebut dins del marc d'aquest contracte si més tard s'estableix que el pagament es va efectuar en violació del Reglament CE 1998/2006, de 15 de desembre, relatiu a l'aplicació dels articles 87 i 88 del Tractat CE referent als ajuts de *minimis*.

ARTICLE 9 – PARTIES REPRESENTATIVES AND COMMUNICATIONS

9.1 All correspondence affecting the terms and conditions of this Contract and concerning its execution shall be made or confirmed in writing. All communications or correspondence between the Parties shall be in English.

All correspondence for either Party shall be sent to both representatives of each Party stated in Articles 9.3 and 9.4, i.e. depending on the subject, addressed to one representative with a copy to the other.

9.3 For the purpose of this Contract ESA BIC Barcelona representatives are:

(a) For contractual and administrative matters:

Ms. Montse Basora i Farré
Entrepreneurship Manager
Barcelona Activa
Llacuna 162-164, 08018 Barcelona. Spain
Tel.: (+34) 93 401 98 00
Fax.: (+34) 93 300 90 12
Email:
montse.basora@barcelonactiva.cat

With copy to:
Mr. Xavier Dumont
Head of Entrepreneurship

ARTICLE 9 – REPRESENTANTS DE LES PARTS I COMUNICACIONS

9.1 Tota la correspondència que afecti els termes i les condicions d'aquest contracte i que tinguin a veure amb la seva execució es faran o es confirmaran per escrit. Totes les comunicacions o correspondència entre les Parts es farà en anglès.

9.2 Tota la correspondència per a qualsevol de les Parts s'enviarà a tots dos representants de cada Part, indicats als articles 9.3 i 9.4, és a dir, segons el tema, adreçada a un representant amb còpia per a l'altre.

9.3 Dins del marc d'aquest contracte els representants d'ESA BIC Barcelona són:

(a) Per a assumptes contractuals i administratius:

Sra. Montse Basora i Farré
Directora d'Emprenedoria
Barcelona Activa
Llacuna 162-164, 08018 Barcelona
Tel.: (+34) 93 401 98 00
Fax: (+34) 93 300 90 12
A/e:
montse.basora@barcelonactiva.cat

Amb còpia a:
Sr. Xavier Dumont

Resource Centre
Barcelona Activa
Tel: (+34) 93 401 98 00
Email:
xavier.dumont@barcelonactiva.cat

(b) For Barcelona Activa's technical support (Article 3 here above) matters:

Mr. Jorge Fuentes
ESA BIC Barcelona Manager
Tel.: (+34) 650 500 745
Email:
jorge.fuentes@barcelonactiva.cat

9.4 For the purpose of this Contract the Incubatee's representatives are:

For technical, contractual and administrative matters:

Mr. Ivan Lloro Boada
President
Doctor Fleming, 6. 08017 Barcelona.
Phone 625850229
Email
ivan.lloro.boada@gmail.com

ARTICLE 10 - PUBLICITY AND VISUAL IDENTITY OF INCUBATEES

10.1 Publicity

10.1.1 The Incubatee shall not produce or disseminate any form of communication material, press releases or other publicity documents, including the Incubatee's advertising and news

Cap del Centre de Recursos per a l'Emprenedoria
Barcelona Activa
Tel.: (+34) 93 401 98 00
A/e: xavier.dumont@barcelonactiva.cat

(b) Per a assumptes de suport tècnic de Barcelona Activa (article 3):

Sr. Jorge Fuentes
Gerent de l'ESA BIC Barcelona
Tel.: (+34) 650 500 745
A/e: jorge.fuentes@barcelonactiva.cat

9.4 Dins del marc d'aquest contracte, els representants de l'Empresa Incubada són:

Per a assumptes tècnics, contractuals i administratius:

Sr. Ivan Lloro Boada
President
C/ Doctor Fleming, 6. 08017 Barcelona
Telèfon 625850229
Email
ivan.lloro.boada@gmail.com

ARTICLE 10 – PUBLICITAT I IDENTITAT VISUAL DE L'EMPRESA INCUBADA

10.1 Publicitat

10.1.1 L'Empresa Incubada no produirà ni difondrà cap forma de material de comunicació, notes de premsa ni altres documents de publicitat, inclosos anuncis i butlletins de

bulletins, which are intended by the Incubatee for the press, internet / web-sites or television, which refer to Barcelona Activa, ESA, ESA BIC Barcelona or any aspect of ESA BIC Barcelona activities, or permit any Third Party to do so, without the prior written consent of Barcelona Activa.

10.1.2 Barcelona Activa shall not produce or disseminate any form of communication material, press releases or other publicity documents which are intended by ESA BIC Barcelona for the press, internet / websites or television, which refer to the Incubatee or any aspect of the Incubatee's activities, or permit any Third Party to do so, without the prior written consent of the Incubatee's contractual representative or his duly authorised representative.

10.1.3 Visual Identity of the Incubatee

10.1.4 The Incubatee shall not use the official emblem of ESA, ESA BICs or ESA BIC Barcelona or any other logo or trademark which may be owned or used by the Agency or Barcelona Activa for any purpose whatsoever, unless stated in this Article.

10.1.5 The Incubatee may place the logo attached hereto in Appendix 4 and the following text line, in full

notícies de l'Empresa Incubada, adreçats per l'Empresa Incubada a la premsa, Internet / llocs web o televisió, que es refereixin a Barcelona Activa, ESA, ESA BIC Barcelona o qualsevol altre aspecte de les activitats d'ESA BIC Barcelona, ni permetrà que ho faci cap tercera part, sense el consentiment previ per escrit de Barcelona Activa.

10.1.2 Barcelona Activa no produirà ni difondrà cap forma de material de comunicació, notes de premsa ni altres documents de publicitat, adreçats per ESA BIC Barcelona a la premsa, Internet / llocs web o televisió, que es refereixin a l'Empresa Incubada o qualsevol aspecte de les activitats de l'Empresa Incubada, ni permetrà que ho faci cap tercera part, sense el consentiment previ per escrit del representant contractual de l'Empresa Incubada o un representant seu degudament autoritzat.

10.1.3 Identitat visual de l'Empresa Incubada

10.1.4 L'Empresa Incubada no farà servir l'emblema oficial d'ESA, ESA BICs o ESA BIC Barcelona ni qualsevol altre logotip o marca registrada que pugui ser propietat o de l'ús de l'Agència o Barcelona Activa per a cap mena de propòsit, si no és que se'n fa esment en aquest article.

10.1.5 L'Empresa Incubada pot afegir el logotip que s'adjunta a

and without amendment, on its promotional material and publicity documents, including exhibition and conference material and its internet site, as long as it is linked to www.esa-bic.es, www.esa-bic.cat and/or www.esa-bic.com and stated as a partner of the company, but not on its products or any other material which it produces: "[name of the techno-starter] enrolled in the ESA Business Incubation Centre Barcelona" is referred to as the Text Line.

10.2 Use of the ESA BIC Logo and Text Line by the Incubatee shall be subject to the following conditions:

10.2.1 (a) the Incubatee shall submit to Barcelona Activa's contractual representative or his duly authorised representative for prior written approval all promotional material and publicity documents, on which the Text Line is to appear or is intended to be used, which approval may be withheld or withdrawn from any material or documents at any time at the Barcelona Activa's discretion;

(b) the prior approval of Barcelona Activa for the use of the logo and/or Text Line shall not constitute an endorsement or approval of the Incubatee's Activity, products or services, or

l'Apèndix 4 i la línia de text següent, completa i sense canvis, als materials promocionals i documents publicitaris, inclosos els materials per a fires i conferències i el seu lloc web a Internet, sempre i quan hi figuri el vincle a *www.esa-bic.es*, *www.esa-bic.cat* i/o *www.esa-bic.com*, i aparegui com a soci de l'empresa, però no en els seus productes ni cap altre material que produeixi: "[nom de l'empresa tecnològica incubada] forma part del Centre d'Incubació d'Empreses de l'ESA a Barcelona" és la referida "Línia de Text".

10.2 L'ús del logotip ESA BIC i de la Línia de Text per part de l'Empresa Incubada estarà subjecte a les següents condicions:

10.2.1 (a) l'Empresa Incubada lliurarà al representant contractual de Barcelona Activa o a un representant seu degudament autoritzat, per a la seva aprovació prèvia, tots els materials promocionals i documents publicitaris on aparegui la Línia de Text o hi hagi la intenció de fer-la servir; aprovació que pot quedar suspesa o retirada de qualsevol material o documents en qualsevol moment a discreció de Barcelona Activa;

(b) l'aprovació prèvia de Barcelona Activa per a l'ús del logotip i/o la Línia de Text no constituirà l'aprovació de l'activitat, productes o serveis

of their quality, technology or suitability for a particular use, neither shall it constitute verification by Barcelona Activa of the compatibility of materials produced by the Incubatee with applicable law and regulations, and the Incubatee shall refrain from using any statements which could suggest otherwise;

(c) any use of the Logo and/or Text Line on amended or revised promotional material and publicity documents shall be subject to the same approval process as the original material and documents;

(d) the Text Line may be translated into a different language other than English, subject to the approval of Barcelona Activa's contractual representative or his duly authorised representative; and

(e) no use of the Logo neither the Text Line shall be made in connection with material, products or documents that:

a. constitute an infringement of law and/or legal provisions;

b. undermine the reputation and dignity of the Agency or Barcelona Activa; and

c. promote or are related to alcohol, tobacco, religion, political affairs, intolerance, violence,

oferts per l'Empresa Incubada, ni garantia de la seva qualitat, tecnologia o adequació per a un ús determinat, ni constituirà verificació per part de Barcelona Activa de la compatibilitat dels materials produïts per l'Empresa Incubada amb les lleis i normatives aplicables, i l'Empresa Incubada evitarà fer servir afirmacions que puguin suggerir el contrari;

(c) qualsevol ús del logotip i/o Línia de Text en materials promocionals i documents publicitaris revisats o esmenats quedarà subjecte al mateix procés d'aprovació que els materials i documents originals;

(d) la Línia de Text es pot traduir a un idioma diferent de l'anglès, sota l'aprovació del representant contractual de Barcelona Activa o un representant seu degudament autoritzat; i

(e) no es podrà fer cap ús del logotip ni de la Línia de Text en relació amb materials, productes o documents que:

a. constitueixin una infracció de la llei o disposicions legals;

b. minin la reputació i dignitat de l'Agència o Barcelona Activa; i

c. fomentin o estiguin relacionats amb l'alcohol, tabac,

firearms, pornography, obscenity, gambling, and narcotic drugs.

10.2.2 The Incubatee shall keep appropriate records of the extent of its use of the Logo and Text Line, stating in particular the nature and time of use of the Logo and Text Line on its material, products and documentation. The Incubatee shall provide the Barcelona Activa's contractual representative or his duly authorised representative with information and documents to evidence such use.

10.2.3 The use by the Incubatee of the Logo and Text Line shall terminate upon the cancellation or expiry of this Contract as described in Article 16, unless specified in writing by Barcelona Activa and the Agency and the following Clauses here below.

10.2.4 Incubatees which successfully conclude the ESA BIC programme ("Alumni") shall be allowed to use the following Text Line, in its marketing material, including exhibition and conference material (not on products nor materials) and its internet site, as long as it is linked to www.esa-bic.es, www.esa-bic.cat and /or www.esa-bic.com and stated as a partner of the company.
"[name of the techno-starter] is an Alumnus of ESA Business

religió, afers polítics, intolerància, violència, armes de foc, pornografia, obscenitat, jocs d'atzar i drogues narcòtiques.

10.2.2 L'Empresa Incubada guardarà el registre de l'abast de l'ús del logotip i la Línia de Text, on descriurà en particular la naturalesa i el temps d'utilització del logotip i de la Línia de Text als seus materials, productes i documentació. L'Empresa Incubada proporcionarà al representant contractual de Barcelona Activa o un representant seu degudament autoritzat informació i documents que demostrin aquest ús.

10.2.3 La utilització per part de l'Empresa Incubada del logotip i la Línia de Text finalitzarà quan es cancel·li o finalitzi aquest contracte com es descriu a l'article 16, si no és que s'especifica per escrit en les clàusules següents i per part de Barcelona Activa i l'Agència.

10.2.4 Les Empreses Incubades que finalitzin el programa ESA BIC amb èxit ("antics alumnes") podran fer servir la nova línia de text següent en els seus materials de màrqueting, inclosos els materials per a fires i conferències (no en els productes ni materials) i al seu lloc web, sempre i quan hi aparegui el vincle a *www.esa-bic.es*, *www.esa-bic.cat* i/o *www.esa-bic.com* i se l'identifiqui

Incubation Centre Barcelona [graduation year])" is referred to as the Text Line.

10.2.5 Alumni using the text line have the obligation to report its use on a yearly basis to the Agency for as long as the text line is used. The Agency may withdraw the right to use the text line at any time for any reason.

10.3 The Agency has set-up and registered "ESA Space Solutions" trademark to be used by techno-starters on their products. To use this trademark, the techno-starter has to enter into a licensing agreement with the Agency and pay a fee. Details can be found on http://www.esa.int/spacesolutionslogo.

ARTICLE 11 - CONFIDENTIALITY

11.1 Each Party shall observe complete discretion with regard to all matters related to the activities of the other Party and each Party will ensure compliance by its employees and agents with the obligations of confidence set out in this Article 11 and assumed by that Party in relation to the other Party.

com a soci de l'empresa. "[nom de l'empresa tecnològica incipient] és antic alumne del Centre d'Incubació d'Empreses de l'ESA a Barcelona [any de graduació])" és la referida nova línia de text.

10.2.5 Els antics alumnes que facin servir la línia de text de més amunt tenen l'obligació d'informar del seu ús cada any a l'Agència durant tot el temps que s'utilitzi aquesta nova línia de text. L'Agència pot retirar el dret de fer servir aquesta nova línia de text en qualsevol moment per qualsevol raó.

10.3 L'Agència ha creat i registrat la marca "ESA Space Solutions" perquè l'utilitzin les empreses tecnològiques incipients als seus productes. Per fer servir aquesta marca registrada, l'empresa ha de signar un acord de llicència amb l'Agència i pagar una quota. Se'n pot trobar informació a *www.esa.int/spacesolutionslogo*.

ARTICLE 11 - CONFIDENCIALITAT

11.1 Cadascuna de les Parts guardarà una completa discreció pel que fa a tots els assumptes relacionats amb les activitats de l'altra Part, i cada Part s'assegurarà del compliment per part dels seus empleats i agents de les obligacions de confidencialitat establertes en aquest article 11 assumides per la Part en relació

11.2 Neither Party shall disclose any documentation, information or materials obtained from the other Party, whether marked (by way of example as, "confidential" or "proprietary information") or un-marked ("Confidential Information"), to any Third Party whatsoever without the prior written consent of the other Party in which case the other Party may require the recipient to sign a non-disclosure agreement. For the purposes of this Article 11, documentation shall include any final documentation deliverable under this Contract with the exception of the Executive Summary.

11.3 Each Party may disclose Confidential Information on a strictly "need to know" basis to
- its employees;
- its professional agents;
- ESA BIC Barcelona partners.

11.4 On the Contract End Date, or upon the earlier termination or cancellation of this Contract in accordance with Article 16, the Receiving Party shall promptly return to the Disclosing Party or otherwise certify the destruction of all Confidential Information, with exception of the Deliverables provided by the Incubatee to Barcelona Activa.

11.5 The obligations in this Article 11 amb l'altra Part.

11.2 Cap de les Parts revelarà cap documentació, informació o materials obtinguts de l'altra Part, tant si es distingeix (per exemple, com a "confidencial" o "informació reservada") com si no ("Informació Confidencial"), a cap tercera part sense el previ consentiment per escrit de l'altra Part, i en aquest cas, l'altra Part por demanar el receptor que signi un acord de confidencialitat. Dins del marc d'aquest article 11, la documentació inclou qualsevol document a lliurar segons s'estipula en aquest contracte amb l'excepció del Resum Executiu.

11.3 Cadascuna de les Parts pot desvetllar Informació Confidencial estrictament en base a la "necessitat de saber" a:
- els seus empleats;
- els seus agents professionals;
- els socis d'ESA BIC Barcelona.

11.4 En arribar la data de fi del Contracte, o si s'esdevé la rescissió o cancel·lació anterior d'aquest contracte segons s'estipula a l'article 16, la Part Receptora tornarà a la Part Reveladora o bé certificarà la destrucció de tota la Informació Confidencial, amb l'excepció dels Lliuraments que l'Empresa Incubada entregui a Barcelona Activa.

shall not apply to Confidential Information:

- which is in the public domain at the time of disclosure or becomes part of the public domain after disclosure otherwise than through a breach of this Contract;
- for which the Receiving Party can provide documentary evidence that it was in its lawful possession prior to disclosure to it by the Disclosing Party or which is lawfully and bona fide obtained thereafter by the Receiving Party from a Third Party who, to the knowledge or reasonable belief of the Receiving Party, did not receive the Confidential Information directly or indirectly from the Disclosing Party when under a duty of confidentiality;
- which, at the time of circulation is already known by the Receiving Party (as evidence in writing) and is not hindered by any obligation not to circulate; or
- which is required to be circulated by governmental or judicial order or applicable law.

11.6 The contents of this Contract are Confidential Information.

11.7 The obligations set out in this Article 11 shall survive the

11.5 Les obligacions d'aquest article 11 no atenyen a la Informació Confidencial:

- que sigui de domini públic en el moment de revelar-la o que passi a formar part del domini públic després de revelar-la per altres vies que no constitueixin incompliment d'aquest contracte;
- per la qual la Part Receptora proporcioni proves documentals que n'era en legítima possessió abans de revelar-la la Part Reveladora o que s'obtingui legítimament i de bona fe posteriorment per la Part Receptora a través d'una tercera part que la Part Receptora tingui constància o cregui que no hagi rebut la Informació Confidencial directament o indirecta de la Part Reveladora mentre es trobava limitada per l'obligació de confidencialitat;
- que, en el moment de circular ja sigui coneguda per la Part Receptora (com a prova per escrit) i no estigui afectada per cap obligació de no circular; o
- que sigui obligatori fer-la circular per ordre governamental o judicial o per llei.

11.6 El contingut d'aquest contracte és Informació Confidencial.

11.7 Les obligacions establertes en

termination, cancellation or expiry of this Contract.

ARTICLE 12 – INTELLECTUAL PROPERTY

12.1 Ownership

12.1.1 The Incubatee shall own all Intellectual Property Rights arising out of the Activity performed under this Contract as may be granted by law, as far as no infringement of Third Party rights occurs.

12.1.2 All rights pertaining to any results arising out of the Activity performed under this Contract shall belong to the Incubatee.

12.2 Foreground IPR

-Software that is considered ESA's Foreground shall not be subject to royalties;

12.3 Use of Intellectual Property Rights by the Agency:

If the Agency or its Member States require the use of Intellectual Property Rights generated under the incubation contract, owned by the Incubatee as described in Article 12.1.1 of this contract, for the performance of the Agency's programmes in the field of space research and

aquest article 11 sobreviuran a la rescissió, cancel·lació o finalització del Contracte.

ARTICLE 12 – PROPIETAT INTEL·LECTUAL

12.1 Titularitat

12.1.1 L'Empresa Incubada serà la propietària de tots els drets de propietat intel·lectual derivats de l'activitat que porti a terme dins del marc d'aquest contracte tal com estableixi la llei, sempre i quan no s'infringeixin els drets de terceres parts.

12.1.2 Tots els drets pertanyents als resultats derivats de l'activitat realitzada dins del marc d'aquest contracte seran propietat de l'Empresa Incubada.

12.2 Drets de propietat intel·lectual dels coneixements adquirits

-El programari que es consideri que pertany als coneixements adquirits per part de l'ESA no estarà subjecte a regalies;

12.3 Ús dels drets de propietat intel·lectual per part de l'Agència:

Si l'Agència o els seus estats membres requereixen l'ús de drets de propietat intel·lectual generats dins del marc del contracte d'incubació, pertanyents a l'Empresa Incubada segons es descriu a l'article 12.1.1 d'aquest contracte, per dur a

technology and applications in space, the Incubatee shall be contacted and offered the work. If within 60 days following the Agency's request, the Incubatee does not decide to or for any reason is not able to confirm its willingness to undertake the requested work, the Agency is automatically entitled to a worldwide, free of charge, irrevocable, transferable, non-exclusive licence to use such Intellectual Property Rights, which licence shall be limited to the territories of the Agency's Member States, with the right to grant sub-licenses in the source code.

In this case, the Agency and its Member States have the irrevocable right to enter into negotiations with and award such contract to or place any other kind of agreement with a third party. The same applies:

- in case the Incubatee does not submit a quotation within the adequately determined tendering period set by the Agency.
- in case that, following a quotation by the Incubatee, negotiation fail despite all reasonable efforts made in good faith by the Agency and the Incubatee.

In case the Agency continues the development with a third party a new branch of the source code shall be created.

terme els programes de l'Agència en l'àmbit de la investigació i la tecnologia espacial i les seves aplicacions a l'espai, es posarà en contacte amb l'Empresa Incubada i li oferirà la feina. Si en el termini de 60 dies següents a la petició de l'Agència, l'Empresa Incubada no decideix o per algun motiu no pot confirmar la seva voluntat d'acceptar la feina sol·licitada, l'Agència automàticament tindrà dret a una llicència mundial, sense càrrec, irrevocable, transferible, no exclusiva per utilitzar aquests drets de propietat intel·lectual, llicència que quedarà limitada als territoris dels estats membres de l'Agència, amb el dret d'atorgar subllicències del codi font.

En aquest cas, l'Agència i els seus estats membres tenen el dret irrevocable d'iniciar negociacions i atorgar el contracte o establir alguna altra mena d'acord amb una tercera part. Escau el mateix:

- en cas que l'Empresa Incubada no entregui un pressupost dins el termini de licitació adequadament establert per l'Agència.
- en cas que, després del pressupost de l'Empresa Incubada, les negociacions fracassin malgrat els esforços raonables de bona fe fets per l'Agència i l'Empresa Incubada.

En cas que l'Agència continués el desenvolupament amb una tercera part, es crearia una nova

12.3.1 When transferring any Intellectual Property Rights, of which the Incubatee retains the ownership in accordance with Article 12.1.1 of this contract, to an assignee the Incubatee shall ensure that the Agency's and its Member States' rights, as set out in Article 12.2.1 of this contract, are reassigned to the new assignee.

12.4 Transfer of Intellectual Property Rights outside the ESA Member States:
The Incubatee shall inform Barcelona Activa's technical representative, as stated in Article 9.3(a), well in advance of its intention to transfer outside the Agency's Member States any Intellectual Property Rights arising from this Contract.

ARTICLE 13 – LIABILITY

13.1 Limitations of Liability

13.1.1 Neither Party excludes its liability to the other Party for:

(a) death or personal injury caused by its negligence or that of its employees or agents;
(b) fraud, including fraudulent misrepresentations; and
(c) liability under Articles 11 and 12.

13.1.2 Limitation of Liability

branca del codi font.

12.3.1 En transferir drets de la propietat intel·lectual, dels quals l'Empresa Incubada en mantingui la propietat segons l'article 12.1.1 d'aquest contracte, a un cessionari, l'Empresa Incubada garantirà que els drets de l'Agència i els seus estats membres, tal com s'estableixen a l'article 12.2.1 d'aquest contracte, es reassignin al nou cessionari.

12.4 La transferència de drets de la propietat intel·lectual fora dels estats membres de l'ESA:
L'Empresa Incubada informarà el representant tècnic de Barcelona Activa, com s'indica a l'article 9.3(a), amb prou antelació de la seva intenció de traspassar fora dels estats membres de l'Agència els drets de propietat intel·lectual derivats del present Contracte.

ARTICLE 13 – RESPONSABILITAT

13.1 Limitacions de responsabilitat

13.1.1 Cap de les Parts queda exclosa de responsabilitat amb l'altra Part per:

(a) mort o lesions personals causades per la seva negligència o la dels seus empleats o agents;
(b) frau, incloses les representacions fraudulentes; i
(c) responsabilitat segons els articles 11 i 12.

13.1.2 Limitació de responsabilitat

Subject to Article 13.1.1, the liability of one Party towards the other under or in connection with this Contract whether arising from negligence, breach of contract or any other obligation or duty shall not exceed, an amount equivalent to 50.000 EURO (Fifty Thousand EURO), per event or series of connected events.

13.2 Infringements of the Law

13.2.1 Barcelona Activa or the Agency shall not be responsible if the Incubatee infringes any existing and/or future national, communal or provincial laws or decrees, rules or regulations in force in Spain or in any other country whatsoever.

13.2.2 The Incubatee shall indemnify Barcelona Activa from and against all claims, proceedings, damages, costs and expenses arising out of any infringement of the Incubatee's obligations under this Contract.

13.3 Infringement of the Rights of ESA BIC Barcelona Partners

13.3.1 The Incubatee shall indemnify the ESA BIC Barcelona partners from and against all claims, proceedings, damages, costs and expenses arising from the infringement of Intellectual Property Rights of third-parties with respect to the subject matter of this Contract - excluding any

Amb subjecció a l'article 13.1.1, la responsabilitat d'una Part davant de l'altra dins del marc o en relació amb aquest contracte tant si sorgeix per negligència, violació de contracte o qualsevol altra obligació o deure no superarà una quantitat equivalent a 50.000 EUR (cinquanta mil euros), per esdeveniment o sèrie d'esdeveniments connectats.

13.2 Infraccions de la llei

13.2.1 Barcelona Activa o l'Agència no seran responsables si l'Empresa Incubada infringeix una llei o decret, norma o disposició existent i/o futurs, nacionals, comunals o provincial vigents a Espanya o qualsevol altre país.

13.2.2 L'Empresa Incubada indemnitzarà Barcelona Activa per qualsevol reclamació, procés, danys, costos i despeses que derivin d'una infracció de les obligacions que l'Empresa Incubada accepta dins del marc d'aquest contracte.

13.3 La infracció dels drets dels socis d'ESA BIC Barcelona

13.3.1 L'Empresa Incubada indemnitzarà els socis d'ESA BIC Barcelona per qualsevol reclamació, procés, danys, costos i despeses que derivin d'una infracció dels drets de propietat intel·lectual de terceres parts en relació amb l'objecte d'aquest contracte –

infringement resulting from the use of documents, patterns, drawings or goods supplied by the ESA BIC Barcelona partners through Barcelona Activa- which may be made, or brought against the ESA BIC Barcelona partners, or to which the ESA BIC Barcelona partners may be put by reason of such infringement or alleged infringement.

13.3.2 Barcelona Activa shall notify the Incubatee immediately of any written claim or notice of infringement of third-party rights that it receives concerning the subject matter of this Contract.

13.3.3 The Incubatee shall immediately take all necessary steps within the Incubatee's competence to prevent or end a dispute and shall assist the ESA BIC Barcelona partners to defend any such dispute, or make settlement in respect of any claim or notice of infringement or suit for infringement.

13.3.4 The Parties shall notify each other of any known Intellectual Property Rights connected with the use of documents, patterns, drawings and goods supplied by one Party to the other or connected with the execution of the specifications laid down by the other Party.

13.4 Compensation for Damage Caused to Goods and Property

excloent-ne les infraccions que resultin de l'ús de documents, patrons, dibuixos o béns subministrats pels socis d'ESA BIC Barcelona a través de Barcelona Activa– que puguin fer o reclamar-se als socis d'ESA BIC Barcelona, o als quals els socis d'ESA BIC Barcelona puguin quedar exposats per raó de la mencionada infracció o suposada infracció.

13.3.2 Barcelona Activa notificarà l'Empresa Incubada immediatament de qualsevol reclamació per escrit o avís d'infracció dels drets de terceres parts que rebi en relació amb l'objecte d'aquest contracte.

13.3.3 L'Empresa Incubada farà immediatament tots els passos necessaris dins de la competència de l'Empresa Incubada per evitar o per acabar la disputa i ajudarà els socis d'ESA BIC Barcelona a defensar-se en la disputa, o arribar a un acord en relació amb qualsevol reclamació o avís d'infracció o demanda per infracció.

13.3.4 Les Parts es notificaran una a l'altra qualsevol dret de propietat intel·lectual conegut relacionat amb l'ús de documents, patrons, dibuixos i béns subministrats per una Part a l'altra o connectat amb l'execució de les especificacions establertes per l'altra Part.

Claims in respect of damage shall be settled as follows.

13.4.1 Direct Damages

(a) The Incubatee shall indemnify Barcelona Activa and ESA BIC partners against, and shall be personally responsible for, direct damage to property and equipment to the extent that such damage is caused by the negligence of the Incubatee and the Incubatee's personnel or agents.

(b) Barcelona Activa and ESA BIC partners shall indemnify the Incubatee against, and shall be personally responsible for, direct damage to the Incubatee's property and equipment to the extent that such damage is caused by the negligence of Barcelona Activa or ESA BIC partners or their staff or agents.

13.4.2 Indirect or Consequential Damages

(a) The Parties shall in no circumstances be liable for indirect or consequential damages such as loss of use, loss of business, loss of data, loss of rights, loss of services, loss of goodwill, Third Party claims to the extent that they

13.4 Compensació per danys causats a béns i a la propietat

Les reclamacions per danys es resoldran com es descriu a continuació.

13.4.1 Danys directes

(a) L'Empresa Incubada indemnitzarà Barcelona Activa i els socis d'ESA BIC i serà personalment responsable de danys directes a la propietat i els equipaments en la mesura que els danys siguin causats per la negligència de l'Empresa Incubada i el personal o agents de l'Empresa Incubada.

(b) Barcelona Activa i els socis d'ESA BIC indemnitzaran l'Empresa Incubada i seran personalment responsables de danys directes a la propietat i equipaments de l'Empresa Incubada en la mesura que els danys siguin causats per la negligència de Barcelona Activa o els socis d'ESA BIC o el seu personal o agents.

13.4.2 Danys indirectes o consegüents

(a) Les Parts sota cap circumstància no seran responsables per danys indirectes o consegüents com ara la pèrdua d'ús, pèrdua de negoci, pèrdua de dades, pèrdua de drets, pèrdua de serveis, pèrdua de bona

represent the indirect loss of a Third Party, loss of revenues or anticipated savings, or for any indirect financial loss or indirect economic loss or for any indirect or consequential loss or damage whatsoever suffered by the other Party.

(b) The Parties shall in no circumstances be liable for loss of profit, whether direct or indirect.

13.5 Damages to Third Parties by the Incubatee

Barcelona Activa shall not be liable for any damage caused by the personnel or agents of the Incubatee to a Third Party during the performance of this Contract.

ARTICLE 14 – CHANGES TO THIS CONTRACT

14.1 Introduction of a Change

14.1.1 For all changes to this Contract, whether requested by Barcelona Activa or initiated by the Incubatee, the Incubatee shall submit a proposal for a CCN.

14.1.2 The Incubatee shall ensure -in liaison with Barcelona Activa- that each change proposal is fully coordinated and that all

voluntat, reclamacions de terceres parts, en la mesura que representin la pèrdua indirecta d'una tercera part pèrdua d'ingressos o estalvis esperats, o per qualsevol pèrdua financera indirecta o pèrdua econòmica indirecta o pèrdua o dany consegüent sofert per l'altra Part.

(b) Les Parts sota cap circumstància no seran responsables de la pèrdua de benefici, ja sigui directe o indirecte.

13.5 Els danys a terceres parts que provoqui l'Empresa Incubada

Barcelona Activa no serà responsable dels danys causats pel personal o els agents de l'Empresa Incubada a una tercera part durant la realització d'aquest contracte.

ARTICLE 14 – CANVIS D'AQUEST CONTRACTE

14.1 Introducció d'un canvi

14.1.1 Per a tots els canvis d'aquest contracte, tant si són sol·licitats per Barcelona Activa o per l'Empresa Incubada, l'Empresa Incubada lliurarà una proposta de CCN (de l'anglès, Contract Change Notice, o notificació de canvi al contracte).

14.1.2 L'Empresa Incubada garantirà –en col·laboració amb Barcelona Activa– que cada proposta de

reasonably foreseeable implications of the change have been considered by the Incubatee and Barcelona Activa.

The Incubatee shall, on the request of Barcelona Activa, provide additional documentary evidence of the affect of the change to both Parties.

14.2 Approval or Rejection of the Change Proposal

14.2.1 Should the change proposal be approved by Barcelona Activa, a corresponding CCN shall be prepared by Barcelona Activa's contractual representatives as stated in Article 9.3(b) and submitted to both Parties for signature.

14.2.2 Should a change proposal be rejected for any reason by Barcelona Activa, the Incubatee shall be informed accordingly, together with the reasons for the rejection. At the request of either Party, the change may be discussed at a Change Review Board, consisting of a contractual and a technical representative of each Party.

14.3 Implementation and Status of an Approved CCN

Upon the signature of a CCN by both Parties, the CCN will have immediate effect and constitutes a binding contractual agreement

canvi sigui totalment coordinada i que totes les implicacions raonablement previsibles del canvi s'hagin considerat per part de l'Empresa Incubada i Barcelona Activa.

L'Empresa Incubada, a petició de Barcelona Activa, proporcionarà proves documentals addicionals dels efectes del canvi per a ambdues Parts.

14.2 Aprovació o rebuig de la proposta de canvi

14.2.1 Si la proposta de canvi és aprovada per Barcelona Activa, els representants contractuals de Barcelona Activa tal com s'exposen a l'article 9.3(b) prepararan el corresponent CCN i el lliuraran a totes dues Parts per a que el signin.

14.2.2 Si una proposta de canvi és rebutjada per qualsevol raó per part de Barcelona Activa, l'Empresa Incubada en serà informada adequadament, i se li donaran els motius del rebuig. A petició de qualsevol de les Parts, el canvi es pot comentar en una Junta de Revisió de Canvis, formada per un representant contractual i un de tècnic de cadascuna de les Parts.

14.3 Implementació i estatus d'un CCN aprovat

Quan totes dues Parts hagin signat l'CCN, l'CCN tindrà un efecte immediat i constitueix un acord contractual vinculant entre

between the Parties. The Incubatee shall implement the change in accordance with the implementation dates agreed in the CCN.

ARTICLE 15 – POST INCUBATION MANAGEMENT

On each anniversary of the end of the Contract Term, during 10 years, subject to losing the right to use the *ESA BIC logo or text line* if non compliant, the Incubatee shall prepare and submit an Annual Performance Report (see Appendix 1, point 5.6 annual performance report) to the Incubation Manager of ESA BIC Barcelona, as stated in Article 9.3(a), as well as to the European Space Agency's Technical Representative, as follows:

Mr. B. Naulais (TEC-ST)
ESTEC
P.O. Box 299,
2200 AG Noordwijk, NL
E-mail: bruno.naulais@esa.int
Tel.: + 31 71 56 54711
Fax.: + 31 71 56 56635

ARTICLE 16 – TERMINATION AND CANCELLATION

16.1 Right of Termination

16.1.1 Each Party will have the right at any time during the Contract Term, without prejudice to its other rights or remedies, to terminate this Contract immediately, and without cause, by one (1) month's written notice to the other Party.

16.1.2 Each Party reserves the right to

totes dues Parts. L'Empresa Incubada implementarà el canvi d'acord amb les dates d'implementació acordades a l'CCN.

ARTICLE 15 – GESTIÓ POST INCUBACIÓ

Cada aniversari de la data de fi del termini de contracte, durant 10 anys, subjecte a la pèrdua del dret de fer servir l'*ESA BIC logotip o Línia de Text* en cas d'incompliment, l'Empresa Incubada prepararà i lliurarà un Informe Anual d'Activitat (vegeu l'Apèndix 1, punt 5.6, Informe Anual d'Activitat) al gerent d'incubació de l'ESA BIC Barcelona, com s'indica a l'article 9.3(a), a més del representant tècnic de l'Agència Espacial Europea que segueix:

Mr. B. Naulais (TEC-ST)
ESTEC
P.O. Box 299
2200 AG Noordwijk, NL
E-mail: bruno.naulais@esa.int
Tel.: (+ 31) 71 56 54711
Fax: (+ 31) 71 56 56635

ARTICLE 16 – RESOLUCIÓ I CANCEL·LACIÓ

16.1 Dret de resolució

16.1.1 Cadascuna de les Parts té dret en qualsevol moment durant el termini de contracte, sense perjudici dels altres drets o solucions jurídiques, a resoldre aquest contracte immediatament, i sense causa, amb un (1) mes de preavís per escrit a l'altra Part.

terminate this Contract, with immediate effect, in the event that the other Party commits a substantial breach of this Contract.

16.1.2 Cada Part es reserva el dret de resoldre aquest contracte, amb efecte immediat, en cas que l'altra Part cometi una violació substancial d'aquest contracte.

16.2.1 In the event of cancellation of this Contract by Barcelona Activa without any fault of the Incubatee, the Incubatee shall on receipt of Barcelona Activa's instructions for cancellation of this Contract, immediately take the necessary steps to implement the instructions. The period by which the Incubatee must implement such instructions shall be determined by Barcelona Activa after consultation with the Incubatee.

16.2.1 En el cas de cancel·lació d'aquest contracte per part de Barcelona Activa sense falta per part de l'Empresa Incubada, l'Empresa Incubada, en rebre les instruccions de Barcelona Activa per cancel·lar aquest contracte, immediatament haurà de fer els passos necessaris per implementar les instruccions. El període de temps del què disposa l'Empresa Incubada per implementar les instruccions el determinarà Barcelona Activa després de consultar-ho amb l'Empresa Incubada.

16.2.2 Barcelona Activa shall indemnify the Incubatee against such part of any loss of profit as is reasonably attributable to the cancellation of this Contract and against any damages resulting from the cancellation of this Contract in particular against any commitments, liabilities or expenditure which are reasonably and properly incurred by the Incubatee and are directly related to this Contract, in so far as the said commitments, liabilities or expenditure would otherwise represent an unavoidable loss by the Incubatee by reason of the cancellation of this Contract.

16.2.2 Barcelona Activa indemnitzarà l'Empresa Incubada per la part de pèrdues de benefici raonablement atribuïble a la cancel·lació d'aquest contracte i per els danys provocats per la cancel·lació d'aquest contracte, en particular pels compromisos, responsabilitats o despeses que s'hagin produït, i siguin raonables i adequats, per part de l'Empresa Incubada, i estiguin directament relacionats amb aquest contracte, en la mesura que els esmentats compromisos, responsabilitats o despeses altrament suposarien una pèrdua inevitable per a l'Empresa Incubada per raó de la cancel·lació d'aquest contracte.

16.2.3 The amount of compensation payable under Article 16.2.2 shall be fixed on the basis of documentary evidence produced by the Incubatee and accepted by Barcelona Activa. In calculating the amount of compensation payable to the Incubatee Barcelona Activa shall take account of the proportion of this Contract completed and shall take into account the provisions of Article 16.2.4.

16.2.4 Barcelona Activa shall in no circumstances be liable to pay any sum which deviates from the provisions set out in Article 7.1 and Article 4 herein or when added to the other sums paid, due or becoming due to the Incubatee under this Contract by Barcelona Activa, exceeds the total contractual payments due by Barcelona Activa to the Incubatee, as set out in Article 7.1.

16.3 Grounds for Cancellation by Barcelona Activa

Barcelona Activa will have the right, without prejudice to its other rights or remedies, after full consideration of all relevant circumstances, which may include consultation with the Incubatee, to cancel this Contract by giving written notice with immediate effect to the Incubatee in any of the following circumstances:

16.2.3 La quantitat de compensació a pagar segons l'article 16.2.2 es fixarà en base a les proves documentals que aporti l'Empresa Incubada i accepti Barcelona Activa. En calcular la quantitat de compensació a pagar a l'Empresa Incubada, Barcelona Activa tindrà en compte la proporció d'aquest contracte que s'hagi completat i tindrà en compte les disposicions de l'article 16.2.4.

16.2.4 Barcelona Activa sota cap circumstància serà responsable del pagament de cap suma que es desvii de les disposicions de l'article 7.1 i l'article 4 d'aquest contracte, o que en sumar-les a d'altres quantitats que hagi de pagar a l'Empresa Incubada en compliment d'aquest contracte Barcelona Activa, excedeixin els pagaments contractuals totals que degui Barcelona Activa a l'Empresa Incubada, com es descriu a l'article 7.1.

16.3 Motius de cancel·lació per part de Barcelona Activa

Barcelona Activa tindrà el dret, sense perjudici dels seus altres drets o solucions jurídiques, després d'una profunda consideració de totes les circumstàncies pertinents, que pot incloure la consulta amb l'Empresa Incubada, de cancel·lar aquest contracte tot donant avís per escrit amb efectes immediats a l'Empresa Incubada en qualsevol

(a) if the Incubatee assigns or transfers this Contract in breach of Article 17;

(b) if the Incubatee becomes insolvent or if its financial position is such that within the framework of the national law of the Incubatee's incorporation, legal action leading towards bankruptcy may be taken against the Incubatee by its creditors;

(c) if the Incubatee conducts fraudulent practices in connection with this Contract, particularly concerning the nature and quality of the Activity or by giving or offering gifts or remuneration for the purpose of bribery to any person, irrespective of whether such bribes or remuneration are made on the initiative of the Incubatee or otherwise; and/or

(d) if the Incubatee has provided incorrect and/or incomplete information regarding:

(a) the Statement of Non Co-incubation;
(b) the Incubatee's legal ownership;
(c) the Incubatee's Chamber of Commerce registration; and/or
(d) the Declaration of State Aid.

16.4 Consequences of Cancellation

Any information, in documentary or other physical form, pertaining

de les circumstàncies següents:

(a) si l'Empresa Incubada assigna o transfereix aquest contracte en violació de l'article 17;

(b) si l'Empresa Incubada es torna insolvent o si la seva posició financera es tal que dins del marc de la llei nacional de l'Empresa Incubada es puguin iniciar accions legals per declarar-ne la fallida per part dels seus creditors;

(c) si l'Empresa Incubada porta a terme pràctiques fraudulentes en relació amb aquest contracte, en particular relacionades amb la naturalesa i qualitat de la seva activitat o donant o oferint regals o remuneració amb l'objectiu de subornar qualsevol persona, independentment de si els suborns o la remuneració es fan per iniciativa de l'Empresa Incubada o no; i/o

(d) si l'Empresa Incubada ha proporcionat informació incorrecta i/o incompleta sobre:

(a) la declaració de No Coincubació;
(b) la propietat legal de l'Empresa Incubada;
(c) el registre de l'Empresa Incubada a la Cambra de Comerç; i/o
(d) la Declaració d'Ajuts Estatals.

16.4 Conseqüències de la cancel·lació

Qualsevol informació, documental

to the Activity carried out by the Incubatee during the Contract Term, remains the property of Barcelona Activa and shall be handed over to Barcelona Activa upon the expiry or cancellation of this Contract. This shall include:

(a) any information and documentation under Article 3.1;
(b) any equipment under Article 3.2;
(c) any software under Article 3.3.

ARTICLE 17 - ASSIGNATION OF THIS CONTRACT

The Incubatee shall not be permitted to assign its rights and/ or transfer its obligations under this Contract in whole or in part.

ARTICLE 18 - DISPUTE SETTLEMENT

18.1 This Contract shall be governed by the laws of Spain.

18.2 The Parties will consult with each other promptly when events occur or matters arise that may occasion a question of interpretation or implementation of the terms of this Contract. Any issue of interpretation or implementation of this Agreement that cannot be settled by the designated points of contact shall be referred to arbitration.

18.3 Any dispute arising out of the interpretation or implementation

o de qualsevol altra forma física, relativa a l'activitat de l'Empresa Incubada durant el termini de contracte, queda en propietat de Barcelona Activa i es lliurarà a Barcelona Activa en finalitzar o cancel·lar aquest contracte. Això inclou:

(a) qualsevol informació i documentació esmentada en l'article 3.1;
(b) qualsevol equipament esmentat a l'article 3.2;
(c) qualsevol programari referit a l'article 3.3.

ARTICLE 17 – ASSIGNACIÓ D'AQUEST CONTRACTE

No es permet a l'Empresa Incubada assignar els seus drets i/o transferir les seves obligacions dins del marc d'aquest contracte de manera total ni parcial.

ARTICLE 18 – RESOLUCIÓ DE CONFLICTES

18.1 Aquest Contracte es regirà per les lleis d'Espanya.

18.2 Les Parts consultaran l'una amb l'altra sense demora quan s'esdevinguin fets o sorgeixin assumptes que puguin ocasionar diferències en la interpretació dels termes d'aquest contracte. Qualsevol diferència d'interpretació o implementació d'aquest Acord que no es pugui resoldre entre els punts de contacte designats se sotmetrà a arbitratge.

18.3 Qualsevol conflicte que sorgeixi

of this Agreement that cannot be settled through the consultations referred to in Article 18.1 above may, at the request of either Party, be submitted to arbitration according to the Rules of Arbitration of the International Chamber of Commerce. The arbitral tribunal shall sit in Barcelona and the language of the arbitration shall be English. The enforcement of the award shall be governed by the rules of procedure in force in Spain.

ARTICLE 19 - DATA PROTECTION

19.1 To the extent that is reasonably necessary, in connection to the Incubatee's activities under this contract, his data may be disclosed to others, including staff of ESA BIC Barcelona, Barcelona Activa and all ESA BIC Barcelona partners, for any studies and/or reporting that may be carried out by the Agency and/or Barcelona Activa.

The Incubatee hereby consents to the recording, processing, use and disclosure of personal data related to him as set out here above (including the recording, processing, use and disclosure of his sensitive personal data to the extent required by reason of the contractor's performance of the activities under this contract) including the transmission of such data between Spain and other countries for the fulfilment of the

arran de la interpretació o implementació d'aquest Acord i no pugui resoldre's amb consulta a les lleis esmentades a l'article 18.1 podrà, a petició de qualsevol de les Parts, ser sotmès a arbitratge segons les Normes d'Arbitratge de la Cambra de Comerç Internacional. El tribunal arbitral tindrà seu a Barcelona i l'idioma de l'arbitratge serà l'anglès. El compliment de la decisió serà governat per les normes de procediment vigents a Espanya.

ARTICLE 19 - PROTECCIÓ DE DADES

19.1 En la mesura que sigui raonablement necessari, en relació amb l'activitat de l'Empresa Incubada dins del marc d'aquest contracte, les seves dades es poden desvetllar a d'altres, com ara personal d'ESA BIC Barcelona, Barcelona Activa i tots els socis d'ESA BIC Barcelona, per a qualsevol estudi i/o informe que pugui dur a terme l'Agència i/o Barcelona Activa.

L'Empresa Incubada consent amb aquest document la gravació, el processament, l'ús i la comunicació de dades personals relacionades amb l'Empresa, tal com s'estableix més amunt (incloent la gravació processament, ús i comunicació de dades personals sensibles en la mesura que es requereixi per raó de l'actuació professional del contractant dins del marc

above requirements.

d'aquest contracte) inclosa la transmissió de dades entre Espanya i d'altres països en compliment de les necessitats esmentades.

Done and signed in two (2) original copies, one for each Party to this Contract,

Fet i signat per duplicat, amb dues (2) còpies originals, una per a cadascuna de les Parts d'aquest contracte,

On behalf of the ESA BIC Barcelona Activa:

En nom de l'ESA BIC Barcelona Activa:

Mr. Jordi Joly i Lena
Chief Executive Manager
Barcelona Activa

Sr. Jordi Joly i Lena
Conseller Delegat
Barcelona Activa

On behalf of the Incubatee:

En nom de l'Empresa Incubada:

Mr. Ivan Lloro Boada
President
ASTRADENTIUM HEALTH TECHNOLOGIES, SL

Sr. Ivan Lloro Boada
President
ASTRADENTIUM HEALTH TECHNOLOGIES, SL.

Ajuntament de Barcelona
Àrea d'Economia, Empresa i Ocupació
Barcelona Activa SAU SPM

Ajuntament de Barcelona

Ç

Carta de apoyo proyecto de investigación: Salud Oral & HS2016
1 mensaje

Anais González <anais.gonzalez@eithealth.eu>
Para: victorlloro@gmail.com <victorlloro@gmail.com>
jue., 20 dic. 2018 a las 12:0

Estimado Victor,

En primer lugar para EIT Health Spain es extremadamente importante que, como ganadores de la convocatoria EIT Health Spain Headstart 2016 sigáis desarrollando el proyecto, y adentrandoos en la fase clínica y de validación.

Después de revisar el Proyecto: "**Salud Oral en Misiones espaciales de larga duración: experiencia previa, necesidades de prevención y tratamiento. Propuesta de diseño de un equipamiento dental aeroespacial**", queda patente no sólo la excelente calidad del proyecto en el que trabajáis, sino también la relevancia de cada una de las actividades que habéis planteado. Encontramos especialmente valioso, el hecho de que dediquéis parte del plan de trabajo a identificar y profundizar las necesidades médicas actuales y las reflejadas en la literatura. Los análisis retrospectivos, son una de las herramientas más valiosas que os permitirán realmente ajustar el diseño a lo que el mercado y los usuarios demandan.

Es por ello que no tendré ningún problema en aportaros una carta de apoyo al proyecto de Tesis del cuál eres autor. La relevancia de la investigación que propones queda patente, especialmente a nivel panaeuropeo, y incidirá de forma clara en los futuros pasos de la investigación del sector aeroespacial. Además no dudamos, que estos resultados se podrán trasladar a aplicaciones directas en el día a día de los dentistas y demás profesionales.

Saludos cordiales,

Anaïs G.

Anaïs González I
Innovation Manager EIT Health Spain

Parc Científic de Barcelona

Baldiri Reixac 4-8 Torre R

08028 Barcelona
Spain

M: +34 618 46 1526

E: anais.gonzalez@eithealth.eu

EIT Health is supported by the EIT, a body of the European Union

Gmail

Victor Lloro <victorlloro@gmail.com>

Your Abstract for AsMA 2022 is Accepted

1 missatge

Charles Reese <pday@asma.org> 10 de desembre de 2021, a les 16:35
Per a: VICTORLLORO@gmail.com

Dear VICTOR LLORO BOADA,

I would like to congratulate you on the acceptance of your abstract ID# 7230, entitled "The importance of periodontal disease in microgravidity." for presentation at the Aerospace Medical Association's 92nd Annual Scientific Meeting. The meeting will be held at the Peppermill Resort Hotel in Reno, NV, May 22-26, 2022.

Your abstract has been accepted as a Panel presentation in the session entitled: "Aerospace Dentistry," to be held 5/25/2022, from
2:00 PM to 3:30 PM in the Tuscany 12 room.

Please take note of this, as your presentation type may have changed.

Every effort was made to keep the presentation type as submitted, but with two additional plenary sessions, the schedule was very tight.

You are listed as the submitting author. Please be sure to share this information with the presenter (if you are not the presenter) and all other authors on the abstract.

If you have a **Panel** presentation, ALL PowerPoint™ Presentations MUST be in 16:9 format and saved to a thumb drive.

All attendees, including presenters, must register for the meeting. Register early to enjoy significant savings. A discounted rate will be available for non-member presenters. Early bird Registration runs from January 2-31. Information is available on the Meetings Page on the AsMA web site: http://www.asma.org.

Check the Meeting Addendum for the most up to date schedule information, which will be posted on the Meetings page of http://www.asma.org web site in April. A meeting app will also be available with up to the minute changes throughout the meeting.

I look forward to seeing you in Reno! If I can be of assistance, please contact me via email at sciprog@asma.org or contact Ms. Pam Day in the home office by email or phone at pday@asma.org or (703)739-2240, ext 101.

Sincere Best Regards,
Charles Reese, M.D., Ph.D
Chair, AsMA Scientific Program Committee
Aerospace Medical Association

PS: Please keep this e-mail for your records

Gmail Victor Lloro <victorlloro@gmail.com>

Your Abstract for AsMA 2021 is Accepted

1 missatge

Vivienne Lee <pday@asma.org> 9 de desembre de 2020, a les 15:43
Per a: VICTORLLORO@gmail.com

Dear VICTOR LLORO BOADA,

I would like to congratulate you on the acceptance of your abstract ID# 5872, entitled "PREVENTION AND CONTROL OF SURFACE POLLUTION DURING USE OF DENTAL SPRAY. CONSIDERATIONS IN MICROGRAVITY CONDITIONS" for presentation at the Aerospace Medical Association's 91st Annual Scientific Meeting. The meeting will be held at the Peppermill Resort Hotel, Reno, NV, May 23-27, 2021.

Your abstract has been accepted as a Panel presentation in the session entitled: "AVIATION DENTISTRY. DIGITAL ADVANCES & COMMON RELATED ISSUES," to be held 5/25/2021, from 4:00 PM to 5:30 PM. Please take note of this, as your presentation type may have changed.

You are listed as the submitting author. Please be sure to share this information with the presenter (if you are not the presenter) and all other authors on the abstract. Check the Meeting Addendum for the most up to date schedule information, which will be posted on the Meetings page of http://www.asma.org web site in April. A meeting app will also be available with up to the minute changes throughout the meeting.

If you have a **Slide** presentation, ALL PowerPoint™ Presentations MUST be in 16:9 format and saved to a thumb drive.

If you have a **Poster** presentation, the poster board area is 8' x 4'. Posters should be available for viewing all day on Wednesday and Thursday. You only need to be present during the session time assigned.

Supplying PDF Files
The Aerospace Medical Association will make all presentations from its Annual Scientific Meeting available to members and attendees after the meeting. If you have a **Poster**, you will be asked to upload it to the Open Water submission site at a later date. If you have a Slide or Panel presentation, the PowerPoint™ presentation will be live captured with audio. Note that before release, presentations will be converted to Adobe Acrobat PDF files by AsMA.

All attendees, including presenters, must register for the meeting. Register early to enjoy significant savings. A discounted rate will be available for non-member presenters. Early bird Registration runs from January 2-31. Information is available on the Meetings Page on the AsMA web site: http://www.asma.org.

I look forward to seeing you in Reno! If I can be of assistance, please contact me via email at sciprog@asma.org or contact Ms. Pam Day in the home office by email or phone at pday@asma.org or (703)739-2240, ext 101.

Sincere Best Regards,
Vivienne Lee, PhD, MRAeS
Chair, AsMA 2021 Scientific Program Committee
Aerospace Medical Association

PS: Please keep this e-mail for your records

Gmail Victor Lloro <victorlloro@gmail.com>

Congratulations! Your abstract has been accepted for AsMA 2015

2 missatges

pday@asma.org <pday@asma.org> 6 de desembre de 2017, a les 19:50
Respon: pday@asma.org
Per a: victorlloro@gmail.com

Wednesday, 06-Dec-2017

Dear Víctor Lloro,

I congratulate you on the acceptance of your abstract 2880036, entitled "**NEEDS FOR DENTAL TREATMENT IN CONDITIONS OF ISOLATION**," for presentation at the Aerospace Medical Association 89th Annual Scientific Meeting at the Hilton Anatole Hotel, Dallas,TX, May 6 - 10, 2018.

Your abstract has been accepted as a Slide presentation; please note that this presentation type may have been changed to fit within the program. It is scheduled to be part of the session "TO DNIF OR NOT DNIF: UNIQUE AIRCREW TREATMENT," May 7, 2018, from 4:00 PM - 5:30 PM in the Ballroom E. Please log on to the ScholarOne Abstract site to accept this invitation.

Please check your messages on the submission site for emails, visa letters, and other announcements using the Message tab to the top right.

Check the Meeting Addendum and final schedule for the most up-to-date schedule information, which will be posted on the Meetings and Events page of the AsMA web site (www.asma.org) in April.

All attendees, including presenters, must register for the meeting. Register early to enjoy significant savings. A discounted rate will be available for non-member presenters. Information and a registration form will be mailed to you in the meeting brochure and are available on the 'Meetings and Events Page' on the AsMA web site at www.asma.org.

I look forward to seeing you in Dallas,TX. If I can be of assistance, please contact me via email at sciprog@asma.org or contact Ms. Pam Day in the home office by email or phone at pday@asma.org, or (703)739-2240, ext 101.

Sincere Best Regards,
Barry Shender, Ph.D.
Chair, Scientific Program Committee, AsMA 2018 Annual Meeting
Aerospace Medical Association

PS: Please print this e-mail for your records

Note: You are responsible for continuing to keep your contact information current. You can update your contact information online. In the future, you will need to log in using your user ID and Password.
Your User ID is: VictorLLoro1984
If you have an account, please use the password you created. If you do not have an account or if you have forgotten your password you can log in here to change/create a new one: Forgot Password Link
*User ID and Password are case-sensitive. This means they must be entered on the login screen exactly as they appear above, using the same capitalization.

Victor Lloro <victorlloro@gmail.com> 26 de febrer de 2021, a les 11:20
Per a: Sergio Alonso <salonso@lidesec.com>

[Text citat amagat]

Gmail Victor Lloro <victorlloro@gmail.com>

Your Abstract for AsMA 2019 is Accepted

3 missatges

Pam Day <pday@asma.org> 19 de desembre de 2018, a les 19:08
Per a: VICTORLLORO@gmail.com

Dear Víctor Lloro,

I would like to congratulate you on the acceptance of your abstract ID# 1461 / Program ID# 99, entitled "What do we know about the relationship between dental health and microgravity conditions?" for presentation at the Aerospace Medical Association's 90th Annual Scientific Meeting. The meeting will be held at the Rio All Suite Hotel, Las Vegas, NV, from May 5-9, 2019.

Your abstract has been accepted as a Panel presentation in the session entitled: Changes of Paradigms in Modern Dentistry, to be held 5/7/2019 10:30 AM (Eastern Time (US & Canada)) to 5/7/2019 12:00 PM (Eastern Time (US & Canada)) in the Brasilia 1 room. The primary session chair as of now is Jose Luis Mompell; joseluismompell@gmail.com. Please take note of this, as your presentation type may have changed. Please be sure to check the Meeting Addendum and final schedule for the most up to date schedule information, which will be posted on the Meetings page of http://www.asma.org web site in April.

You are listed as the presenting author. Please be sure to share all necessary information with all other authors on the abstract.

If you have a **Slide** presentation, ALL PowerPoint™ Presentations MUST be in 16:9 format and saved to a thumb drive.

If you have a **Poster** presentation, the poster board area is 8' x 4'. Posters should be available for viewing all day on Wednesday and Thursday. You only need to be present during the session time assigned.

Supplying PDF Files
The Aerospace Medical Association will make all presentations from its Annual Scientific Meeting available to members and attendees after the meeting. If you have a Poster, you will be asked to upload it to the Open Water submission site. If you have a Slide or Panel presentation, the PowerPoint™ presentation will be live captured with audio. Note that before release, presentations will be converted to Adobe Acrobat PDF files by AsMA.

The file-naming convention for providing your presentation is as follows:
201905_99_Lloro

All attendees, including presenters, must register for the meeting. Register early to enjoy significant savings. A discounted rate will be available for non-member presenters. Early bird Registration runs from January 2-31. Information is available on the Meetings Page on the AsMA web site: http://www.asma.org.

I look forward to seeing you in Las Vegas! If I can be of assistance, please contact me via email at sciprog@asma.org or contact Ms. Pam Day in the home office by email or phone at pday@asma.org or (703)739-2240, ext 101.

Sincere Best Regards,
Walter W. Dalitsch III, M.D., M.P.H., FAsMA
Chair, AsMA Scientific Program Committee
Aerospace Medical Association

PS: Please keep this e-mail for your records

Victor Lloro <victorlloro@gmail.com> 26 de febrer de 2021, a les 11:19
Per a: Sergio Alonso <salonso@lidesec.com>

[Text citat amagat]


STEM
Science | Technology | Engineering | Mathematics
International Organization
ONLINE SUMMIT ON ASTROPHYSICS AND SPACE RESEARCH (CASR - 2020)
NOVEMBER 12-13, 2020 | LISBON, PORTUGAL
CERTIFICATE OF ATTENDANCE
Víctor Lloro Boada
Health University of Barcelona campus, Spain
for attending as an Invited Speaker at the
CASR-2020 Online Conference during November 12-13, 2020.
BILL QUIRK
ASSEMBLY MEMBER
20TH DISTRICT, USA
PRAVEEEN POTHALA
PRESIDENT STEMIO,
SINGAPORE
CASR-2020 COMMITTEE MEMBERS
THOMAS GREENE
NASA, USA
DAVID LEISAWITZ
NASA, USA
VALENTINA ZHARKOVA
UK
HUI LI
China


CASR 2020
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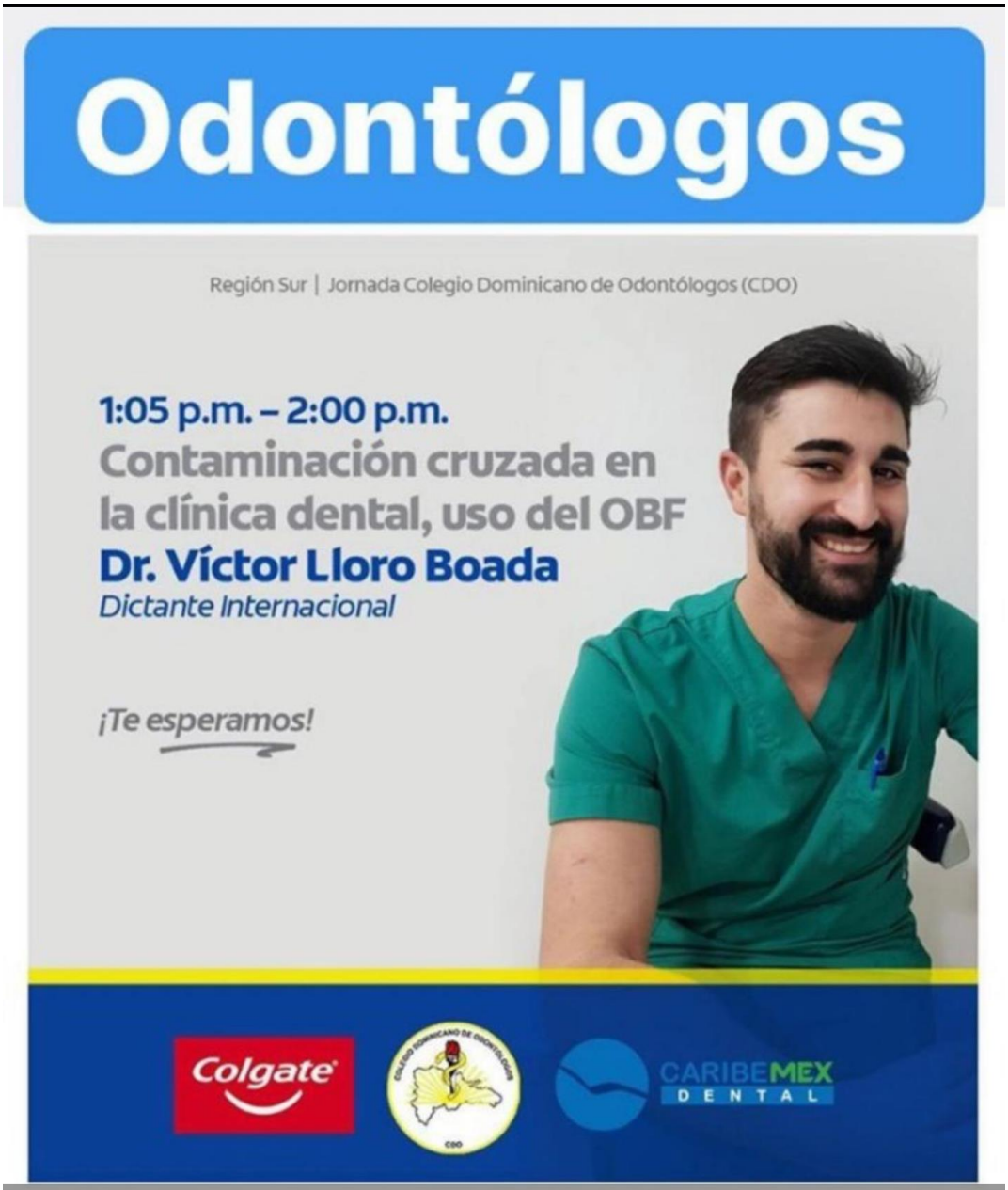
International Organization
Is oral health affected in long period
space missions only by microgravity?



SABADO 8 DE AGOSTO, EL CREADOR DEL OBF EXPONE SUS EXPERIENCIAS SOBRE LA CONTAMINACION CRUZADA EN NUESTROS CONSULTORIOS Y LA FORMA DE REDUCIRLO. ! PARTICIPA!

esa

European Student Education Programme and the 7th Student Parabolic Flight Campaign

Certificate of Participation

The European Space Agency and its Education Department is committed to encourage students to actively prepare for, and participate in the building of their future through a better knowledge of (space) technology and sciences. One of the most exciting projects of this programme is the annual Student Parabolic Flight Campaign that takes place every year in Bordeaux.

This certificate is awarded to

Victor Llano

in recognition of your enthusiastic participation to the Student Education Programme by participating in the ZERO-G experience of the 7th Student Parabolic Flight Campaign. While implementing and performing your team experiment, you have contributed to the demonstration of the effects and benefits of weightlessness in the "Space" environment.

Bordeaux 29th June – 16th July 2004

Philippe Willekens
Administrator for Education Projects

Jean-Jacques Dordain
Director General