UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY
Oral Microbial Communities in States of Hyposalivation
Aim 1 (Healthy Controls, Normal Salivation)

1. Introduction to medical research

This is a medical research study initiated by Dr. David Relman, MD, at Stanford University. Your study doctor Ava Wu, DDS, from the Department of Orofacial Sciences at the University of California San Francisco (UCSF) will explain this study to you. Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You should discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask Dr. Wu.

2. Why is this study being done?

The purpose of this study is to learn how changes in salivary flow alter the structure of human oral microbial communities over time, predisposing individuals who cannot produce enough saliva to oral disease. We believe that the information obtained from this study will allow us, in the future, to develop novel salivary enhancement therapies diagnostics, as well as ecologically-based therapeutics that target the altered microbial communities present in individuals with long-term low salivary output.

3. Who pays for this study?

The National Institute of Dental and Craniofacial Research, a division of the National Institutes of Health.

4. How many people will take part in this study?

About 159 people will take part in this study. This includes a maximum of 59 individuals who have normal salivary function and a maximum of 100 individuals who have Sjögren's syndrome. Sjögren's syndrome is an autoimmune disorder characterized by a long-term reduction in salivary flow. You are being asked to take part in this study because you are a healthy, non-smoking adult over the age of 18 with normal salivation.

5. How is eligibility to participate determined?

You will need to have the following "screening" exams, tests, or procedures to find out if you can participate in the main part of the study.

5.1. Dental Examination: You will have a 2.5-hour dental examination, without x-rays, similar to dental exams done for regular dental care. This will include an examination of:

- Oral Mucosal Health: We will look for signs of disease on oral mucosal surfaces (e.g., tongue, cheeks, inner lips, etc.).
- Dental History: We will record the number and location of teeth, fillings, crowns, bridges, and prosthetic devices. We will also examine teeth for cavities, but we will not be able to detect cavities between teeth, as this requires x-rays.
- Oral hygiene: We will look at the presence of plaque on each of your teeth. We will record sites where plaque is found, and we will provide you with an assessment of your oral hygiene habits at the end of the study.

5.1. Dental Examination, continued…

- Periodontal Evaluation: We will insert a periodontal probe below the gumline at each of six locations surrounding all teeth to measure the depth of periodontal pockets and to assess bleeding upon probing and to measure gumline recession.

- Salivary Flow Rates: We will perform two separate tests to evaluate salivary function. We will ask you to drool into a test tube for 5 minutes, and then we will ask you to drool into a test tube while chewing on paraffin or unflavored gum. The amount of saliva collected during each trial will depend on how much saliva you produce, but the total volume will not exceed a tablespoon per collection trial.

- Questionnaires: We will ask you to complete two questionnaires which ask detailed questions about your medical history, medication usage, dental history, dietary habits, oral hygiene habits, geographic, and biographic background. You may be asked to complete these online at a secure website or using paper copies.

5.2. Evaluation of Eligibility: We will tell you the results of your dental examination, so that you may share these results with your regular dentist. You may not be allowed to participate in the study if any of the following applies to you:

1. You have fewer than 15 natural, non-implant, teeth.
2. You have had extracted any central incisor, canine, or first molar, or they have a crown or artificial tooth at any of these sites
3. Your unstimulated whole saliva flow rate is less than 0.3 or exceeds 0.8 mL/min.
4. You are under the treatment of a physician for any chronic medical condition.
5. You take on a daily basis any medication other than birth control.
6. You have used oral, systemic antibiotics or antifungals within the 6-month period preceding enrollment.
7. You are required to take antibiotics before dental treatment.
8. You have a history of stimulant or heroin abuse or of eating disorders.
9. You smoke or use chewing/dipping tobacco or quit using tobacco products within the 6-months preceding enrollment.
10. You are lactating, pregnant, or intending to become pregnant.They have had any dental treatment during the 1-month period preceding enrollment and cannot or will not abstain from dental treatments during their enrollment.
11. You use a night-time mouthguard, retainer, or other intra-oral device on a daily basis and are unwilling or unable to discontinue its use during study enrollment.
12. You routinely use a c-PAP machine.
13. You do not have a clinically healthy mouth (i.e., any of the following applies):
    a) You have mean Clinical Attachment Loss (CAL) greater than 4 mm;
    b) You have more than four teeth with a maximum Probing Depth (PD) of 5 mm; and/or:
        - Any of the sites with PD of 5 mm bleeds upon probing
        - There is more than one site per quadrant with a maximum PD of 5 mm

c) You have more than 10% of sites with Bleeding upon Probing (BOP);
d) You have indicators of oral mucosal disease;
e) You have active, unrestored caries.

14. You have experienced dry mouth for a full week at any time during the preceding 6-months.

5.3. Training: Since in the main part of the study we will ask you to collect oral samples from yourself at home, if you are eligible and choose to participate, we will train you on dental anatomy and the procedures you will need follow in order to collect samples from yourself at home. This training will involve a few short quizzes.

6. What will we ask you to do during the main part of the study?

If the screening exams, tests or procedures show that you are eligible to be in the study, and you choose to take part, you will be ask you to do the following.

6.1. Clinical Sampling Appointments: We will ask you to attend five-sequential appointments (2 to 2.5-hours) each week at UCSF. Appointments will be scheduled at the same time/day each week, over the course of 29 days. We will ask that you abstain from eating, drinking, or performing oral hygiene for the 2-hour period preceding your clinical appointments. At each appointment, we will perform some or all of the following:

- Salivary Flow Rates: We will perform two tests to evaluate salivary function. We will ask you to drool into a test tube for 5 minutes, and then we will ask you to drool into a test tube for 5 minutes while chewing on a piece of paraffin or unflavored gum. The amount of saliva collected will depend on how much saliva you produce, but we expect the total volume will not exceed a tablespoon per collection trial.

- Tooth Samples: We will independently sample microbial communities inhabiting the front and back surfaces of each tooth. Foam swabs, paper points, and/or dental curettes will be used to collect independent samples above and/or below the gumline from the front and back surface of each tooth.

- Oral Mucosal Samples: Seven oral surfaces (e.g., upper inner lip, lower inner lip, right cheek, left cheek, roof of mouth, floor of mouth, and tongue) will be swabbed with a foam swab.

- Plaque pH Measurements: Using a standard instrument for measuring dental plaque pH (i.e., acidity), we will measure dental plaque pH over a maximum period of 40 minutes before and at several times after you gargle a 50% sugar/water solution. You will be asked to place your finger in a cup containing a salt solution while we touch a small electrode to each tooth surface.

- Training Assessments: At each clinical appointment, we will assess your comprehension of dental anatomy and the home sample collection protocol. This training (i.e., calibration) will include both lessons and quizzes.

- Alginate Impression**:** On a single Clinical Sample Collection Appointment, we may ask you to allow us to take an alginate impression of your teeth (i.e., a dental mold).

- Imaging of Dentition & Oral Mucosa. On a single Clinical Sample Collection Appointment, we may take radiographic images of the dentition using3D radiography. In addition, we may pictures of the oral cavity, but we will not take full face images.

6.2. Home Sample Collection: Over the course of 29 consecutive days, we will ask you to collect dental, saliva, and oral mucosal samples from yourself at home. We will ask you to collect samples at the same time each day, first thing upon waking, preferably before noon.

- Oral Samples: At most, we will ask you to collect a saliva sample, samples from at most seven oral mucosal services, and samples from at most 12 teeth using the instructions and instruments we provide. We will ask that you abstain from eating, drinking, or performing oral hygiene for the 2-hour period preceding sample collection. Sample collection should take approximately 30 minutes per day.

- Storing Samples: We will ask you to store samples in your home freezer, not the refridgerator, as the samples must remain frozen after they have been collected.

- Transporting Samples: We will ask you to transport the frozen samples to your clinical sampling appointments at UCSF, following the instructions we provide, and using the materials we provide.

- Keeping a Lab Notebook: We will ask you to keep a lab notebook, which we will provide, where you can record the time that you took samples, any problems you noted while sampling, any drugs you consumed that you do not normally take, as well as feelings of oral dryness in response to the questions asked.

- Using the Oral Hygiene Kit. The Oral Hygiene Kit contains a toothbrush, toothpaste, dental floss, a dental mirror, and a recipe for mouthwash. We will ask you to use this kit throughout the study unless you have a routine prescribed by your regular dentist.

- Notify us of any serious illness. Please contact the study coordinator, Danielle Drury at (415)-476-2045, should you succumb to any illness (e.g., have a fever, need to take antibiotics) during study enrollment.

7. What is the total time commitment & what is the study schedule?

If enrolled, you will be asked to: 1) attend an in-person 2.5-hour dental examination, 2) attend 5 sequential 2 to 2.5-hour clinic appointments once per week, on the same day each week, over 29 days, 3) collect oral samples from yourself on 29 consecutive days, and, 4) record information about yourself, daily, in a Lab Notebook. In total, the maximum amount of time required is about 29.5 hours.

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7.1. Overview of experimental procedures. An overview of the study is shown in **Figure 1**, which is divided into two panels (Top panel 1A, and the Bottom panel 1B).

1A: Top

1B: Bottom

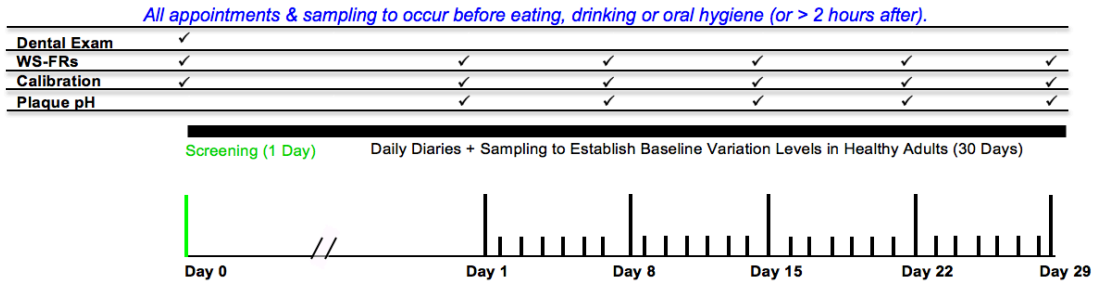

Figure 1: A schematic of the experimental procedures. As seen in 1B (Bottom Panel), clinic appointments, which last 2-2.5 hours, are scheduled for Days 1, 8, 15, 22 and 29. At all appointments (except for screening), plaque and oral mucosal samples will be collected by a clinician. We will also ask you to collect samples from yourself each day from Day 1 to Day 29. Home sampling is expected to take ~30 minutes per day.

The grid in 1A (Top Panel) describes the procedures that will be performed at each clinical appointment. WS-FR indicates salivary flow rate measurement; calibration indicates training on dental anatomy; plaque pH indicates plaque acidity measurement.

7.2. Home Sample Collection Protocol. The following schedule describes the summary of procedures to be performed as part of the Home Sample Collection Protocol Schedule.

Day 1-Day 29 (29 Days)
Follow Home Sample Collection Protocol (~30 minutes each day)

1. Take oral samples from yourself, following this protocol, at least two hours prior to (or after) any clinical sampling appointments, first thing upon waking before eating drinking or engaging in oral hygiene.
2. Make an entry in your Lab Notebook.
3. Use your Oral Hygiene Kit.

7.3. Clinical Sample Collection Schedule. The following schedule describes the summary of procedures to be performed at each clinical sample collection appointment.

Day 0
Attend UCSF Dental Clinic for Screening Examination (2.5 Hours)

1. Attend dental appointment to determine eligibility for enrollment.
2. Includes dental examination, without x-rays.

Day 1, Day 8, Day 15, Day 22 (4 Days)
Attend UCSF Dental Clinic for Clinical Appointment #1-4 (2-2.5 hours each)

1. Bring your completed lab notebook with you to your appointment.

2. Transport any samples you collected during the week to your clinical sample collection appointment.

Day 29 (1 Day)

Attend UCSF Dental Clinic for Clinical Appointment #5 (2-2.5 Hours)

1. Bring any remaining samples you've collected with you to your appointment.
2. Bring your Lab Notebook with you to your appointment.
3. Bring all leftover supplies with you to your appointment.

8. What will we do with the samples we collect during this study?

8.1. Samples will be banked: Clinical specimens (e.g., plaque, saliva, and oral mucosal samples) will be stored and analyzed to describe the oral microbial communities associated with health and disease. They may be used for future research. Clinical specimens will be stored at the Stanford University School of Medicine in the Laboratory of Dr. David Relman, MD. Only Dr. Relman and the study staff will have access to banked samples. Samples will be identified only by a coded number, which means laboratory researchers will not have access to any of your personally identifying information. Samples will be kept until the research project is completed and that will be no later than December 31, 2025.

8.2. You may revoke consent: If you decide, at any time, that you do not want your specimens or information to be used for this or future research, you must notify the Principal Investigator in writing at: David Relman, MD, Department of Microbiology and Immunology, Stanford University Medical Center, 299 Campus Drive, Fairchild D300, Stanford, CA 94305-5124. If you revoke your permission, we will destroy any remaining identifiable specimens and information if they are no longer needed for your care. However, if any research has already been done using any specimen, the data will be kept and analyzed as part of those research studies

9. What will we do with the data we collect during this study?

9.1. Use of data: Data may be used to develop new drugs, tests, treatments, or products. In some instances these may have potential commercial value, and you will not share in any financial benefits.

9.2. Use of personal information: All data will be identified by a numbered code that will not be linked to your name. The key that links you to your coded number is kept under lock and key at UCSF, under the supervision of Dr. Ava Wu, DDS. Study data will be shared broadly with the scientific community, but only in coded form. Your personal health information cannot be used for additional research without additional approval from you or a review committee.

9.3. Clinical Information: We will store the medical, dental, and demographic information we collect, including your Participant History Questionnaire, Drug Recording

Form, Eligibility Screening Examination Form, Lab Notebooks, as well as measurements taken during the clinical sample appointments (e.g., plaque pH measurements), among other study documents. The data will be shared broadly with the scientific community but only in coded form.

9.4. Genetic Information: We are not specifically seeking to characterize genetic information about you. Rather, the purpose of this study is to examine the genetic composition of bacterial communities in samples taken from your mouth. The genetic information about the microbes in your mouth will be shared broadly with the scientific community in coded form – with no information personally identifiable to you.

Sometimes specimens used in microbial genetic research also result in the generation of host genetic information. We will not use or share any genetic information that is generated that is specific to you. Genetic information that results from this study does not have medical or treatment importance at this time. To safeguard your privacy, genetic information obtained in this study will not be placed in your medical record.

9.5. CBCT Radiographs & Photographs: We will use the photographs and radiographs we take, if we take any, to analyze how bacterial communities differ across space as a function of your specific dental anatomy. CBCT radiography may reveal occult dental caries, as a benefit to you, but CBCT in the context of this study is for research purposes, not medical purpsoes. To safeguard your privacy, we will not take full face photographs, only images of your oral cavity.

10. How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy.

10.1. Medical Records. Some information from your medical records will be collected and used for this study. If you do not have a UCSF dental record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF dental record. Therefore, people involved with your future care and insurance may become aware of your participation in this study, and of any information added to your dental record as a result of your participation. However, this research will not change the care you receive.

10.2. Research Records, including Photographs. Study tests that are performed by research labs, and information gathered directly from you by the researchers, including oral cavity photographs, will be part of your research records, but will not be added to your medical record.

10.3. Access to your Personal Information. Your personal information may be given out to certain agencies if required by law. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The University of California

- The UCSF Committee on Human Research
- The National Institute of Dental and Craniofacial Research
- Other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

10.4. Publications. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your name will not be used in any published reports from research performed using your specimens.

11. What risks are involved with donating specimens for research?

11.1. Confidentiality: Donating specimens may involve a loss of privacy, but information about you will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. The manager of tissue bank, Dr. David Relman, MD, and select tissue bank staff members will have access to de-identified information about you, but they will not release any personally-identifying information about you.

11.2. Genetic Information Risks: There is a risk that your taking part in a genetic study may influence insurance companies and/or employers regarding your health. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. Although your name will not be associated with any sample, samples will be associated with other facts about you such as the information that was shared in the Participant History Questionnaire and Drug Recording Form.

This information is collected because we expect to learn which factors related to salivary dysfunction predispose humans to oral infections. Thus it is possible that the results of this study could one day help people of the same race, ethnicity, or sex as you. However, it is also possible that genetic traits might come to be associated with you or a group with which you identify. In some cases, this could reinforce harmful stereotypes.

12. What side effects or risks can I expect from being in the study?

12.1. Likely risks: The following side effects are expected to likely occur.
Some bleeding of your gums may occur during the examination. This bleeding may cause you discomfort when you brush your teeth for the remainder of the day or for several days following your dental exam.

Some sensitivity of the tooth surface may occur when plaque pH is measured. If this happens, please inform the investigator, and the procedure will be discontinued if intolerable.

12.2. Women of Childbearing Potential. If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk or risks during radiography, if you are asked to take 3D CBCT images.

12.3. Radiation Risks Associated with 3D CBCT. CBCT scans, like conventional x-rays, expose you to radiation. The amount of radiation you will be exposed to is the equivalent to what you would receive from several days in the sun. The dose of radiation used for CBCT examinations is carefully controlled to ensure the smallest possible amount is used that will still give a useful result. However, all radiation exposure is linked with a slightly higher risk of developing cancer. But the advantages of the CBCT scan outweigh this disadvantage.

12.4. Other Side Effects & Unknown Risks. You may experience side effects while on the study. Everyone taking part in the study will be monitored for side effects. However, doctors don't know of all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.You should talk to your study doctor about any side effects you experience while taking part in the study.

13. Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study. However, this study will help doctors learn more about microbial populations in the human mouth and how microbial communities change in health and disease. It is hoped that this information will help in the treatment of future patients with dry mouth and reduced salivary function. In addition, if you are asked to have 3D CBCT radiographs taken, the results may reveal occult dental caries.

14. What are the costs of taking part in this study?

You will not be charged for any of the study activities.

15. Will I be paid for taking part in this study?

15.1. Token of Appreciation. In return for your time, effort and travel expenses, you will be paid a maximum of $245 for completing the entire study. If you withdraw from the study early, you will receive: 1) $20 per each of five completed, clinical sample collection appointments; and 2) $5 per day for each of 29 days of self-sampling that you complete. In addition, for the duration of each clinical visit, you will be given a parking sticker to cover the cost of your parking in the UCSF garage.

15.1. Timeline. You will be paid by check, and you should receive the check four to six weeks after your last visit.

15.2. Regulations. You must give the researchers your address and Social Security number so the check can be processed. Payment for research participation is considered taxable income. If you are paid more than $600 total in a calendar year for participation in research studies, the University will report this income to the Internal Revenue Service.

16. What happens if I am injured because I took part in this study?

16.1. Notify Dr. Ava Wu. It is important that you tell your study doctor, Ava Wu, DDS, if you feel that you have been injured because of participation in this study. You can tell the doctor in person or call her at (415)-794-5539.

16.2. Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the UCSF Committee on Human Research at (415)- 476-1814.

17. What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time.

No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

18. What other choices do I have if I do not take part in this study?

Please talk to your doctor about your choices before deciding if you will take part in this study. Your other choices may include:

- Getting no dental examination
- Getting standard dental examination without being in the study.

19. Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or if you decide to stop. He or she will tell you how to stop your participation

safely. The study doctor may terminate your participation in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

20. Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact Dr. Ava Wu at (415)-794-5539, or contact the study coordinator, Danielle Drury, at (415)-476-0535. Alternatively, you may contact the Principal Investigator of this study, Dr. David Relman, at (650)-852-3308.

21. Who can I contact outside the study team?

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at (415)-476-1814.

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22. CONSENT

Please read each sentence below and think about your choice. After reading each sentence, initial the "Yes" or "No" box. If you have any questions, please talk to the study doctor or nurse. No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat diseases associated with salivary gland dysfunction.

YES	NO

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems *(for example: diabetes or heart disease).*

YES	NO

3. Someone may contact me in the future to ask me to take part in more research.

YES	NO

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Person Obtaining Consent

_____ _____
Date Witness (If needed)

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