

Clinical Trials Research: BETWEEN THE LAB BENCH AND CHAIRSIDE PRACTICE

BY MARK WITTEN



Dr. Alan Lowe

The long and winding journey from a bright idea to a new product or therapy that significantly improves the health and quality of life of patients locally, nationally and internationally is challenging, exciting and potentially very rewarding for both the originator and the beneficiaries.

Dr. Alan Lowe has walked and sometimes run every step of that dental clinical research translation journey. It began with his early studies of patients with sleep disorders and simple oral appliances such as Snore Guard® in the 1970s and 1980s, and led to the invention, development and testing of his pioneering oral appliance Klearway™ in clinical research trials in the 1990s. This was followed by the highly successful licensing, marketing and sale of 42,000 Klearway appliances with a retail value of \$12.6 million over the past two decades, supported by more clinical trials to further assess the effectiveness of the device in the treatment of snoring and obstructive sleep apnea (OSA) in adults and children.

As director of UBC Dentistry's Frontier Clinical Research Centre (FCRC), Lowe is

eager to share his wealth of expertise in helping other investigators to embark and progress on their own research journeys. The FCRC is the first dedicated centre for all types of dentistry-related, patient-based research in Canada. It provides spacious and well-equipped facilities, specialized services and a clinical trials manager, Sundus Hussain, who has the hands-on clinical trials experience needed to support researchers in developing and testing promising ideas for new patient-based dental treatments, devices, materials and procedures in clinical research trials.

"Clinical trial design is incredibly complex but there is little training for clinical trials research in dental school. The FCRC is a go-to place in one location that increases clinical research options for our faculty, graduate students, clinical educators, dentists

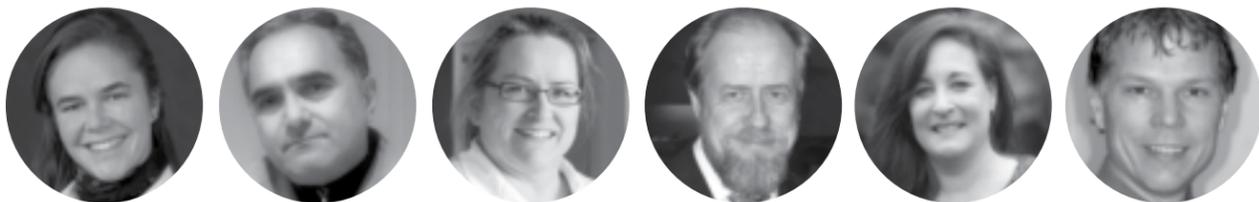
and dental hygiene professionals in the community, as well as industry and corporate sponsors. We can help to streamline and speed up the clinical research process by providing support for investigators through every step of a clinical study," says Lowe, professor and chair, Division of Orthodontics, UBC Dentistry.

In his first year as director of the FCRC, Lowe has overseen the launch of 14 new clinical research studies in areas ranging from root canals and implant stability measurement systems to oral cancer screening and obstructive sleep apnea treatments. "A clinical trial centre at a university is meant to advance the science of dentistry, and the studies we have underway cover the gamut of clinical dentistry," says Lowe.



Support for the Frontier Clinical Research Centre

The Frontier Clinical Research Centre is supported by a generous gift from Frontier Dental Laboratories Inc. to enhance dentistry-related patient-based research and knowledge transfer in Canada. Frontier Dental Laboratories, based in Vancouver, is a full-service dental laboratory, focusing on everyday crown and bridge, as well as high-quality aesthetic restorations, smile design, full-mouth reconstruction, and implants. For more information, visit www.frontierdentallab.com



From left to right: Drs. Fernanda Almeida, Babak Chehroudi, Denise Laronde, Markus Haapasalo, Leanne Donnelly and Ross Bryant.

Tracking Adherence: CPAP Versus Oral Appliance

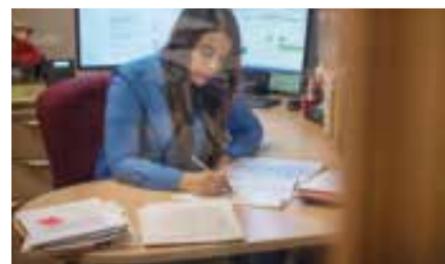
Good long-term adherence to treatment is essential for patients with obstructive sleep apnea to gain the optimal health benefits. OSA is a chronic, life-threatening condition that affects 10 to 15 percent of Canadian adults, and is associated with cardiovascular disease, hypertension and stroke. The two main treatment options for OSA are continuous positive airway pressure (CPAP), which involves a nasal mask attached to an apparatus that forces air into the lungs, and mandibular advancement oral appliances that work by holding the jaw closed while moving the tongue and jaw forward to open the airway.

Dr. Fernanda Almeida, an associate professor in the Department of Oral Health Sciences, is conducting a randomized clinical trial that will objectively compare the adherence of patients who have mild to severe obstructive sleep apnea with CPAP versus mandibular advancement splints (MAS). The clinical trial is designed to compare the effectiveness of both treatments in reducing symptoms. This will be the first study to measure adherence objectively in comparing the two treatments; to date, researchers and clinicians have had to rely on patients' subjective views of their own MAS compliance, which is often inaccurate. The study is fully funded by a Canadian Institutes of Health Research (CIHR) grant.

An Ottawa-based company, Braebon Medical Corp., has designed a miniaturized adherence monitor called DentiTrac® that it provided for the study to accurately monitor the amount of time patients wear the removable oral appliance. (With CPAP, newer machines have tracking systems that can reliably track patient adherence.) The DentiTrac micro-recording device is embedded in the oral appliance and can store up to six months of data. The

adherence tracker will allow the research team to objectively measure differences in patient adherence to CPAP versus MAS treatment.

Almeida's study is a cross-over trial in which each of the 60 patients will receive the two treatments separately for one month. It will be followed by an observational trial in which patients will have access to both treatments at home and be allowed to choose on a daily basis the treatment to use. "The results of this study will provide new evidence to help patients and physicians in making future decisions on the preferred mode of therapy. A secondary goal is to assess if there is an improvement in treatment adherence and a reduction of symptoms if the patient's treatment preference is taken into account," explains Lowe.



Sundus Hussain

Easing the Clinical Trials Pathway

As clinical trials manager at the FCRC, Sundus Hussain plays a valuable role in streamlining and accelerating all clinical research processes for investigators conducting or wishing to conduct clinical research trials. "It's become a lot simpler now for faculty to do clinical research trials because we have a foundation laid to support and help them with each step in the process. Most faculty are very busy and don't have the time to handle all of the various tasks and details. They want to do clinical research, but in some cases may not

know what a clinical research trial entails," says Hussain, who also guides graduate students in all aspects of clinical research and provides clinical training as needed.

The clinical trials manager assists investigators with five processes: initiating, planning, executing, monitoring and controlling, and analysis and review. She ensures the protocol, informed consent form, patient charts, database, case report forms, questionnaires and other data collection documents are ready and are created using the appropriate ethics board template. She assists with the preparation of these documents as well.

Hussain has extensive experience with a wide range of ethical applications for various clinical projects and has been very successful in obtaining Research Ethics Board (REB) approval for FCRC projects. She can set up study-specific databases, and ensure that data entry completion and verification is occurring according to set study timelines and that all queries are resolved in a timely fashion.

Creating a positive environment for study participants is also crucial. "You can't recruit and retain patients unless you can create a positive relationship with them and make their participation in the study a positive experience. I develop a comfortable relationship with each patient so the study visits become something they look forward to, where they get the treatment they want from compassionate health care professionals," says Hussain.

New Tool to Assess Implant Stability

Clinical professor Dr. Babak Chehroudi and UBC Dentistry colleagues have developed a promising new percussion-based implant stability measurement system (PISMS), which could be a critical tool for early detection of implant failure and enabling corrective

measures to avoid implant loss. Although high success rates for implants are reported, there are large and increasing numbers of failures due to the growing numbers of implants placed. Both conventional clinical methods and commercially available implant stability measurement devices lack sensitivity and are unable to predict failure reliably.

Chehroudi is working on a pilot study involving 50 patients to determine whether the PISMS assessment method is more specific and sensitive in predicting early loss of implant-supporting tissue and implant failure than the current commercially available devices. Chehroudi's device works by applying a gentle tap on implants and generating percussive sound signals that are collected by sensors. The signals are then processed to identify resonance frequency and damping of the dental implants simultaneously. The PISMS probe has been successfully used to assess the stability of implants placed in simulated bone blocks of different densities.

The long-term goal of Chehroudi's clinical research is to bring to market a low-cost, highly accurate and reliable dental implant stability-measuring device that allows early detection of implant failure, and early intervention to reduce the frequency of implant failures and costs of replacement. "This is a brand new device developed by UBC Dentistry. Chehroudi is testing its effectiveness in measuring implant stability and reliability in clinical practice. A key goal of this pilot project is to get industry to look more closely at the potential for collaboration and commercial development of this device, which could provide important health benefits for patients and an economic benefit to Canada," says Lowe.

Community Screening to Detect Oral Cancer Early

Oral cancer is a substantial yet often unrecognized global health issue with a high mortality rate, mainly due to the late stage at which it is diagnosed. The disease is more common than cervical and ovarian cancer, and has a lower five-year survival rate than breast and prostate cancer. Oral cancer screening of patients can be effective at finding early disease, but it is challenging for clinicians to identify which oral premalignant lesions (OPLs) will progress to oral cancer.

Dr. Denise Laronde, an assistant professor in the Department of Oral Biological & Medical Sciences, is doing a study in which 200 patients identified with OPLs through a biopsy will be screened for high-risk OPLs using a research-validated, predictive test. One goal of the study is to assess the effectiveness and practicality of this test as a screening tool to identify high-risk patients. A second and larger goal of the study is to create a new high-risk clinic to manage patients from the community who have been identified through this test to be at high risk of progressing to oral cancer.

Laronde and her colleagues at UBC and the BC Oral Cancer Program developed the only validated chairside test to assess the risk of progression to oral cancer, which is based on the molecular profile of the patient's OPL. This predictive test uses a genome marker-based technology (gMART) to accurately classify OPLs at low, medium or high risk of progression to oral cancer. Laronde's study will use an enhanced version of the test, known as gMART+, which integrates quantitative pathology analysis and has even higher predictive value.

Laronde, who was trained and worked as a dental hygienist earlier in her career, has a vision for the clinic to be community-centred, with high-risk patients identified and triaged to it via dental networks to be developed through the BC Cancer Agency community screening initiative and followed by an oral medicine specialist. Patients identified as low-risk may not need as frequent follow-up, reducing the demand for health resources, and they will be spared unnecessary interventions. "Stratification of risk of progression will help clinicians to identify patients at high risk of progression to oral cancer. This will lead to earlier intervention in those patients at the highest risk of progression and better health outcomes," says Lowe.

Testing Faster, Fresher, Simpler Methods

Some of the other studies underway include a root canals outcome study by Dr. Markus Haapasalo comparing a single-cone technique using bioceramic sealer—which can be done in less time than traditional techniques—with two traditional methods. Dr. Leanne Donnelly is comparing the clinical effectiveness of

Nufresh, a natural-ingredients oral rinse, against chlorhexidine (the dental industry standard anti-bacterial rinse). Dr. Ross Bryant is doing several studies investigating implant overdentures (replacement teeth retained by implants) with magnetic attachments and comparing the durability of one-implant and two-implant overdentures.

Dr. Fernanda Almeida is doing another study involving 60 patients to assess the effectiveness of a tongue stabilizing device (TSD) in treating patients with obstructive sleep apnea and better understand how this therapy works. TSD is a preformed appliance for OAS that protrudes the tongue and improves upper airway structure and function during sleep. It is simpler and more economical than other therapies, such as CPAP and MAS, and may offer similar benefits. Almeida wants to determine whether TSD therapy will improve OSA symptoms and lead to effective nasal breathing and reduce swallowing frequency during sleep. "This treatment hasn't been investigated very thoroughly and the results may be very helpful," says Lowe.

As UBC Dentistry, faculty and students launch and develop a wide range of clinical research projects through the FCRC. Lowe aims to also involve more clinical educators, dental hygienists, dentists and industry partners who are closer to the demands of the profession.

To have a meaningful impact, the research should not stop when a clinical trial ends. Drawing on his own experience working with industry and companies to commercialize new devices and treatments, Lowe will be helping some investigators to engage in fruitful collaborations with industry and corporate sponsors. The goal will be to translate their research findings into new devices, dental materials and oral health products to improve the health of patients in Canada and globally. "There are a lot of new products and developments happening in dentistry today. The timing is right for a dedicated clinical trials centre because it opens up options for clinical research to take advantage of these exciting opportunities," says Lowe.

To find out more about the Frontier Clinical Research Centre, visit www.fcrc.dentistry.ubc.ca