# Clinical Research in Oral Health

Edited by

**William V. Giannobile, DDS, DMSc**

**Brian A. Burt, PhD, MPH, BDSc**

**Robert J. Genco, DDS, PhD**

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# Dedications

*To my wife, Angela and son, Anthony for their love, patience, encouragement, and support*

*To my students who inspire and challenge me in my daily professional life*

*To my mentors who instilled in me a love for my career in clinical research*

*To my parents who made me believe in myself*

– William Giannobile

*To my wife Elizabeth, whose never-ending support is crucial to the production of this book. In addition, I salute all those dedicated research colleagues who have contributed so much to my research down the years.*

– Brian A. Burt

*My efforts in preparing this book are due in great part to the lessons I learned from my mentor, Dr. D. Walter Cohen; to the diligence and creativity of my clinical research colleagues; and to the enduring support of my wife, Frances.*

– Robert Genco

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# Preface

Translational research is not only good science, but it is science that helps people. In creating this book, the editors (Drs. William V. Giannobile, Brian Burt, and Robert Genco) with the able assistance of an impressive collection of experts have created the essential dental investigators' handbook for translational research. This book presents the current best practices for conducting clinical research and will serve the needs of oral health investigators, trainees, and clinicians who seek to become better clinicians. The principles of the book are founded upon the profession's recognition of the central importance of evidence-based dentistry for clinical decision making. Dentistry has evolved beyond an apprenticeship "arts and craft" training model of disease management to a scientific model that includes lifelong learning and scientific evidence-based patient management and disease prevention. This book provides all the necessary tools that clinicians need to understand the underlying scientific basis for patient care. Understanding the scientific process is critical to be an effective dental health care provider in this postgenomic era and this book provides an excellent blueprint for transforming clinicians into clinical scientists.

Technically, the book is an impressive collection of topics presented by top leaders in the field. There are several unique aspects to this compilation that make the publication unprecedented. Special care has been applied to craft the presentation of the material as being specifically oriented to the needs of the dental investigator. Careful discussions of study design, biostatistical considerations, ethical and regulatory issues, grant writing and publication, data management, and data analysis are tailored for dental research and include many examples that make the information accessible to the reader and easily interpretable. Additional sections deal with the current national trends for dental research that include the utilization of practice-based networks and the adoption of new technologies to dental practice. Finally, the sections on publication and systematic reviews provide the tools needed for the clinician to interpret and apply the current scientific knowledge to the patient that is sitting in the chair. Thus, this book will provide important skills for not only the clinical scientist in training, but it will enrich the clinical scientist that is within every dental health care provider and enable better health care to emerge. In this manner, this book not only provides the reader with the skill set needed for conducting translational research, but it is a scientific blueprint that will enable each of us to be better clinicians to serve the health of the public.

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# Acknowledgments

First, I would like to thank the authors of this textbook for their tireless, dedicated, and fruitful efforts in assembling this book. The editors believe it is a first of its kind book in the rapidly evolving area of clinical and translational research in the oral health arena.

I dedicated this book in part to my devoted mentors in clinical research including my coauthors Bob Genco and Brian Burt. Your insights and experience have greatly benefited this book's development and realization. I also appreciate the mentoring from my clinical research role models, Sig Socransky, Max Goodson, Anne Haffajee, Klaus Lang, Ron Nevins, and Sam Lynch. You each have played important parts in my clinical research career and its connection to clinical translation. Each of you serves as an important inspiration to me as well as to our field of oral health research.

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To my role models and mentors in the clinical care arena of my career—Alden Leib and Peter Billia. Both of you represent the best of what dentistry and patient care is all about.

I would like to acknowledge all of my colleagues in the Department of Periodontics and Oral Medicine University of Michigan. This group of individuals has greatly enriched my scientific life. I also greatly appreciate all of the clinical members of the Michigan Center for Oral Health Research and the Michigan Institute of Clinical and Health Research who have challenged me to best understand how teamwork is crucial in patient-related research.

I would like to thank Sophia Joyce of Wiley-Blackwell for approaching me to initiate this textbook. I have greatly appreciated your insights and support during the book's progress. I also appreciate the quality efforts on the planning and production of the text from Shelby Allen and the rest of the team at Wiley-Blackwell. Finally, I acknowledge Karen Gardner for her excellent attention to detail, tenacity, and dedication to our efforts in the assembly of the first edition of this textbook.

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# Clinical Research in Oral Health

# 1

# Clinical and translational research: implications in the promotion of oral health

**William V. Giannobile,** DDS, DMSc

The field of clinical and translational research (CTR) has undergone tremendous growth and development over the last few years. Public pressure has helped bring CTR into focus as a high priority to drive basic science discovery to generate tangible advances to benefit society and oral health care. This trajectory of bringing "bench-to-bedside," or in the case of dentistry, "bench-to-chairside," research is important for development of the entire "translational continuum" (Figure 1.1). According to the National Cancer Institute Translational Research Working Group, translational research is defined as "research that transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce the incidence, morbidity and mortality of disease" (National Cancer Institute, 2009). Translational research encompasses both the acquisition of new knowledge about oral disease prevention, preemption, and treatment, and the methodological research required to develop or improve research tools (Lenfant, 2003). In 2008, leaders within the organization "Agency for Healthcare Research and Quality (AHRQ)" (www.effectivehealthcare.ahrq.gov) described the need for three tiers of evidence translation: the first translating basic science into clinical efficacy data (T1), the second (T2) using patient-oriented outcomes and health services research to develop knowledge about clinical effectiveness, and the third (T3) using implementation research for continuous measurement and refinement of treatment implementation (Dougherty and Conway, 2008) (Table 1.1). Two critical areas of CTR that affect human oral health include (1) the process of applying discoveries generated during laboratory research and in preclinical studies to the development of trials in humans; and (2) research aimed at enhancing the adoption of best practices in the community (Zerhouni, 2007). Given that the majority of oral health care

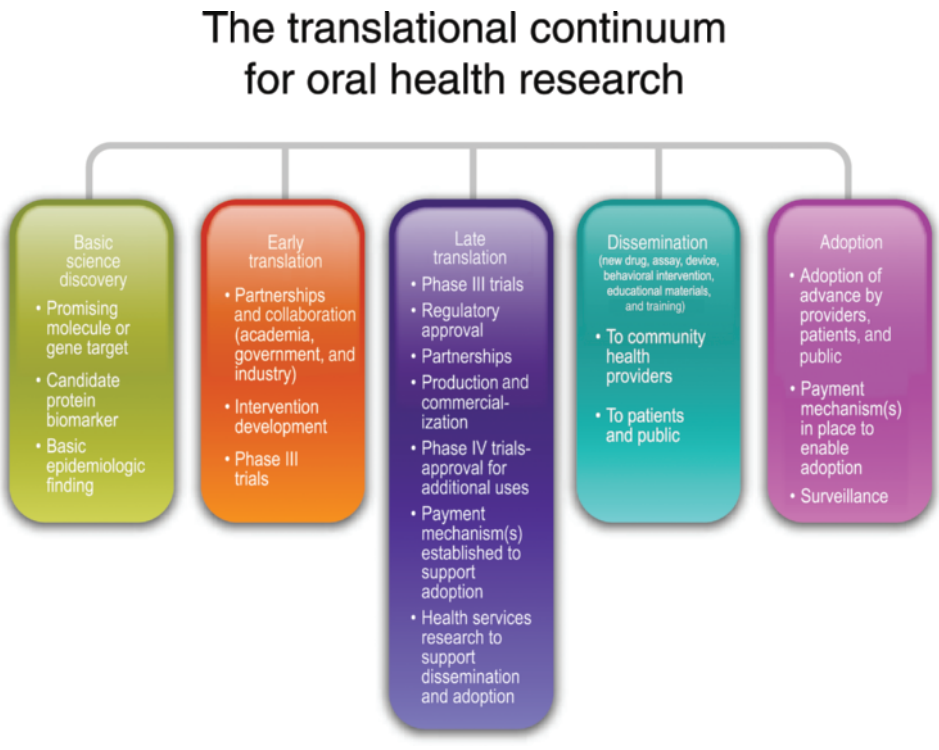


*Figure 1.1 The translational continuum from basic science discovery to eventual adoption to dental practice. Adapted from National Cancer Institute, 2009.*

Table 1.1 Examples of three translations required to improve the quality of oral health research.

| Translational tier | Type of research | Product of research |
|---|---|---|
| T1 | Clinical efficacy research | Proof that locally delivered antibiotics are beneficial when used adjunctively with scaling and root planing to reduce pocket depths |
| T2 | Comparative-effectiveness and oral health services research | Establishment of 3-month recall intervals is beneficial to treat periodontal patients |
| T3 | Implementation research | Identification of oral health screening strategies to diagnose oral cancer at earlier stages |

practitioners such as dentists and dental hygienists are in private practice, there is a great need for the dissemination of new research findings into the oral health community from university, private, and hospital-based research entities (ADA News, 2007). Based on this large practice community available, there has been a widespread efforts in the utilization of practice-based research networks to better allow for clinical translation and to implement greater numbers of impactful "effectiveness" trials (see Chapter 14) (Curro et al., 2009). For the field of oral health research and dentistry, there have been renewed efforts in enhancing the efficiency of clinical trials for the promotion of global health (Barnett and Pihlstrom, 2004).

## 1.1 Challenges to the translation of clinical research to clinical practice

There is a great demand to bring cutting-edge therapeutics to patients in the face of ever increasing dental costs that drive the oral health care industry to seek collaboration with multiple entities to stimulate innovation (Melese et al., 2009). With the development of effective "business models" for new dental devices or biologics, one needs to consider a host of different supportive government, industrial, and academic agencies from the initial concept until the eventual product to affect oral health (see Figure 1.2). There is a multitude of

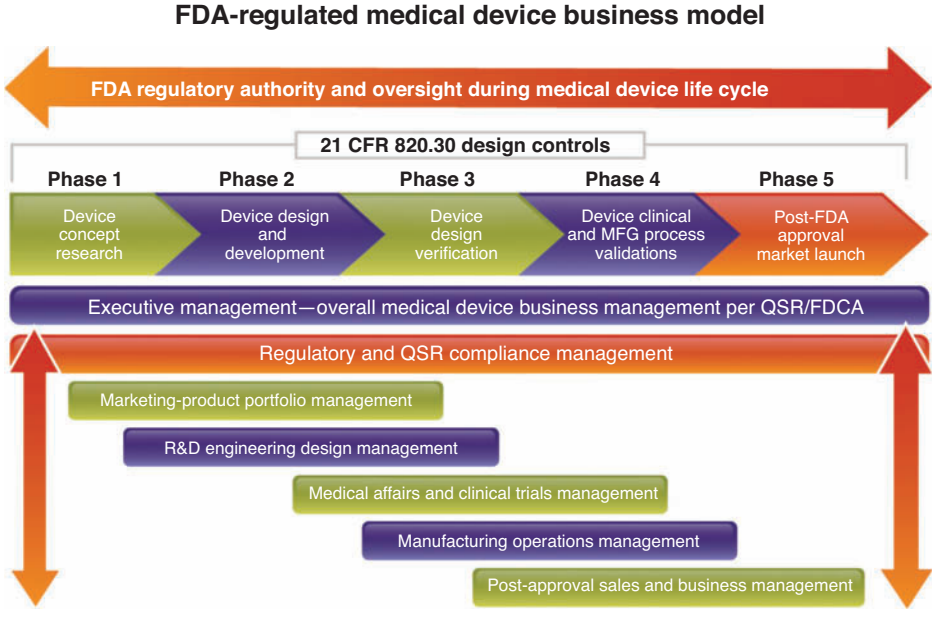


*Figure 1.2 FDA/EMEA regulated dental device business model. Design controls are considered (phases 1–5) for the development of a new dental device considering a host of regulatory steps to gain approval of the prototype device.*

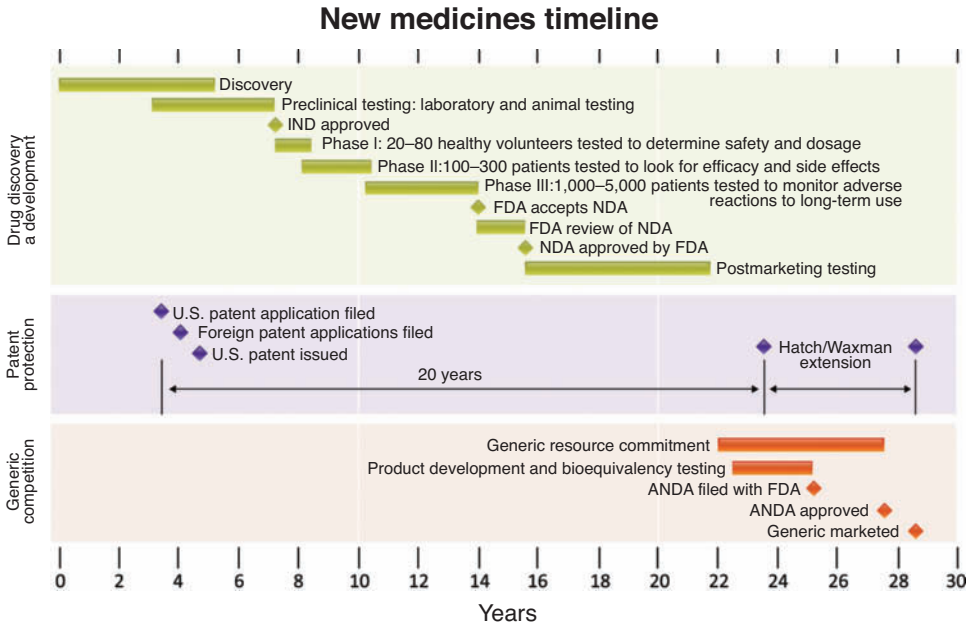


*Figure 1.3 New medicines timeline. This trajectory demonstrates the steps required for the development of a new drug. FDA, Food and Drug Administration; NDA, new drug application; IND, investigational new drug; ANDA, abbreviated new drug application. Adapted from Pharmaceutical Research and Manufacturers of America (PhRMA website: www.phrma.org).*

challenges to new drug or device development to affect patient health, and these trajectories typically take at least a decade or more due to technological, regulatory, and safety hurdles (Figure 1.3). Many cite the "art and science" of dentistry and its practice in oral health care delivery. Much is known about the science, but little in the proper application of the "art." The role of science in dental medicine is clear; however, what is less clear is the art on how dental innovations are implemented. The "art" part of medicine is "the combination of medical knowledge, intuition, and judgment" (Fauci et al., 2008). New approaches from the scientific standpoint demonstrate a high throughput of new knowledge as evidenced by the growth and expansion of dental and oral health-related research publications (see Chapters 17 and 18). However, moving this newly gained information from the research arena to clinical practice, making it relevant to oral health care providers and patients, requires true coupling of art and science and *clinical translation* (Lenfant, 2003). Improvements in health care delivery could be greatly impacted if investigators could better improve the translation of new knowledge to the clinical arena (Institute of Medicine of the National Academies, 2001; Berwick, 2003) (see also Chapters 15 and 16) (Text box 1.1). This becomes apparent about the implications of the translational aspects of bench-to-chairside translation given that the steps of basic science discovery to preclinical research and finally human studies are not necessarily successive steps, but are interdependent (Figure 1.4) (Willett, 2002).

**Text box 1.1**

**Importance of translational research in oral health research**

- Challenge in conversion of basic research to "chairside"
- Rate of new product development makes application to practice more difficult

The ramifications of oral health research findings (such as the discovery of the values of fluoride in drinking by Dr. Frederick McKay and then the "translation" of this concept by GV Black) greatly transformed dentistry into a prevention-based profession, instead of the previous "reconstruction-only" type of one (Tabak, 2004). Dentistry has been involved in a myriad of advances from the bench-to-bedside in areas such as new dental biomaterials to reconstruct lost tooth structure, to the tissue engineering of lost periodontal support (Nakashima and Reddi, 2003). Dental implants are some of the most common osseous implants placed into the human body and have relied on years of research in oral and craniofacial health (Gotfredsen et al., 2008). Other areas such as oral cancer detection and prevention have not fared as well. Head and neck cancer is one of the more common cancers that afflicts Americans, and it has been estimated that more than 8,000 people in the United States will die from this cancer this year. Unfortunately, survival rates for patients have not significantly improved over the past 30 years, and as such, there is much work to do in this area (Michaud et al., 2008).

The framework for the emerging vision of CTR is well captured following the construction of the Clinical and Translational Science Award (CTSA) program by the National Institutes of Health (NIH) in 2006–2007 by then director, Dr. Elias Zerhouni. He proposed the framework for the new vision based on the 4Ps: *predictive, personalized, preemptive*,

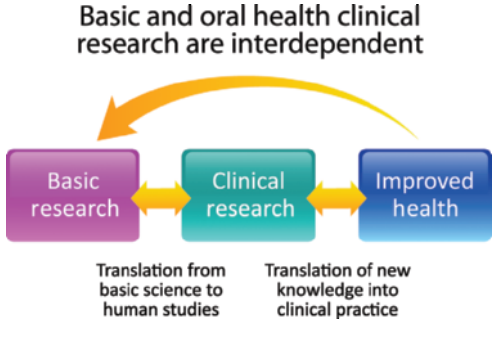


*Figure 1.4 Interdependence of discovery and patient-oriented research in the generation of new knowledge.*

and *participatory* medicine (Zerhouni, 2007). Clinical dental practice via this approach will advance more rapidly when we better understand the fundamental causes of oral diseases at their earliest molecular stages so that one can reliably predict how and when a disease will develop and in which patients; based on emerging data in the pharmacogenomics or the identification of the fact that specific patient populations are most responsive, a personalized medicine approach can be considered. These approaches will aid the dental practitioner in the identification of those patients who are responders and nonresponders to innovative dental drugs and devices for enhanced safety and clinical effectiveness. The use of metabolomics holds significant promise for improving disease diagnosis, prognosis, and disease management. Given the improvements in our abilities to prognosticate and identify patient risk factors and inherited genetic factors for disease, we can use a *preemptive* approach to deliver less invasive, more preventive, types of therapies or treatments. Finally, if the translation of clinical therapies is to have an impact on clinical practice and in patient care to enhance public trust, we need to encourage more active *participation* from patients and dental communities in shaping the future of dental medicine and global oral health.

## 1.2 Health technology assessments—identifying research priorities for oral health research

The use of health technology assessments (HTA) is a rich source of systematically generated information that have the potential to be used by granting agencies to support "researchable" questions that are relevant to decision makers and the public at large in the funding of clinical research (Scott et al., 2008). Traditionally, in order to receive Food and Drug Administration (FDA), European Medicines Agency (EMEA), or other international regulatory approvals (see Chapter 4), explanatory or mechanistic trials are most often utilized for new dental products (Tunis et al., 2003). These investigations recruit highly homogenous patient populations and determine how new drugs, devices, or biologics work under ideal conditions (efficacy trials; see Chapter 11). These types of clinical studies rarely satisfy all of the critical needs of health care decision makers at the policy level. In contrast to efficacy trials, pragmatic clinical trials assess the results of studies in "real-world" conditions whereby patients are exposed to a variety of environmental factors and comprise a heterogeneous racial/ethnic profile of individuals. These types of investigations can add to promote more generalized dental/oral health, since these are considered as effectiveness trials (see Chapters 12 and 13). The use of HTA results to identify research gaps can allow funding agencies to address the differences in research agenda priorities among different constituencies in the generation of clinical research programs (see Chapter 5). There are typically fewer research gaps than evidence gaps, since while it would be helpful to know the entire field (evidence gap), most of the time decision makers need to be satisfied and prioritize aspects within the evidence gap that would be most impactful to the field given time and resources available (see Chapter 18 and Figure 1.5). However, care must be given not to threaten personalized medicine and look at every targeted therapies for specific patient populations, as the broad strokes approach of comparative-effectiveness research can possibly marginalize such patient-specific therapeutics (Garber and Tunis, 2009).