# 1

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

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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

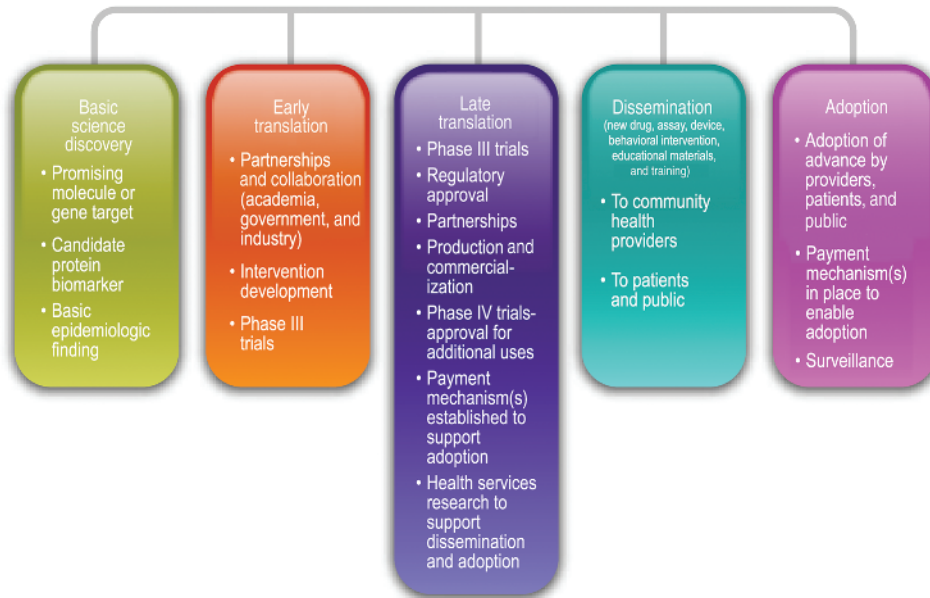# The translational continuum for oral health research



*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
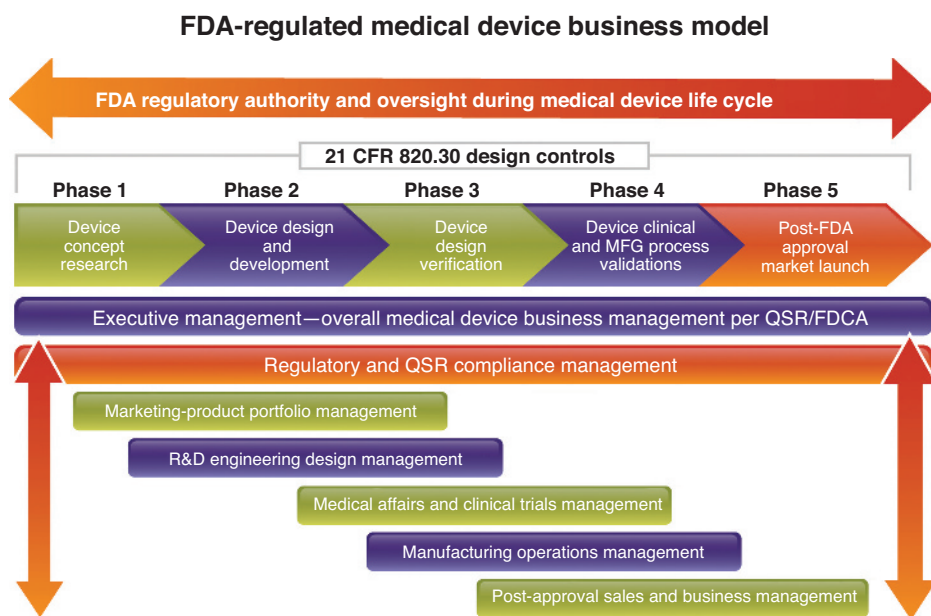
**FDA-regulated medical device business model**



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.*
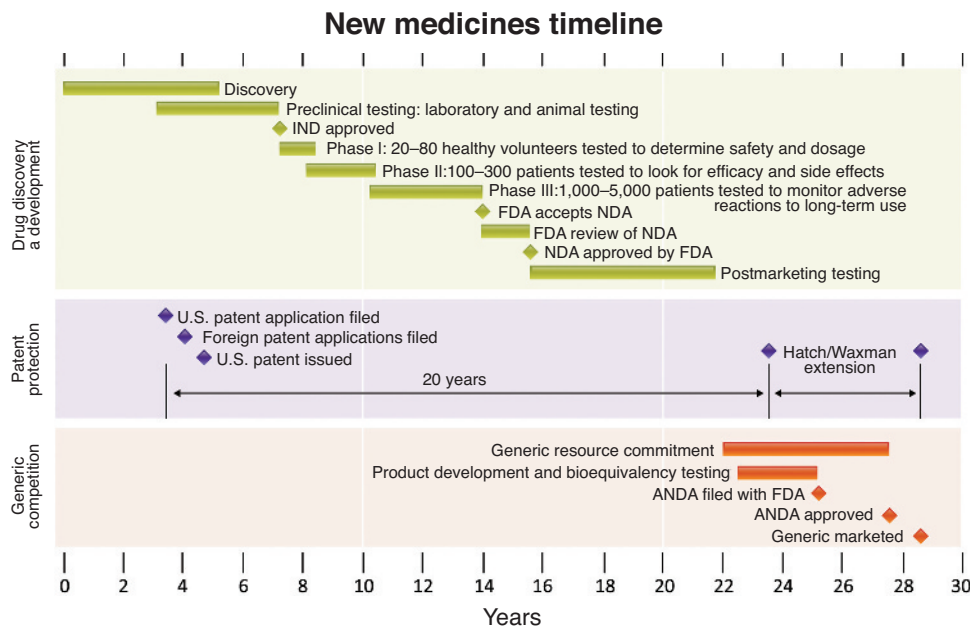
## New medicines timeline



*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,*
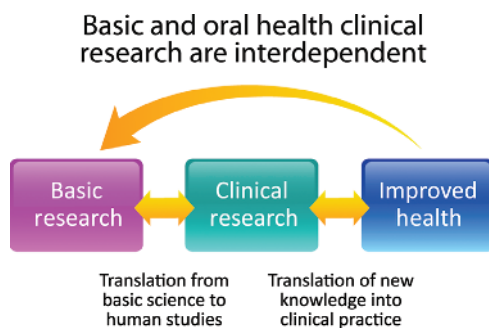
## Basic and oral health clinical research are interdependent

Basic research ⟷ Clinical research ⟷ Improved health

Translation from basic science to human studies

Translation of new knowledge into clinical practice

*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).
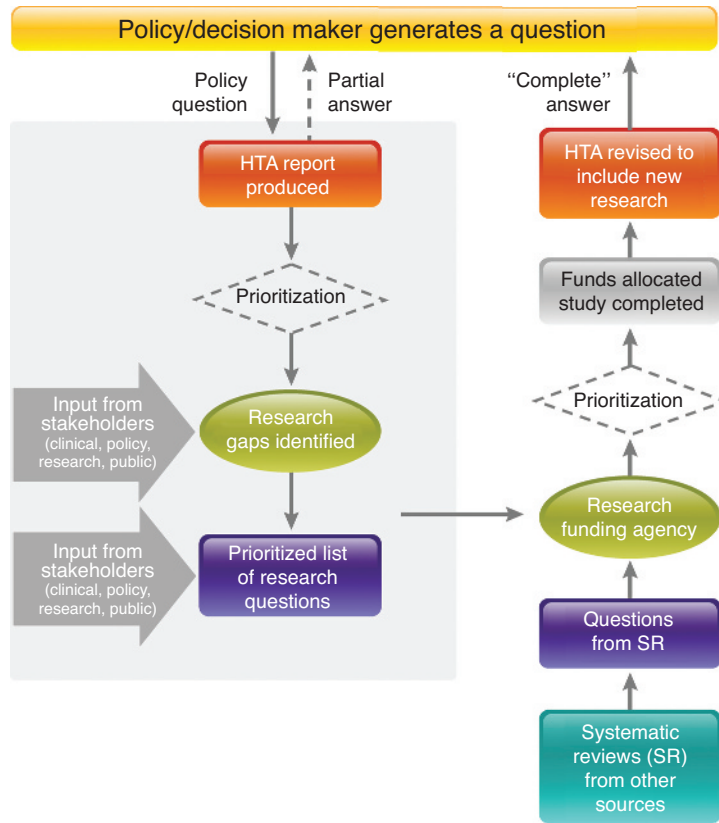
*Figure 1.5* *Flow diagram of the conceptual framework for the feedback loop involving research gaps identified by HTA (Scott et al., 2008).*

## 1.3    Comparative-effectiveness research (CER)

CER is defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care." (IOM Report, 2009). The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels. In June 2009, the Institutes of Medicine (IOM) published a report on CER as a way to identify what therapies work for which specific patients under discrete clinical situations (IOM Report, 2009). The U.S. Congress, in the American Reinvestment Act (ARRA) of 2009, appropriated $1.1 billion to support this nation's efforts to accelerate CER. Through the use of ARRA, the IOM developed national priorities for research questions to be addressed by CER and

supported by ARRA funds. The IOM committee identified three report objectives: (1) to establish a working definition of CER; (2) to develop a priority list of research topics to be undertaken with ARRA funding using broad stakeholder input; and (3) to identify the necessary requirements to support a robust and sustainable CER enterprise (IOM Report, 2009). The use of the development of these important elements of CER will provide greater reality and application to innovations being developed for CTR. Given that many research studies (e.g., randomized controlled clinical trials) utilize homogenous patient populations (i.e., research participants that have been recruited to fulfill stringent inclusion and exclusion criteria), the use of CER could be a valuable arena to further the development of personalized medicine. Examples of CER may be the utilization of systematic reviews of the literature that can be applied toward clinical practice guideline development (see also Chapter 18). The utilization of large established databases from research consortia or third party dental insurance companies may be resources to capture broad and heterogeneous patient populations that represent more of the "real-world" patients that oral health clinicians treat (see Chapters 6 and 16). Thus, the goal of CER is better decision making by patients and oral health care providers including dentists and dental hygienists. A key aspect of the clinical translation aspect of this approach is that CER will require effective methods to disseminate and promote these findings to better exploit their adoption into clinical practice.

In summary, CTR is revolutionizing the way that research is being envisioned and applied for the driving of innovations in oral health care delivery. By exploiting the many opportunities in academic, governmental, foundational, and private oral health care entities for the support of "transformative" patient-based research, we will enrich our understanding of the mechanisms of oral disease as well as cultivate novel approaches for the prevention and treatment of oral afflictions.

## Acknowledgments

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