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Lawrence A. Tabak, DDS, PhD
Director
National Institute of Dental and Craniofacial Research
Office of the Director
31 Center Drive
Building 31 Room 2C39, MSC 2290
Bethesda, MD 20892

Dear Dr. Tabak:

The American Academy of Orthopaedic Surgeons (AAOS), representing over 17,000 board-certified orthopaedic surgeons and researchers, welcomes the opportunity to respond to the National Institutes of Health (NIH) / National Institute of Dental and Craniofacial Research (NIDCR) Request for Comments to the new strategic plan to guide the NIDCR research efforts over the next five years (2009-2013).

As the preeminent provider of musculoskeletal education to orthopaedic surgeons, the AAOS applauds your decision to seek input from the scientific community on the NIDCR strategic plan. The AAOS envisions opportunities for strategic partnership in the future; bone repair and regeneration, tissue engineering, and incorporating and acknowledging disparities in clinical trials are among areas of future research in the field of orthopaedics.

Specifically, the AAOS would like to present the following recommendations to the NIDCR in response to the posted questions:

1. **Looking forward, should NIDCR increase its use of targeted research to ensure that key research areas with promise are addressed? If so, what priority areas would you recommend that NIDCR pursue? Targeted research is research solicited by the Institute via initiatives, RFAs or RFPs.**

   Yes, NIDCR should increase its use of targeted research to ensure promising key research areas are addressed. The AAOS recommends that bone repair and regeneration be considered a priority area of research for the NIDCR. The AAOS recently hosted an NIH-supported research symposium on this topic (2007 AAOS *Fracture Repair: Challenges and Opportunities* Research Symposium), and produced the following future research directions in order to plan treatments and predict outcomes for patients with fracture and to translate basic science technologies into clinically effective treatments. These comments pertain to craniofacial fractures as well as to those of long bones.

- What are the co-morbid medical conditions (e.g., diabetes, obesity, age, smoking, infection) and physical factors that interfere with bone repair?

- What therapeutic modalities interfere with bone repair/fracture healing (e.g., non-steroidal anti-inflammatory drugs, chemotherapy, radiation therapy) and what strategies are in place or are under investigation to determine how to overcome their inhibitory effects?

- Why do certain fractures in certain bones heal more predictably than others? What drives these differences? Are they simply related to blood supply or do local hormonal or cellular mechanisms play a role in determining healing capacity?

- Is it really possible to accelerate the healing of normal fractures? What means (local/systemic) can be used to accomplish this and by how much can we expect to be able to accelerate healing under normal conditions?

- What are the most effective synergies of cells, molecules, scaffolds, and physical forces that can enhance fracture healing? How do we identify these combinations most cost-effectively How will it be possible to incorporate these concepts into clinical care paying attention to safety, efficacy, and required duration of treatment?

- When designing clinical trials, what are the potential impacts of socioeconomic, racial, ethnic, and psychological factors on stratifying patients with regard to treatment?

The AAOS would also like to recommend efforts focusing on mobility research funding – while this concept spans multiple NIH institutes, we believe it should be an important focus of the NIDCR in particular because of the Institute's long standing interests in temporomandibular joint disorders, osteogenesis imperfecta, bone formation and mineralization mechanisms, and pain.

2. In your view, what are the truly "transformative" areas that could have the greatest benefit for advancing dental research?

Bone repair and tissue engineering are two broad areas of research that have significant impact on not only the future of practice and care in dental and craniofacial health, but also orthopaedics. As the current strategic plan document states, the NIDCR was a pioneer in the study of the chemical properties and molecular structure of collagen, an integral part of bones, teeth, and the periodontium. Further advancing the NIDCR world-class research program in matrix and developmental biology will continue to develop the field bioengineering with regard to bone development, scaffolds for tissue growth, and biomimetics for use in diseases and disorders of the teeth, gums, bones, muscles, and connective tissues.

3. What can be done to augment and accelerate the role and significance of dental and craniofacial research in the growing framework of translational research?

By having focused and methodological clinical trials, the NIDCR and other organizations can accelerate the framework of clinical research. The AAOS has identified the following goals in relation to clinical trials (relevant also to dental and craniofacial), which will be further developed at a 2009 symposium. Clinical trials will take the knowledge from basic research to clinical insights, creating new and improved methods to treat and prevent diseases of the bone and connective tissues. The following objectives can help form a foundation for developing clinical trials in the dental and craniofacial arena, and we offer these ideas to help assist in strengthening the NIDCR framework:

I. Identify the cultural barriers that exist in clinical trials:

Enumerate and articulate strategies to address the cultural/practical issues to performing added orthopaedic clinical trials, due to:

A) Lack of regulatory requirement to perform trials;
B) Lack of organizational champion;
C) Culture of surgery (lack of perceived need, unwillingness to change practice, promotion of divergence in clinical practice, acceptance of low quality study designs);
D) Lack of expertise/capacity to direct trials;
E) Lack of infrastructure;
F) Lack of financial incentive;
G) Lack of funding; and
H) Institutional Review Boards (IRB).

II. Identify the methodological issues in randomized clinical trials, which include:

A) Recruitment challenges: equipoise, willingness of surgeons to randomize, impact of patient and surgeon's preferences, generalizability;
B) Blinding;
C) Cross-over: impact on sample size, distortion of efficacy, means of minimization;
D) Subgroup analysis: pre-planned vs. ad hoc myths and realities;
E) Economic evaluation alongside the clinical trial;
F) Loss to follow-up: how to prevent and manage;
G) Placebo controlled trial; and
H) Long term outcomes.

III. Develop and prioritize research inrandomized clinical trials (RCT), as they are costly and time consuming, and should be prioritized as such. An RCT should ideally address a problem or issue that is:

A) Prevalent and costly;
B) That will remain as relevant and important after the study is done as it is when the study is designed;
C) For which there is genuine uncertainty;
D) For which clinicians will have equipoise;
E) For which patient preferences are not clearly already established; and
F) Than can be answered in a reasonable length of time.

4. What should be NIDCR's position on funding "high risk/high reward research"? What in your view constitutes "high risk/high reward"?

There should be more emphasis on "high risk/high relevance" studies. These studies have great potential, albeit unproven. "High risk," refers to those studies that do not have the preliminary data (or already completed data) to demonstrate a concept that could change the health of many. But unless there is investment in such studies, new discoveries will be limited as study sections look to see sufficient completed data to validate extending a study.

5. In realistic terms, what can--and should--NIDCR do to expand and enhance the "pipeline" for new dental and craniofacial researchers?

The first problem in attracting new investigators into the pipeline is their observation that established investigators are struggling to get funding, even with excellent priority scores. As they see these investigators leaving the Academic community, they are driven to make choices other than academic medicine and dentistry. Thus, mechanisms must be established for long-term funding of new investigators (with periodic peer review), and funds need to be obtained from the Federal government to allow both these new investigators and established investigators to continue their research without being threatened by one another.

The second problem is the process, although the new NIH peer review changes may address some of these. In order to attract, train, and support new clinician-scientists who have interests and skills in basic science research, clinical research, and outcomes research pertaining to bone repair, tissue engineering, and dental and craniofacial surgery, the administrative process must be streamlined. IRBs, institutional animal care and use committees, and other review bodies must find ways of accomplishing their tasks without introducing roadblocks or inefficient practices. Methods and opportunities for conducting multi-national trials that incorporate large numbers of centers each contributing small numbers of patients will be a difficult but worthwhile goal to pursue.

6. Please provide any additional input that you think would be useful to NIDCR in developing its 2009--2013 Strategic Plan.

The AAOS recognizes the pioneering role the National Institute of Dental Research (now NIDCR) had in developing bone research in the United States, and looks forward to enhancing the interaction among our constituents and those Institutes at NIH that support musculoskeletal research. Since the burden of disease in this area is higher than that cancer and heart disease, we

believe that this enhanced interaction will improve the health of the nation. According to the 2008 *Burden of Musculoskeletal Diseases in the United States* publication of the United States Bone and Joint Decade (USBJD) and the AAOS:

- Musculoskeletal medical conditions were reported by 107.67 million adults in the U.S. in 2005 in the National Health Interview Survey (NHIS), representing nearly one in two persons aged 18 and over of the estimated 2005 population.
- The rate of chronic musculoskeletal conditions found in the adult population is nearly twice that of chronic circulatory conditions, which include coronary and heart conditions, and more than twice that of all chronic respiratory conditions.
- On an age adjusted basis, which accounts for differences in the age distribution of the health care database sample and the actual population, musculoskeletal conditions are reported by more than 48% of the population, or 48.3 persons per 100 population. This compares to a rate of 27.8 and 23.6 per 100 population for circulatory and respiratory conditions, respectively.

The AAOS is appreciative for the opportunity to provide feedback. We look forward to our continued dialogue and partnerships with the NIDCR in the future. If you have any questions about our comments, please feel free to contact Erin L. Ransford, AAOS Medical Research Coordinator, Office of Government Relations, at 847-384-4319 or ransford@aaos.org.

With Kind Regards,

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