Introduction to Resubmission Application

We appreciate the reviewers' careful consideration of the 2009 UCLA CTSA proposal. We have thoroughly revised this proposal in response to their critique. The application reflects new leadership and increased commitment to clinical and translational science. This revised proposal was developed in consultation with many CTSA leaders throughout the country including all of the Program Directors in the West Coast Consortium (please refer to **Institutional Letters**). In 2009, Dr. A. Eugene Washington was recruited to UCLA as the new Vice Chancellor for Medical Sciences and Dean of the David Geffen School of Medicine (DGSOM). Viewing the National CTSA initiative as a critical element for UCLA, Vice Chancellor Washington immediately launched the application revision, appointing Dr. Steven M. Dubinett as the Clinical and Translational Science Institute (CTSI) Program Director (PD) and Associate Vice Chancellor for Translational Science. Dr. Dubinett has been a faculty member at UCLA for 22 years and has led major translational research programs in lung cancer. He has extensive experience in academic administration, research mentorship and peer review. Changes in the distribution of Dr. Dubinett's effort and activities to allow sufficient time to direct the UCLA CTSI are described in the budget description. This includes an eight-point transition plan outlining specific details (refer to Administrative Core budget justification on page 186).

We have maintained the strengths of our previous application. During the past year we further developed the implementation plan. We have broadened multidisciplinary participation and increased integration. Unless otherwise noted in the Program sections, changes are indicated by a line in the left margin.

"Many of the programs lack representation on the Executive Oversight Committee (EOC)." The governance plan has been modified in accord with the critique. The EOC now has direct participation of all program area key functions with every member having voting rights (refer to Overview and Governance **section 5.3.**).

"It is not apparent what specific function (the Internal and External Advisory Committees) serve and how advice /counsel will be able to effect change, if necessary." The External Advisory Board (EAB) functions as an interface with the scientific community and offers an outside perspective to the UCLA CTSI. The EAB will include academic leadership from other CTSAs, leaders from industry and foundations. The EAB's impact will be direct and change will be effected via their reports to the PD and EOC. The primary mission of the Internal Advisory Board (IAB) is to provide advice to the EOC. The IAB provides an interface with the professional Schools at UCLA and CDU as well as partner institutions and community members. Vice Chancellors A. E. Washington and James S. Economou serve as co-chairs. To maximize efficacy, members will focus on specific goals relevant to their expertise. As academic and administrative leaders, the IAB will effect change via the co-chairs, the EOC and PD (refer to Overview and Governance **section 5.4.4.**).

The reviewers noted that the proposed structure seemed to be similar to having four separate GCRCs. In response, we have reorganized the governance structure and delineated our new plans for modernizing our clinical research infrastructure. This is summarized in Overview and Governance and presented throughout the application. We have transcended geographic and institutional barriers to integrate our clinical research infrastructure across multiple locations. Integration plans are discussed throughout the application.

"There is no plan detailed that would overcome barriers to integration across multiple locations… it is not clear how the proposed structure is significantly different than current support for the four clinical research centers." We have further integrated our existing programs and broadened our community outreach. This integration and expansion is being facilitated by the receipt of $15,000,000 over the next 5-years to transform the way we undertake participant research (see letter from the UCLA Health System CEO, Dr. Feinberg). We are re-engineering our clinical research infrastructures and changed the name of the PCIR function to Clinical and Community Research Resources (CCRR) to reflect this new approach. We are introducing many measures to overcome barriers, such as: **1)** weekly EOC meetings with all programs and Associate Directors. **2**) Weekly administrative integration meetings (in person or videoconference) chaired by the Executive Director, who will be responsible for the daily operation and oversight of the Office of the Institute staff, with partner site administrators. Such administrative meetings already are underway to unify the CTSI partner institutions. The Chief Research Facilitator in the Office of Investigator Services (OIS) attends all integration meetings. The site specific Associate Directors participate in these meetings on a biweekly basis. The Executive Director will make regular reports on site integration to the Program Director and the EOC. **3)** Increasing interaction among CTSI investigators through the **CTSI Virtual Home** and the OIS (see CCRR and Regulatory Programs). **4)** Sharing common protocols, standard operating procedures (SOPs) including Good Clinical Practice (GCP), and teaching materials across CCRR sites. **5**) Centralizing laboratories that follow Good Laboratory Practice

(GLP). **6)** Easing research approval barriers via creation of single, UCLA-wide scientific advisory committee and an institution-specific, CTSI-specific Institutional Review Board (IRB) for proposals seeking CTSA support and resources. **7)** Cross-training research staff to support inpatient, outpatient and community research as needed. **8)** Initiating Mobile "Chaperone" Services to link the CTSI partners and communities. **9)** Assessing and modernizing CCRR staffing to provide an appropriate distribution of research nurses, phlebotomists, and community health workers based on research needs.**10)** Creating a promotora program to engage community members in research education and encourage their participation in research projects (see CCRR **section 2**).

There were several suggestions regarding the Community Engagement and Research Program (CERP) which have been addressed below. Additional critiques are addressed within the CERP narrative.

"*No defined process to resolve potential conflicts between academic and community partners."* We have established a formal conflict resolution plan for mitigating any conflict between academic and community partners. This includes external dispute resolution and/or local, internal mediation (see CERP **section 6.5.2.**).

"The level of effort for Ms. Loretta Jones (Healthy African American Families Executive Director) dedicated to CERP is not clear. She and her organization are critical community partners." We identified Healthy African American Families as a key partner and have allocated it more resources in accord with its value within the CTSI. Ms. Jones is now a CTSI Associate Director (please refer to CERP **section 7**).

"The proposed Health Services Research (HSR) function is highly significant, but there is little apparent integration with the community outreach and engagement aspects of the CERP." The previous HSR key function has been integrated entirely with CERP to co-develop research priorities with communities; advance a broader scope of translational research including comparative effectiveness, implementation, dissemination and diffusion research; and bring cutting-edge methods into community-partnered research. **Specific Aim 4** in CERP is now devoted to building HSR methods into partnerships to accelerate design, production and wide adoption of evidence-based practice and behavior.

The reviewers praised many aspects of the Biostatistics, Study Design and Clinical Data Management Program (BSD-CDM). Several suggestions were noted and these are now addressed as follows:

"The level of effort proposed for the BSD-CDM Program leaders appears insufficient." We have more than doubled the budget for this program. We have increased the senior leadership of this program to include four leaders and added five master's level statisticians (with half of the support from institutional funding). Please refer to BSD-CDM **section 6.1.1.** and **Budget Justification**.

"There does not appear be a defined mechanism for obtaining evaluative feedback from investigators. The evaluation and tracking plan mentions the quality of services. It is not clear how this will be defined and measured." We provide greater detail about our regular feedback methods and metrics for assessing access and service quality, our financial mechanisms and our plans for community-based statistical research. As has been our practice over the last year, periodic internet-based surveys will assess needs, availability and use of resources, and track satisfaction with CTSI programs and services. A 2010 CTSI-wide survey identified biostatistics priorities and the bioinformatics survey obtained over 900 responses from investigators, administrators and trainees.

"Given the close integration with CERP, it seems there may be a missed opportunity to expand the research program focus to address particular research design and biostatistics problems encountered in community-based research." To increase our capabilities in community-based research, we have added three outstanding members to our team with extensive biostatistical experience in community settings: Drs. Belin, Crespi and Sugar (please refer to BSD-CDM **section 7** and **Biosketches**).

"Biostatistical training topics do not appear to address interdisciplinary and transdisciplinary communication and cross-cultural issues that can hamper optimal collaboration between statisticians and clinical investigators. It is not clear if or where training plans specifically address the special issues associated with vulnerable populations and community-based research." The BSD-CDM is developing a consulting short course and hands-on mentoring for biostatistics students and junior statistical investigators on communication. The consulting short course will be led by experienced faculty statisticians (Gjertson, Horvath, D. Elashoff) and involve CTSI investigators from CTSI-ED and CERP. Direct mentoring will pair students, staff and junior faculty statisticians with experienced faculty statisticians well-versed and active in translational clinical research including community-partnered research, including Drs. Belin, Sugar and Crespi. Mentoring sessions include

consulting meetings with CTSI collaborators at all stages of the statistical design process. These new initiatives add to existing course offerings from the Biostatistics Department (e.g. in the K30 curriculum) currently being taught by our CTSI faculty Drs. Gjertson and Horvath. The new course addresses special issues associated with vulnerable populations and community-based research and is being expanded to allow full access for CTSI investigators (refer to BSD-CDM **section 6.3.1**)

"There are no clearly identifiable programs that focus on novel technology and methodology development. It is unclear how aspects of the grant program aimed at developing novel translational technologies and methodologies will be implemented." The Pilot and Collaborative Translational and Clinical Studies Program, **Specific Aim 2** and the Center for Translational Technologies **Specific Aim 2** cover the development of novel clinical and translational technologies and methodologies. We are instituting Novel Translational Technologies and Methodologies Grants (up to three awards annually of up to $100,000 each). These awards foster the development of any research tool, technique, or resource with the potential of bridging critical gaps in the conduct of translational biomedical science. The Pilot/Collaborative program describes these and other mechanisms.

The Biomedical Informatics Program (BIP) received several critiques. BIP is thoroughly revised in concert with the critique and with extensive consultation from leading experts in bioinformatics from other CTSAs.

The reviewers noted it was "*unclear whether [we] have evaluated tools that have been developed at other CTSAs*." We are actively adopting several CTSA shared tools including i2b2 (Harvard University), REDCap (Vanderbilt University), Honest Broker, RDS, and TIES (all University of Pittsburgh). We plan to continue adding other CTSA-derived tools to our program (refer to BIP **sections 5.** and **6.2.4.**).

Related to the BIP's Research Data Repository (RDR), the panel noted "*the description of the federated Research Data Repository lacks detail… it is uncertain if the repository will contain identified or de-identified data… harmonization of models and data elements is not described.*" The RDR is now described in greater operational and logistic detail (refer to BIP **section 6.2.**), including clarification that **the RDR contains only de-identified data**, and clarification of the methods for de-identifying protected health information (PHI) at each health care delivery partner using the Pittsburgh CTSA's Honest Broker system.

Reviewers noted that "*description of the hardware, software, and networking measures to ensure data security is missing.*" The current BIP proposal now describes how the Virtual Home and the Research Data Repository (RDR)-related systems will adhere to strict data security measures, at levels prescribed by the Federal Information Management Security Act (FISMA), including hardware and software policies, access controls, training, and documentation. Additional details of the data security plans are provided under "Data Safety and Monitoring" in the Protection of Human Subjects section of the proposal.

The reviewers noted that "*clinical data collection and trials software are not described in detail, and it is unclear what systems are currently in place in each institution or how investigators will effectively access these resources.*" In response, we describe the Velos eResearch system, which now serves as our Clinical Research Management System. In addition, we are currently planning the linkage of clinical trial drug administration from the Investigational Pharmacy to data entry and validation in Velos (**sections 5.** and **6.2.3.**).

A criteria-specific concern was that *"There is no mention of how this CTSI will interact with other CTSAs*." We joined the **Sharing Partnership for Innovative Research in Translation (SPIRiT),** the CTSA program's first virtual consortium focused on data sharing (see **Institutional Letters**). We are partners in the CTSA West Coast Consortium and Greater Los Angeles CTSA Coalition. We have consulted with leading experts in the other CTSA informatics groups. Related to Investigators, a concern was that "*details about steering committee and working group meetings are not provided.*" **Section 6** clarifies BIP governance and workgroup operations.

"Translational research topics, training, and resources focused on pediatrics are underdeveloped." Our depth and resources in translational pediatrics are detailed in multiple key functions. A new transdisciplinary **Committee on Maternal, Child and Adolescent Health** (CMCAH) guides research strategies, provides advice to the EOC and develops training opportunities. Led by Kathleen Sakamoto MD (Vice Chair of Research, Department of Pediatrics) and Neal Halfon MD (Associate Director of the CTSI and Director of the Center for Healthier Children, Families and Communities), this group of 23 leading investigators combines expertise across the translational continuum and multiple disciplines. The CMCAH roles are described in Overview and Governance. A representative from the CMCAH serves on EOC.