RESEARCH STRATEGY – EPIBIOS4RX ADMINISTRATIVE CORE

1. SIGNIFICANCE

Ensuring success of the Cores and Research Projects, to achieve the goals and objectives of EpiBioS4Rx is the primary responsibility of the Administrative Core. We have put considerable thought into the administrative structure of this complex multicenter international research program, and have drawn from over twenty years of extensive multi-departmental and multi-institutional collaborations, during which similar systems have been refined and fine-tuned to maximize the cooperative efforts of clinical, biological, computer science, mathematical, and organizational expertise. Although there are now several NIH funded federated studies, beginning with the Alzheimer's Disease Neuroimaging Initiative (ADNI), EpiBioS4Rx will be a unique model for future large scale, multi-site, multi-modality, translational studies of epilepsy. Creating an effective Center Without Walls (CWOW) will enable aggregation of data, and efficient cooperation among scientists. In this way we will advance epilepsy research at a far greater pace than could be achieved without the coordination made possible by our project. It is particularly important to note that our PIs are all leaders in their fields with considerable NIH funded experience, and have enthusiastically embraced this multi-PI project resulting in a unique team of complementary expertise tested and honed during the planning grant (P20 NS080181). The multiple PI arrangement is essential because of the multidisciplinary nature of EpiBioS4Rx, as each PI has expertise relevant to part of the overall vision and only together will they complement each other to achieve the overall goals and objectives. **Governance has been carefully crafted and agreed upon, with one Director who will have primary administrative responsibility, supported by an Executive Committee of all the PIs and the NINDS Program Officer that oversees the vision of the Center, and a larger Steering Committee, that includes all members of the Executive Committee plus other Research co-PLs, responsible for making critical decisions in a democratic fashion. Because of the size of the executive committee, a smaller Management Committee made up of the Director, Contact PI, the NINDS Program Officer, and a fourth member rotated every year among the other 5 co-PLs will aid the Director in managing day to day affairs.** A primary significance of the Administrative Core is not only to ensure the effective function of EpiBioS4Rx, but also to serve as a model for other multicenter programs that will undoubtedly be the future of much epilepsy research. A Charter, universal protocols, common data elements, regulatory provisions, plans for data sharing, and an Authorship Agreement have been created. The Administrative Core will also facilitate collaborative efforts within and without EpiBioS4Rx, promote career development for trainees and young investigators, and stimulate new research projects. The most important significance of this Administrative Core will be to ensure the success of our Research Projects, to create universal shared resources for the epilepsy community, to include an open shared epilepsy-specific bioinformatics portal, a standardized preclinical protocol for testing potential antiepileptogenic interventions with a list of the most promising preventive therapies, a population of subjects for future clinical trials of antiepileptogenic treatments, and a public engagement program to ensure patient involvement, adequate recruitment, and retention. **The Scientific Premise of EpiBioS4Rx is: Epileptogenesis after TBI can be prevented with specific treatments; the identification of relevant biomarkers and performance or rigorous preclinical trials will permit the future design and performance of economically-feasible full-scale clinical trials of antiepileptogenic therapies.**

2. INNOVATION

The innovation of our Administrative Core can be found in three areas. First, we have created a charter that specifically outlines the policies that will guide EpiBioS4Rx. This charter is the product of past efforts by the leadership in other multi-site projects and the work conducted during the planning phase of this project. A relatively formal document at this stage provides evidence of our programmatic maturity and the administrative requirements for cooperation among senior accomplished investigators. Second, the charter outlines a bold sharing philosophy that embraces a true Center Without Walls concept and welcomes contributions and participation across the globe. Third, we describe very comprehensive communication methods including electronic systems, phone calls and face-to-face meetings. This rigorous approach will facilitate the coordination among geographically distributed leadership and participants. It provides a ready-made documentation system and will help us plan and adapt as new data and findings present themselves.

3. APPROACH

3.1. Progress Report

3.1.1. Workshops: Five workshops were held at UCLA during the P20 planning grant (Appendix 1). These were organized by a coordinated effort of the UCLA Seizure Disorder Center and the Laboratory of Neuro

Imaging (LONI), initially when the latter was at UCLA, and later after it was relocated to USC. This effort is one example of the collaboration between these two programs that will enable the function of the Administrative Core to be shared jointly by UCLA and USC.

3.1.2. Charter and Publication Policy: The EpiBioS4Rx Charter and Publication Policy have been crafted to define the leadership structure and guiding principles for collaborative relationships of the CWOW, and to ensure that EpiBioS4Rx members receive fair and adequate acknowledgement for their participation. An undertaking of this magnitude necessitates a precisely defined level of coordination and interactivity. The structure of the partnership must be such that each participant works directly toward the goals of the project and contributes to an ongoing adjudication of the project progress, while they themselves are subjected to the same critical assessment. That is, the partnership is equitable both in responsibility and accountability. We have given considerable thought to the organizational structure for EpiBioS4Rx and will draw from over twenty years of extensive multi-departmental and multi-institutional collaborations of LONI, during which similar systems have been refined and fine-tuned to maximize the cooperative efforts of clinical, biological, computer science, mathematical, and organizational expertise. The collaborative practices described here were developed in keeping with the mission and philosophy of a successful multidisciplinary program.

3.1.3. Publications: EpiBioS4Rx investigators instigated, and were co-authors on, a number of scientific research and review articles concerned with issues related to the development of antiepileptogenic interventions, and the importance of biomarkers in this effort directly and indirectly related to the EpiBioS4Rx workshops and other functions of the P20 planning grant. See the Overall Component and individual Cores and Research Projects for details on these and other research publications supporting the P20 planning grant.

3.1.4. Public Engagement: Considerable effort has been focused on establishing a coalition of epilepsy and TBI consumer groups and soliciting their participation in realizing effective clinical trials, as described in the Public Engagement Core.

3.1.5. Preliminary data: These are described in the individual Cores and Research Projects.

3.2. Administrative Core Functions

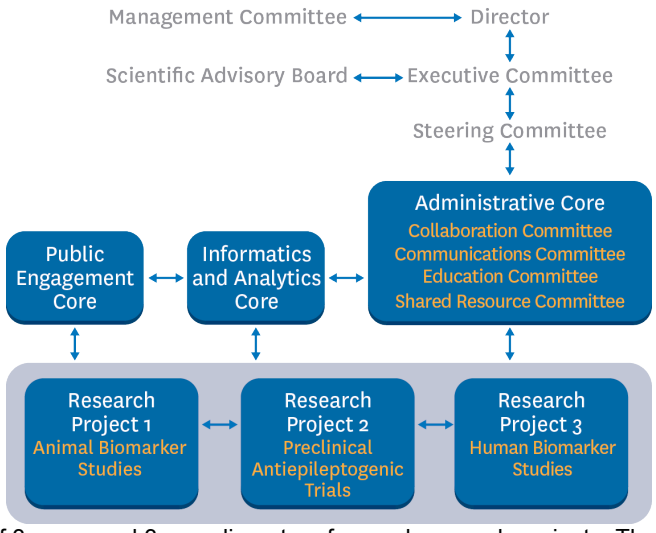


Figure 1. EpiBioS4Rx will consist of 3 cores and 3 complimentary focused research projects. The Administrative Core (Engel/Toga) will provide logistical support and has 4 standing committees (Collaboration, Communication, Education, and Shared Resource). The Public Engagement Core (Moshé/Jette) will interact with a consortium of consumer groups and health organizations. The IAC (Toga) will service the 3 Research Projects on: Animal biomarker studies (Pitkänen/O'Brien/Staba), Preclinical antiepileptogenic trials (Galanopoulou/Pitkänen/O'Brien), and Human biomarker studies (Vespa/Engel). The governance structure under the leadership of the Director (Engel) will consist of an Executive Committee made up of all the PIs and the NINDS Program Officer, and a Steering Committee made up of the Executive Committee members and the co-PLs. A separate Contact PI (Toga) will be necessary because EpiBioS4Rx is based at USC. A Management Committee made up of the Director, the Contact PI, the NINDS Program Officer, and a rotating member of the other PIs will assist the Director in day to day affairs. There will also be an external Scientific Advisory Board.

EpiBioS4Rx is a federated consortium of international research centers organized into an Administrative Core for logistical support and shared resources, an Informatics and Analytics Core (IAC) for data and analytic support, a Public Engagement Core to support trial recruitment and retention, and 3 focused complementary Research Projects. Collaboration with extramural research, consumers, and health organizations is integral to EpiBioS4Rx' goals and objectives.

The EpiBioS4Rx Administrative Core will provide leadership and expertise regarding the Center's charter, universal protocols, regulatory provisions, and plans for a data sharing program. It will facilitate collaboration within and between the Center's Cores and Research Projects, promote the career development of trainees and young investigators, coordinate collaboration with other NINDS- and non-NINDS-funded programs, stimulate and evaluate new collaborative research beyond the current EpiBioS4Rx proposal, and support activities of the Public Engagement Core. The Administrative Core will also provide reporting of Center activities to NINDS.

3.2.1. Specific Aim 1: To provide leadership and expertise regarding the Center's charter, universal protocols, regulatory provisions, and plans for a data sharing program.

3.2.1.1. Leadership: EpiBioS4Rx will have 7 Principal Investigators (PIs) who are all leaders in complementary overlapping fields essential to the successful completion of the Specific Aims and long-term objectives of this CWOW (see also the section on Multiple PIs). We realize that it is unusual to have 7 PIs; however, the complexity of EpiBioS4Rx makes it essential that we have leadership expertise for all of the diverse areas of effort, ranging from clinical observation studies, to animal models, to preclinical and clinical drug development, to molecular and cellular analysis, to detailed bioinformatics, that includes EEG as well as neuroimaging and molecular and cellular data, to public outreach. We have carefully organized the leadership structure under a single Director, who will have overall responsibility for meeting the EpiBioS4Rx goals and objectives, and defined roles for each of the other 6 PIs. Jerome Engel, Jr., MD, PhD is Director of the UCLA Seizure Disorder Center. He will be Overall Director and lead Project Lead (PL) of the Administrative Core. He will also be co-PL of *Project 3* and will participate in *Project 1*. He is a clinical epileptologist and basic neuroscientist with extensive experience in research on epileptogenesis in patients and experimental models of human epilepsy (including TBI/PTE), and an international authority in the field of epilepsy biomarkers, particularly those derived from EEG recordings and neuroimaging. Dr. Engel is highly regarded nationally and internationally for his leadership abilities. Asla Pitkänen, MD, PhD, is a basic scientist at the University of Eastern Finland. She has been a pioneer in development and study of animal models of TBI and PTE, and is currently acknowledged as the preeminent investigator in this field. Dr. Pitkänen will be PL on Research *Project 1* on animal biomarkers of epileptogenesis using the rat TBI/PTE model, and also co-PL on *Project 2*. Aristea Galanopoulou, MD, PhD, is Director of the Laboratory of Developmental Epilepsy at Albert Einstein College of Medicine, and an expert in epileptogenesis in animals. She has been engaged in developing rigidly standardized preclinical protocols for trials of potential anti-seizure and antiepileptogenic compounds and will be PL on Research *Project 2* on preclinical antiepileptogenic trials. Terence O'Brien, MD, is Head of the Department of Medicine and the Epilepsy and Neuropharmacology Research Group at the Royal Melbourne Hospital, University of Melbourne, an expert on all aspects of experimental TBI and PTE, including molecular biology and experimental and clinical pharmacology, and also a highly regarded clinical epileptologist. He has a track record in successfully taking novel therapies from pre-clinical to clinical trials. He will play a leadership role when *Projects 1 and 2* combine efforts to begin preclinical trials, and will also be involved in the clinical *Project 3*. Paul Vespa, MD, is Director of the UCLA NeuroICU. He is a neurologist and neurointensivist with a background in clinical neurophysiology and epilepsy. He has focused his research on clinical TBI, including seizures and epilepsy in this condition, and is a recognized leader in the TBI and neurointensivist community. Dr. Vespa will be PL of Research *Project 3*, on parallel studies of human biomarkers of epileptogenesis using patients with TBI/PTE. Arthur Toga, PhD, is Director of the Laboratory of Neuro Imaging (LONI) at USC. He will be the Contact PI and co-PL of the Administrative Core, because USC is the award site, as LONI has the necessary infrastructure to support this large complex program. LONI developed the bioinformatics platform to identify biomarkers for ADNI, as well as several other multicenter projects on Parkinson's disease, Huntington's disease, and other brain disorders. Dr. Toga will also be PL of the IAC and will oversee the integration, storage, analysis, and sharing of data derived from Research *Projects 1-3*. LONI is currently the most sophisticated bioinformatics program for biomarker studies in the world; with work done during the P20 planning grant, LONI now also includes EEG, making it an epilepsy-specific bioinformatics platform, also ideal for analyzing results of preclinical antiepileptogenic trials. Solomon Moshé, MD, Director Child Neurology and Director of Clinical Neurophysiology at Albert Einstein College of Medicine, is highly regarded for his accomplishments in translational research. He is well connected with patient advocacy groups through his leadership role in national and international epilepsy organizations, and will be PL of the Public Engagement Core. As a group, the PIs represent the forefront of research in every discipline needed to accomplish the Specific Aims of this CWOW, and long-term objectives of EpiBioS4Rx. Importantly, the planning grant enabled the group to coalesce into an integrated and productive team working together towards a common purpose. All PIs share responsibility and authority for leading and directing the work within their components, as well as

the overall center. The Director is responsible for communication between the NINDS and PIs and co-investigators within the components. PIs and Directors can be changed according to the wishes of the component leadership, with the advice and consent of the Executive Committee and the Steering Committee, as described in the Charter. The Director will be aided in day-to-day affairs by the Management Committee, described in the Charter. The Executive Committee will coordinate its efforts with weekly teleconferences. The Steering Committee will coordinate its efforts with monthly teleconferences. The 7 PIs have been conducting regular teleconferences by telephone or Skype for over 2 years and plan to continue this practice. Dr. Engel, as Director, will chair the Executive and Steering Committees. These committees will be responsible for the governance of the CWOW as outlined in the EpiBioS4Rx charter. An annual face-to-face meeting of all EpiBioS4Rx investigators is a crucial component of this organizational structure.

3.2.1.2. Organization: The primary objective of our organizational management is to facilitate interactions and communication between all components of EpiBioS4Rx and to handle the day-to-day support operations necessary for EpiBioS4Rx productivity and longevity. This includes, but is not limited to, scheduling meetings between investigators at multiple campuses, preparing progress reports for members, organizing regular mechanisms of communication, and coordination of milestones and deliverables. The Administrative Core has the responsibility for facilitating information exchange, monitoring the utilization of physical and human resources, adjusting structural and functional aspects of the project as needed to meet its intended goals, establishing and maintaining operational mechanisms for the scheduling and holding of meetings, budgetary control and oversight, programmatic reporting, and instigating collaborations, outreach programs, and commercial relationships as appropriate to the Center's objectives.

3.2.1.3. Charter: The collaborative nature of the Center specifies that EpiBioS4Rx is **openly shared** and, as such, everyone is entitled to access to the shared database, analytic tools, and other resources, as detailed in the EpiBioS4Rx Charter. (The only restriction to this policy is the limited biosamples; although data derived from them will be shared, the samples themselves will not, and data from outside EpiBioS4Rx investigators will respect any data sharing restrictions they impose.) Data, tools, and other resources provided by collaborators from outside EpibioS4Rx will be welcomed. However, in order to ensure that these collaborating investigators are comfortable with an open model and to respect their local policies, we will utilize a system whereby access control is maintained by the investigators depositing data and tools. They will have the ability to remotely, through a website, control who sees what data and when. The objective here is to lead by example. We have learned in other settings that people appreciate the control and ultimately turn to an open model when the benefits are apparent. Publications resulting from the use of EpiBioS4Rx data must acknowledge EpiBioS4Rx. All data distributed by EpiBioS4Rx cannot then be re-distributed by others.

EpiBioS4Rx Charter

1. Rationale

Epilepsy is among the most serious health burdens worldwide. Despite decades of research that has succeeded in elucidating fundamental neuronal mechanisms of epilepsy, and yielded over fifteen new antiseizure drugs and novel non-pharmacological therapies, there remain no treatments that prevent or cure epilepsy, other than surgery, nor are there uniform strategies to identify and validate such interventions. A major obstacle to research in this area is the fact that studies from single institutions are invariably underpowered to answer the most important questions. It is now clear that the best opportunity to realize effective antiepileptogenesis will come from large collaborative research efforts by multidisciplinary teams of basic and clinical neuroscientists with access to extensive patient populations, appropriate animal models, and cutting-edge analytic methodology. EpiBioS4Rx has been created to address this pressing need.

EpiBioS4Rx is a federated consortium of international research centers organized into an Administrative Core for logistical support, an IAC for data and analytic support, and multiple complementary Research Projects. Each research component of EpiBioS4Rx is multicenter with multiple PIs. This charter describes our philosophy and rules of engagement in order to achieve common goals, and to ensure that all individual investigators receive adequate acknowledgment and compensation for their contributions to the overall collaborative effort. Collaboration with non-EpiBioS4Rx members and programs is encouraged, and development of new EpiBioS4Rx projects and related grant proposals, particularly by young investigators, will be promoted.

2. Leadership

2.1. Principal Investigators (PIs) and Director: Overall leadership and leadership of individual components will consist of multiple PIs, one of whom will be designated Director. All PIs share responsibility and authority for leading and directing the work within their components, as well as the overall center. The Director is responsible for communication between the NINDS and PIs and other investigators within the components. The PIs and Director can be changed according to the wishes of the component leadership, with the advice and consent of the Executive Committee and the Steering Committee.

2.2. Executive Committee: The Executive Committee consists of the PIs of the 3 Cores and Research Projects, and the NINDS Scientific Program Officer. The Executive Committee will be chaired by the Director of the Administrative Core, will be responsible for the overall logistical direction of EpiBioS4Rx, will carry out standing weekly to monthly teleconferences, and at least one annual face-to-face meeting.

2.3. Management Committee: Day to day business of the Center will be overseen by the Director with the aid of a Management Committee to also include the Contact PI, the NINDS Scientific Program Officer, and a fourth member, which will rotate every year among the other PIs.

2.4. Steering Committee: The Steering Committee will consist of the Executive Committee plus the co-PLs of each of the Research Projects. The Steering Committee will be responsible for all strategic and operational activities of EpiBioS4Rx, including the development and implementation of policies and procedures, conformance with regulatory provisions, prioritization of scientific goals, publications, and decisions about collaborations with other investigators and new research proposals. The Steering Committee will be chaired by the chair of the Executive Committee, and decisions will be made, whenever possible, by consensus. When necessary, however, decisions will be made through a simple majority vote, with each member having one vote. The Steering Committee will have standing monthly teleconferences and at least one annual face-to-face meeting. For specific issues regarding establishment of priorities, development of common protocols, review of progress, redefining scientific objectives, conflicts regarding data and resources, new collaborations and research proposals, and preparing annual written reports, the Steering Committee can establish subcommittees made up of members of the Steering Committee or other co-investigators of EpiBioS4Rx.

2.5. Scientific Advisory Board: EpiBioS4Rx will have a Scientific Advisory Board made up of prominent investigators in fields relevant to antiepileptogenesis and at least one lay advocate. The Scientific Advisory Board will assist in ensuring a high standard of research, and will take part in the annual EpiBioS4Rx meetings.

2.6. Co-Investigators and Consultants: Co-Investigators and Consultants are official members of EpiBioS4Rx, will contribute data to the EpiBioS4Rx open shared database, and by contributing data agree to the open model of EpiBioS4Rx. Co-Investigators will participate in prospective research studies of the EpiBioS4Rx Research Projects, as designated in the original grant proposal, as well as in EpiBioS4Rx grants that may be proposed and funded in the future. Co-Investigators will have budgets and receive financial support for this participation. Consultants will participate in EpiBioS4Rx by contributing data to the EpiBioS4Rx shared database, and by utilizing this database to carry out research projects. Consultants will not all receive financial support from EpiBioS4Rx for these research projects, but can use this work and EpiBioS4Rx resources to apply for individual grant support from governmental and non-governmental sources. PIs, co-PLs, co-Investigators and Consultants may not unilaterally share EpiBioS4Rx data with non-members of EpiBioS4Rx. Data will be shared directly from the IAC to ensure that data sharing can be tracked. Co-investigators and consultants will otherwise adhere to regulations governing the use of the EpiBioS4Rx shared database as specified in the IAC.

3. Guiding Principles

3.1. All PIs, co-PLs, co-Investigators, and Consultants of EpiBioS4Rx Cores and Research Projects are members of EpiBioS4Rx and will agree to an openly shared model for data and tools.

3.2. Data deposited into EpiBioS4Rx by those from outside EpiBioS4Rx will be shared with all members of EpiBioS4Rx, in accordance with the rules and regulations of the IAC. Non-EpiBioS4Rx contributors will have control over access to their data and tools by any other non-EpiBioS4Rx scientists requesting data and tools.

3.3. Research Projects can be added or removed from EpiBioS4Rx according to the wishes of the project leadership and available funding, with the advice and consent of the Steering Committee.

3.4. Changes in the leadership and membership of Cores and Research Projects can be made according to the wishes of the individual Cores and Research Projects, with the advice and consent of the Steering Committee.

3.5. All PIs, co-PLs and co-investigators will agree to provide progress reports in a timely fashion, and contribute to preparation of annual reports due to NINDS and other oversight bodies.

3.6. All members of EpiBioS4Rx will sign data sharing agreements and adhere to the spirit and letter of these to the fullest extent, incorporating NIH policies, procedures, and recommendations.

3.7. All members of EpiBioS4Rx will sign publishing and authorship agreements and adhere to the spirit and letter of these to the fullest extent.

3.8. All members of EpiBioS4Rx will sign conflict resolution agreements. The Executive Committee, in consultation with the Steering Committee, will settle disputes arising from EpiBioS4Rx activities with direct dialogue and mediation when possible. When this is not possible, a dispute resolution panel composed of 3 members: one from the Executive Committee, one from the NINDS, and one from the Scientific Advisory Board will settle the dispute by a majority vote. This decision can be appealed in accordance with PHS regulation 42 GFR Part 50, subpart D and DHHS regulation 45 CFR part 16.

3.9. The Steering Committee will review and approve new proposals for collaborative projects and new research funding applications. It will also evaluate projects that appear not to maintain research productivity and otherwise underperform, or that have completed their contractual agreement. All EpiBioS4Rx members will sign "sunsetting" agreements that require agreement to abide by a simple majority vote of the Steering Committee on such matters.

3.2.1.4. Scientific Advisory Board: An external Scientific Advisory Board will be appointed to provide additional expertise in areas relevant to the goals and objectives of EpiBioS4Rx. The Scientific Advisory Board will also provide outside advice on the governance of EpiBioS4Rx when needed, as defined in the EpiBioS4Rx Charter.

3.2.1.5. Data Safety Monitoring Board (DSMB): The DSMB will consist of 6 investigators with expertise in clinical and preclinical drug trials and drug development: Dr. Jacqueline French, NYU, expert in clinical trials and organizer of the AED and Pipeline Conferences; Dr. Emilio Perucca, U. Pavia, expert in clinical trials for new antiepileptic therapies; Dr. Patrick Kwan, U. Melbourne, expert on both clinical and preclinical antiepileptic therapy trials; Dr. Nathalie Jetté, U. Calgary, expert on outcome assessment and clinical trials; Dr. Thomas Bleck, Rush, expert in neurocritical care, epilepsy and clinical trials for status epilepticus; and Dr. Roy Twyman Vice President at Janssen Research & Development and expert in preclinical antiepileptic trials and all stages of drug development. The DSMB will monitor the procedures and progress in *Project 2*, review the data obtained from *Projects 1-3* and advise on the best and most clinically relevant decisions on study design, evaluation, prioritization and interpretation of data, selection of the treatments that will advance onto the next stage of development, and the preparation of the human cohort for future clinical trial. The DSMB will participate in the annual meetings of EpiBioS4Rx. Decisions on GO/NO GO of a treatment will be done in coordination with the PIs of *Projects 1-3* and the Public Engagement Core. DSMB members will also interact via phone or emails, as needed, with the *Project 2* PL (Galanopoulou) and *Project 3* PL (Vespa).

3.2.1.6. Troubleshooting and Problem-Solving: Obstacles, anticipated and unanticipated, will be brought to the attention of the Executive Committee at our regular weekly conference calls. When a problem occurs, it will be posted on the electronic bulletin board with a brief description. One of the team leaders will be assigned to develop a means by which to solve the problem within an anticipated timeframe for its resolution. All members of EpiBioS4Rx will sign conflict resolution agreements, so, if necessary, the Executive Committee, in consultation with the Steering Committee, will settle disputes arising from EpiBioS4Rx activities with direct dialogue and mediation when possible, or by a specially appointed Dispute Resolution Panel, as detailed in the EpiBioS4Rx Charter.

3.2.2. Specific Aim 2: To facilitate collaboration within and between the Center's cores and Research Projects, promote the career development of trainees and young investigators, coordinate collaboration with other NINDS- and non-NINDS-funded programs, and stimulate new collaborative research.

3.2.2.1. Meetings and Teleconferences: Administrative Core personnel will provide logistical support for site meetings, teleconferences, and annual in-person meetings, and coordinate effective collaboration across all components of EpiBioS4Rx. Weekly teleconferences for the Executive Committee and monthly teleconferences for the Steering Committee will include videoconferencing when necessary. Teleconference and videoconference facilities will also be made available to individual projects and investigators as needed to facilitate their specific aims. Emphasis will be given to developing milestones that lead to enhanced technical capacities, collaborative research efforts, and biomedical education. EpiBioS4Rx will support an annual meeting of all members to be held in association with a national conference, most likely the annual meeting of the American Epilepsy Society to reduce costs. In addition EpiBioS4Rx will organize and host an annual CWOW conference, on a rotating basis, at NINDS expense, as specified in the RFA. Both EpiBioS4Rx Administrative Core sites are fully capable of hosting this conference. UCLA was the site of the workshops for the P20 planning grant (see Appendix 1). The Institute for Neuroimaging and Informatics at USC has a state-of-the-art 50-seat theater that can be turned into a conference room with full audio, visual, and teleconferencing capabilities. In addition, breakout rooms are available for smaller satellite meetings. Both sites are staffed with experienced event coordinators and technical personnel capable of organizing and running a conference of any size. Formal reports will be compiled to summarize discussions during teleconferences and annual meetings, and these will be used to prepare quarterly progress reports for all projects.

The program has a responsibility to communicate information about the product of its efforts. The first priority includes functional, usable, essential tools, and strategies to help our center answer research questions. We believe the best way to do this is to produce high quality, peer reviewed publications, describing carefully conducted research and the results of those experiments. Nevertheless, there are many other venues that are appropriate to disseminate information about our developmental research. The most obvious of these, and most commonly used, is the World Wide Web. We will create meaningful, instructional, and interesting web content that is constantly updated to reflect the current state of our research and other activities of our program (EpiBioS4Rx.loni.usc.edu). This dedicated site will contain links to data, software, publications, tutorials, course notes, streaming video of symposia, and information on training opportunities and future events. Other publication media such as books and periodicals, as well as published videos and web content, will help inform colleagues about our work. Our group is well known for its production of visual and useable materials including CDs, text books, review articles, and book chapters and will continue to do this as a mechanism for disseminating information about our activities and resources and how to use them.

Group	Electronic Bulletin Board	Conference Calls	Meetings	REPORT		
				TRACKING MATRIX	STATUS BOARD	WRITTEN SUMMARY
PI, Project, & Core Leaders	Continuous	Monthly	Quarterly	Continuous	Continuous	Annually
Advisory Board	On Request	Quarterly	Annually	On Request	On Request	On Request
Inter-Program Liaisons	On Request	Quarterly	As Needed	On Request	On Request	On Request
Trainees	Continuous	Alternate Months	Annually	Continuous	Continuous	Annually

Table 1. Monitoring and tracking tools. The above tools, the media they utilize and the intervals for their release/update, are provided. Through these tools the Administrative Core will monitor and distribute information about the progress, problems and finances of EpiBioS4Rx activities.

Tracking of the Overall Program*:* The Administrative Core will track the progress of software development as well as the validation and testing of all aspects of this program. Specific levels of monitoring and reporting will be followed.

Between Cores and Tasks*:* In addition to the weekly conference calls of the Executive Committee and the monthly conference calls of the Steering Committee, each Core leader and the Research Project PIs will have monthly meetings or conference calls with their component team. This system has worked extremely well in

our other funded projects helping us to maintain focus and keep projects running efficiently. A detailed TRACKING MATRIX will continue to be employed and distributed to consortium participants in order to provide a monthly set of achievable goals. These goals serve both as a guide and a means by which to monitor progress within the EpiBioS4Rx constellation of activities. In addition to these monthly contacts, our electronic bulletin board will permit any EpiBioS4Rx participant to post accomplishments, problems, or unexpected opportunities that arise during the intervals between the conference calls. Developed resources (software, software documentation, source codes, data sets, calibration standards, correction models, etc.) will be posted in a separate electronic bulletin board known as the STATUS BOARD, with level of development defined. Thus, constituents can see the developmental stage of any software, system, or data set. In addition to these means of posting and tracking accomplishments and problems within EpiBioS4Rx, we have developed a series of meetings, described below, that will occur at regular intervals throughout each year for the duration of the funding period. All these approaches have been refined and their success demonstrated with previous efforts.

With the Scientific Advisory Board*:* Conference calls with the external Scientific Advisory Board members will occur in conjunction with our monthly conference calls as needed (approximately quarterly) to address particular problems or opportunities. This arrangement will occur at any point during the proposed five years of funding commensurate with the intensity of algorithm and tool development. Additional meetings with Advisory Board members may be scheduled at national and international conferences.

With Inter-consortia Liaisons (see Consortium Activities): Frequent communication with individuals from other consortia and R01 projects in this and other initiatives will occur as needed. We have demonstrated our ability to perform these functions on a regular basis and have developed interesting collaborations with other efforts in the Human Connectome Project, BIRN, GAAIN, and other programs in which we participate. Access for inter-program liaisons to the STATUS BOARD, TRACKING MATRIX, and email communication on our electronic bulletin boards will be provided at their request.

TOOL (MEDIUM)	REPORTING INTERVAL
1. TRACKING MATRIX by month (e-bulletin board)	Continuous
2. Software, hardware, dataset STATUS BOARD (e-bulletin board)	Continuous
3. Annotated bibliography (e-bulletin board, hardcopy)	Continuous/Monthly
4. Verbal communication (conference calls)	Continuous
5. Problems, accomplishments (e-mail)	Continuous
6. Site-specific meetings (physical gathering)	Bi-Weekly/as needed
7. Written reports (hard copy)	Annual
8. Drafts of manuscript, preprints, reprints (hard copy)	As Needed
9. Financial reports (hard copy)	Monthly
10. Problem/trouble-shooting listing (e-bulletin board)	Continuous

Table 2. EpiBioS4Rx Communications. This table lists the types of communication, participating individuals and the intervals for their occurrence. These activities, when combined with the monitoring and tracking tools listed in Table 1, provide a means by which to communicate information on progress, problems and opportunities both within and outside EpiBioS4Rx.

With the Funding Agency: Given that this program will use a 'U' funding mechanism, we anticipate close coordination with a designated program and scientific officers. We will develop appropriately convenient and efficient reporting mechanisms beyond those outlined here to satisfy specific requirements of this type of oversight. An annual progress report will be prepared for the funding agency. Included in that report will be key components from the STATUS BOARD and the TRACKING MATRICES for the overall project. Representatives of the funding agency are invited to participate in any and all aspects of our EpiBioS4Rx communications and these communications will be made available to the agency using whatever mechanism is requested along with our annual progress reports.

Outside Laboratories and Commercial Interests: We anticipate continued interest and requests for information from universities outside EpiBioS4Rx and inter-consortia liaisons as well as commercial interests

and private industry. We will welcome these interests and, within the guidelines of our participating institutions and the federal funding agencies, will be open to sharing all information with them.

3.2.2.2. Facilitating career development*:* A priority of the Administrative Core, as well as the CWOW, is to promote careers of young investigators. The Administrative Core will oversee mentorship of trainees and young investigators involved with EpiBioS4Rx research projects, and will encourage young investigators to be primary authors on EpiBioS4Rx publications, as well as PIs on associated research proposals. An **Education Committee** will develop novel approaches to recruit trainees and young investigators into epilepsy research through the use of the EpiBioS4Rx website, Webinars, presentations at national and international meetings, and personal networking, which will also include dissemination of information regarding funding opportunities such as mentored NIH awards for young investigators.

3.2.2.3. Collaboration: A **Collaboration Committee** will oversee efforts to develop and maintain collaborative relationships with programs and individuals carrying out research relevant to the goals and objectives of EpiBioS4Rx. These will include the clinical TBI consortia: Track TBI (Manley), Center TBI (Menon), ADAPT (Bell), Banyan (Hayes), NINDS-funded projects such as Epi4K (Lowenstein), EpGP (Lowenstein), FEBSTAT (Shinnar), the Center for SUDEP Research (Lhatoo and Noebels), the cerebral malaria project (Birbeck), a potential cysticercosis project (Garcia and Del Brutto), non NINDS-funded projects such as EPITARGET (Kokaia), the Human Epilepsy Project (HEP) (French), NGOs such as the Epilepsy Foundation (EF) (Gattone), the International Bureau for Epilepsy (IBE) (Gattone/Covanis), the VA Epilepsy Centers of Excellence (Parko), and other consumer groups and health organizations, as detailed in the Public Engagement Core, as well as industry. The Collaboration Committee will be responsible for stimulating new research collaborations and evaluating the scientific excellence of proposed collaborative projects. This committee will also manage public relations and identify potential commercial candidates for cooperative partnership agreements.

3.2.2.4. Common data elements (CDEs*)*: EpiBioS4Rx will use the epilepsy and TBI CDEs developed by NINDS (http://www.commondataelements.ninds.nih.gov) for clinical studies. Animal epilepsy and TBI CDEs have been developed by EPITARGET and will be available for our use if EpiBioS4Rx is funded. A joint AES/ILAE Task Force is also developing CDEs for animal studies, which might be appropriate for future studies. CDEs and Case Report Forms (CRFs) for animals will be utilized in concert with the human TBI CDEs and CRFs (http://www.commondataelements.ninds.nih.gov/tbi.aspx#tab=Data_Standards) to harmonize the methodologies between the four preclinical sites (Kuopio, Melbourne, Los Angeles, Einstein) and the clinical studies. These CDEs and CFRs will be complemented by tailor-made EpiBioS4Rx CDEs available at EpiBioS4Rx website.

3.2.2.5. Publication Policy*:* A detained publication agreement has been created to ensure that all members and collaborators receive appropriate credit for the contributions to EpiBioS4Rx publications.

EpiBioS4Rx Publications Policy

This authorship agreement will apply to all original research papers, abstracts, platform presentations, posters, press releases, and any other material generated for public dissemination through EpiBioS4Rx activities. Two guiding principles govern the publication policy: 1. All work originating from EpiBioS4Rx Cores or Research Projects must acknowledge the EpiBioS4Rx Study Group on the title page, 2. The Steering Committee must approve the intention to prepare all communications acknowledging the EpiBioS4Rx Study Group as early as possible, and all EpiBioS4Rx members must approve the final submission of work related to their efforts. Work intended for the public will be of two types: *primary* and *secondary*.

Primary material: All work that addresses the specific aims of the Cores and/or Research Projects of EpiBioS4Rx as described in the original grant proposal, or in subsequent NIH funded EpiBioS4Rx Research Projects.

Secondary: Work resulting from unanticipated findings that have led to additional research directions as long as EpiBioS4Rx is funded by NIH.

Co-authorship of EpiBioS4Rx communications will require meeting all four criteria of the International Committee of Medical Journal Editors (ICMJE).

1. Substantial contributions to the conception or design of the work; or the acquisition, or interpretation of data for the work; and

2. Drafting the work or revising it critically for important intellectual content; and

3. Final approval of the version to be published; and

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

For selected *primary* papers that are particularly large in scope, involving the work of many investigators where no single person has taken an important lead role, there will be no named authors on the title page. The title page will name only "The EpiBioS4Rx Study Group," and individual contributions of the authors will be listed at the end of the manuscript.

For *primary* papers that include a minimum number of coauthors who had principal responsibility for conceiving the research design, collecting the data, and most importantly, writing the manuscript, "The EpiBioS4Rx Study Group" should always be designated on the title page after the coauthors' names. All other coauthors should be listed at the end of the manuscript indicating their qualifications for authorship. Additional collaborators who do not meet ICMJE criteria can be cited in the acknowledgments.

The first coauthor has the principal responsibility for writing the manuscript, and will also be designated as corresponding author, with responsibility for submitting the manuscript, corresponding with the publisher, overseeing the revisions, and proofing the final page proofs. The co-PLs of the Core or Research Project from which the work originated, and the Steering Committee, will approve which of the coauthors meeting all four ICMJE criteria are to be listed on the title page, and which at the end of the manuscript, and approve the order of their citation. Junior investigators below the rank of full professor, including graduate students and postdoctoral fellows, will be encouraged to be first authors, as well as coauthors, who are cited on the title page. There will be no designated senior author; the senior author will be the EpiBioS4Rx Study Group.

Coauthors of *secondary* papers will be those responsible for identifying the findings to be reported, collecting and analyzing the data, and writing the manuscript. As with *primary* papers, the first coauthor assumes the responsibility for writing the manuscript and serving as corresponding author. It is anticipated that *secondary* communications will have only a few coauthors and that all may be cited on the title page. As with *primary* communications, the PIs of the Core or Research Project from which the work originated, and the Steering Committee, will approve who should be credited with co-authorship, based on the ICMJE criteria, the order of co-authorship, and who should also be cited in the acknowledgments. The EpiBioS4Rx Study Group should also be acknowledged in place of a senior author on the title page.

There is no requirement that coauthors of EpiBioS4Rx publications be members of EpiBioS4Rx. It is anticipated that there will be times when collaborations with nonmembers, including other NIH- and non-NIH-funded consortia, contribute importantly to a publication, and these individuals, and consortia, should be listed as coauthors if they meet all four ICMJE criteria, and acknowledged if not.

It is important that co-authorship be determined at the time the intent to prepare a communication is initially submitted to the Steering Committee, and that all coauthors agree to be cited, as well as to the placement of their names in the citing of coauthors. Changes to authorship can be made during the preparation of the manuscript if all coauthors agree.

All co-investigators of EpiBioS4Rx should receive a copy of all EpiBioS4Rx manuscripts five days prior to submission, and be given an opportunity to comment, the principle of "no surprises." The coauthors and Steering Committee will determine whether comments require manuscript revision.

All disputes regarding publication or other public release of data generated by the EpiBioS4Rx Study Group, including co-authorship and acknowledgments, will be mediated by the Steering Committee, or if necessary,

resolved by a simple majority vote of an Adjudication Committee consisting of one member of the Executive Committee, the NINDS Program Officer, and one member of the Scientific Advisory Board.

3.2.2.6. Oversight of activities, protocols, regulatory provisions, and data confidentiality:

Electronic Bulletin Boards and E-mail: We have networks and resources for continuous electronic mail and electronic bulletin boards. The monitoring of the content of those materials including the software, hardware, data set, STATUS BOARD and the TRACKING MATRICES will be the responsibility of the Data Management and Informatics and the PI.

Troubleshooting and Problem Solving: Any obstacles will be brought to the attention of the principal investigator as well as the section and core leaders at our regular monthly conference calls. When a problem occurs, it will be posted on the bulletin board with a brief description. The IAC will develop a means by which to solve the problem with an anticipated time frame for its resolution.

Annotated Bibliography: The Administrative Core will monitor the published literature by means of an electronic library search, review of journals, and personal communication with project investigators, trainees, advisory board members, inter-consortia liaisons and leaders in the field. Relevant publications of interest to the consortium members will be posted in the form of an annotated bibliography on the electronic bulletin board. This approach will broaden the knowledge base of all participating investigators and trainees.

Ethics and Regulatory compliance: We have an obligation not only to protect the data but to ensure data use is by investigators who have taken the appropriate ethics and other related coursework and maintain current certification.

3.2.2.7. Data and Code Sharing Policy: As a result of experience with many other projects where we participate in the collection and archiving of data, we have developed a data and software sharing policy that is fully open. We lead the Informatics Core of ADNI (among several others) where the standard for big data sharing was conceived. The policy of the Shared Resource Facility, to be overseen by a **Shared Resource Committee**, will be unimpeded, unfettered, full open sharing of data and software without delay.

3.2.2.8. Intellectual Property*:* There will be no proprietary intellectual property as all methods, data, and results will be openly shared. Anyone participating in our EpiBioS4Rx CWOW will adhere to our open sharing policy. Our sharing plans are equally simple. We have adopted an open sharing, without embargo, policy. All data and results will be archived in our database and portal systems described in the Shared Resource Facility and made available to any investigator. A simple application for an account will be required so that we may tabulate usage and provide metrics of utility in progress reports. Biosamples or other data that are limited will not be shared in the same open way, however.

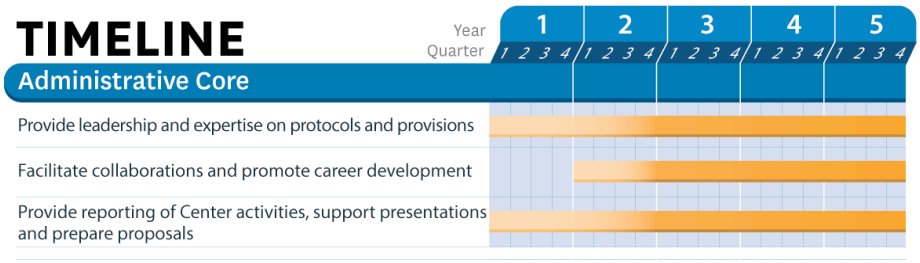
3.2.3. Specific Aim 4: To provide reporting of Center activities to NINDS members, and to relevant oversight committees, facilitate and provide logistical support for presentations of data at scientific meetings, publications, and preparation of additional research proposals and applications to regulatory agencies.

3.2.3.1. Annual reports: The Executive Committee will be responsible for organizing intramural reports of EpiBioS4Rx teleconferences and meetings, as well as publications and other deliverables, into the annual progress reports required by NINDS. Given that EpiBioS4Rx will be conducted through a “U” funding mechanism, representatives of NINDS will be invited to participate in all aspects of the Administrative Core activities, and we anticipate close coordination with a designated program officer. As appropriate, progress reports will also be provided to participating institutions, non-EpiBioS4Rx collaborative partners, and other funding agencies.

3.2.3.2.Scientific Productivity: The Administrative Core, along with the IAC, will provide resources to facilitate scientific publications, preparation of additional grant proposals, presentations at meetings, and dissemination of information regarding EpiBioS4Rx and the findings of its research to the scientific community, and to the general public via a website. A **Communications Committee** will oversee these efforts and ensure that all communications from EpiBioS4Rx meet the highest scientific standards and adhere to the principles of the EpiBioS4Rx Charter and Authorship Agreement, and will also explore novel ways to disseminate the results of our efforts and facilitate the application of our research productivity.

3.2.3.3. Regulatory Agencies*:* At such time that potential biomarkers and/or antiepileptogenic interventions are identified by EpiBioS4Rx researchers, the Administrative Core will be responsible for executing the process necessary to obtain biomarker qualification, and/or investigational new drug approval, as needed, from the US Federal Drug Administration, and similar approval from the European Medicines Agency.

4. TIMELINE



5. MILESTONES