Intramural Clinical Research Steering Committee (ICRSC): Presentation to the National Cancer Advisory Board February 3, 2009

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The Issues: Optimizing Clinical and Translational Research in the IRP

- The Clinical Center and the intramural culture create opportunities for clinical and translational investigation that have not been fully utilized
- Managing the costs of intramural clinical research continues to be a challenge
- Numbers of clinical protocols and clinical investigators in the IRP have decreased
- Productive career paths in clinical investigation should be more clearly delineated
- The protocol generation and review process should be re-engineered to make it more user-friendly, more efficient, and more consistent across the IRP while continuing to protect human subjects

Intramural Working Group Charge to Streamline Clinical Research

- **October 11, 2006: IWG invited Dr. Lane to chair a committee to streamline clinical research processes and to report to Clinical and Scientific Directors**
- **Spring, 2008: "Manhattan project" designation by IC Directors' committee on clinical research**
- **October 30, 2008: Completed a two-year process with engagement of IWG, Clinical Directors, Scientific Directors, ABCR, NIH clinical research community, and the NIH Steering Committee**
- **October 30, 2008: NIH Steering Committee approved formation of the Intramural Clinical Research Steering Committee (ICRSC), to make specific recommendations within 2 months**
- **December 4, 2008: Follow-up presentation to the NIH Steering Committee**

Functions of the ICRSC

(Charter Approved by NIH Steering Committee 12/7/08)

- Advises the NIH Deputy Director for Intramural Research (Michael Gottesman) and the NIH Director
- Provides guidance on standards and strategies for the development, review, and implementation of human subjects protocols, including IRB operations, support, and accountability, and ethical interactions with the pharmaceutical industry (including technology transfer)
- Provides guidance and strategies for the development, review, and implementation of human subjects research more broadly, including the scientific review of protocols, and the BSC review of clinical programs

Membership of the ICRSC

- Chair---Dan Kastner, NIAMS; also designated as Deputy Director for Intramural Clinical Research (DDICR)
- Two IC Directors
  - Griff Rodgers, NIDDK
  - Betsy Nabel, NHLBI
- Two Scientific Directors
  - Lee Helman, NCI
  - Richard Nakamura, NIMH
- Four Clinical Directors
  - Bill Gahl, NHGRI
  - Markus Heilig, NIAAA
  - Carter VanWaes, NIDCD
  - Richard Cannon, NHLBI
- Two Tenured Clinical Investigators Expert in Clinical Investigation
  - Steve Holland, NIAID
  - Shelia Zahm, NCI
- One IRB Chair
  - Howard Austin, NIDDK/NIAMS IRB
- One IRB Administrator
  - Jean Radcliffe, NINDS, Neurosciences IRB
- Ex officio
  - Cliff Lane, NIAID, MEC Chair
  - John Gallin, CC Director
  - Chair, CC Bioethics Department
  - Charlotte Holden, Office of Human Subjects Research Head

Additional Responsibilities of the ICRSC Chair/Deputy Director for Intramural Clinical Research (DDICR)

- With the DDIR, reviews and approves appointments of tenure-track clinical investigators
- With the DDIR, reviews the career pathways of Staff Clinicians
- Serves on the NIH Clinical Compensation Panel, NIH Compensation Committee, Central Tenure Committee (ad hoc), and Board of Scientific Directors (ex officio)

ICRSC Meetings

- Second and fourth Monday of the month, 4 p.m., Medical Board Room
- Initial meetings on November 24, December 1, 15, and 29, 2008
- Have focused on the protocol generation and review process
- Invited presentations
  - Dr. Barbara Karp, Neurosciences IRB
  - Dr. Steve Rosenfeld, Western IRB
  - Dr. Mike Klag, Hopkins

Protocol Review Process: Areas of Consensus

- Clinical investigators need more support in the preparation and implementation of human subjects protocols
- Scientific review of human subjects protocols should remain the domain of the specific ICs, but should be made more consistent across the IRP
  - Emphasize scientific rigor
  - Take advantage of the IRP's special resources
- There should be trans-NIH oversight and support for nomination and training of IRB chairs and members
- The ethical review process could be streamlined while still ensuring human subjects' protection

Protocol Generation and Review Process: Areas of Majority Agreement

- It would be desirable to transition from the current number of 11 IC-specific IRBs to 6 thematic trans-NIH IRBs that can:
  - Provide specialized expertise
  - Decrease NIH vulnerabilities by increasing the consistency of review across the NIH
  - Eliminate potential conflicts of interest
  - Increase the frequency of IRB meetings by having subpanels within each IRB, as is done by the Neurosciences IRB
  - Increase efficiency by concentrating IRB and support staff into a critical mass
  - Increase the pools from which IRB members can be drawn, both to permit rotations and to avoid conflicts of interest

Implementation Plan: PSCs

Transition towards six thematic Protocol Service Centers (PSCs), each of which would include an IRB and support for protocol preparation

- **Maintain scientific review within the individual ICs**
- **PSCs would provide support services for protocols associated with the respective IRBs**
- **Align IRBs with lead ICs (NCI, NCI-Epidemiology, NIAID, NIDDK, NHLBI, Neurosciences)**
- **Take advantage of current IRB expertise**
- **Enlist DDICR to provide oversight to eliminate conflicts of interest**
- **Let lead and participating ICs nominate IRB members and manage protocol support services**
- **Avoid the potential downsides of NIH centralization**
- **Encourage innovation by allowing PSCs to pilot their own approaches to streamline protocol generation and review**
- **Tentative agreement with NCI, NIAID, and NIDDK as lead ICs for PSCs dealing with cancer, immunology/infectious disease, and endocrine/metabolic/general medicine, respectively**

Implementation: Details of the PSCs

Support services provided by PSCs

- Biostatistical support/collaboration for study design, power calculations
- Protocol navigators
  - Assist in protocol-writing
  - Assist in meeting various administrative requirements
  - Assist in responding to stipulations
  - Guidance on FDA requirements
  - Could be dedicated senior research nurses
- Protocol tracking and management
- Could pilot real-time changes to protocols/consents during IRB meeting, subject to PI approval

Resources for PSCs

- Budget, FTEs, and space provided by lead and participating ICs
- Total cost for IRB and support services, including new and existing resources: $1 – 3 million per year
- Eventual identification of consolidated space centrally
- Modest increase in central resources for oversight and training

Pursuit of Best Practices

- Comparisons of practices piloted by individual PSCs
- Randomized assignment of selected protocols to outside IRBs of established excellence for critical evaluation of our review process

Implementation: Training

- Train IRB members and investigators in electronic protocol-writing tools such as ProtoType
- Provide field trips to observe other outside IRBs of recognized excellence
- Contract with the Western IRB to provide training to IRB staff and members?
- Broaden investigator participation in NIH IRBs
  - At least some use of rotations
  - Encourage connections with the clinical research community
  - Investigators participate actively in the review process

Implementation: Opportunities to Streamline the Review Process Without Compromising Human Subjects' Protections

- Creation of a special panel, either NIH-wide or within PSCs, for:
  - Continuation of protocols left open for data analysis
  - Annual review of low-risk protocols, such as natural history protocols
- Harmonize NIH and FDA policies on adverse event reporting
- Selective delegation to outside IRBs of recognized excellence
  - Multicenter protocols
  - Drug-company sponsored protocols

Metrics (still under discussion)

- **Short term:**
  - **Length of time from scientific clearance to protocol submission to decision and final approval**
  - **Feed-back from clinical investigators, following up on the IWG committee chaired by Cliff Lane**
- **Long term:**
  - **Numbers of new protocols**
  - **Numbers of M.D.'s as PIs**
  - **Mean age of PIs**
  - **Quality of review process**

Future Discussions

- **Promoting uniform and harmonized scientific review of protocols**