National Cancer Institute Clinical Trial Cooperative Groups

Perspectives from the

National Surgical Adjuvant Breast and Bowel Project

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Presentation Goals

Overview of National Cancer Institute Cooperative Group Trial Program for cancer-related trials.

Individual Group (NSABP) perspective – example of the group organization and how it conducts its research

Current NCI initiatives affecting Cooperative Groups

What is a Cooperative Group?

Cooperative Groups are research networks formed by the National Cancer Institute (NCI) to bring researchers, cancer centers, and doctors together to

- identify important questions in cancer research, and
- design and conduct clinical trials to answer these questions.

Cancer Cooperative Groups are located throughout North America, Europe, Australia, and New Zealand.

Overview of the Clinical Trials Cooperative Group Program

- The Clinical Trials Cooperative Group Program was conceived in 1955 when Congress was approached with a proposal to increase support for studies of chemotherapy for cancer.

- Emphasis is placed on definitive, randomized Phase 3 studies and the developmental efforts preliminary to them.

Overview (continued)

The Cooperative Groups have been instrumental in the following:

- **The development of new standards of cancer patient management.**
- **The development of sophisticated clinical investigation techniques.**

Cooperative Group Program
Major Objectives

- To conduct large multicenter trials for the investigational agents sponsored by the NCI.
- To enable the rapid accrual of patients while reducin the possible bias of studies carried out at a single or a few institutions.

Major Objectives (continued)

Through the Cooperative Group mechanism, the NCI has established an apparatus that:

- **is constantly in place,**
- **has considerable flexibility in resource allocation, and**
- **can accomplish rapid testing of promising new cancer therapies in large patient populations.**

Alternatives to Cooperative Groups

The alternative to the Cooperative Group mechanism involves costly and unwieldy resources for a pharmaceutical company to conduct trials on a similar scale.

In terms of acceptance in the research community, Cooperative Group trials remove the possibility of bias sometimes associated with a trial run by a pharmaceutical company.

Cooperative Group Program Goals

Therapy: The highest priority is to conduct therapeutic research aimed at improving the survival and quality of life for persons with cancer.

Adjunct Research: The goal is to address scientific questions about molecular genetics, epidemiology, pathology and other cancer-related topics using:

- **the database of patient information accumulated in the course of treatment research, and**
- **the large-scale collection of biologic samples with subsequent correlation of specific features with patient outcome.**

The Scope of the Cooperative Group Program

Approximately 20,000 new patients are accrued onto Group treatment studies each year.

12,000 new patients are evaluated annually on ancillary laboratory correlative studies, and many times the combined number are in follow-up.

Thousands of individual investigators participate in Cooperative Group protocols.

Cooperative Group Organization

- The Cooperative Groups are heterogeneous in their research objectives and their structures.

- The common thread, however, is the development and conduct of large-scale trials in a multi-institutional setting.

Cooperative Group Organization (continued)

Groups fit into 4 categories:

- Groups that are specifically disease-oriented (e.g., gynecologic oncology)
- Groups that are designed to deal primarily with high technology, single modality studies (e.g., radiation therapy)
- Groups in which the investigators have a particular expertise (e.g., pediatricians)
- Multimodal National Groups

Current List of NCI-funded Cooperative Groups

1. American College of Surgeons Oncology Group (ACOSOG)
2. Cancer and Acute Leukemia Group B (CALGB)
3. Children's Oncology Group (COG)
4. Eastern Cooperative Oncology Group (ECOG)
5. Gynecologic Oncology Group (GOG)
6. National Surgical Adjuvant Breast and Bowel Project (NSABP)
7. North Central Cancer Treatment Group (NCCTG)
8. Radiation Therapy Oncology Group (RTOG)
9. Southwest Oncology Group (SWOG)

How do Cooperative Groups receive their funding?

Each Cooperative Group is supported to continually generate new trials compatible with its particular areas of interest and expertise, as well as with national priorities for cancer treatment research.

Unlike most other major NIH cooperative clinical trials efforts, the Cooperative Group structure and funding are not usually linked to any specific clinical trial(s).

Funding (continued)

The NCI awards grants to the Cooperative Groups through a peer-reviewed application process, currently renewable on a 3- or 6-year basis. Progress reports are required annually for continuation of the award.

Cooperative Groups also receive funding support from other sources, such as pharmaceutical companies, advocacy groups, technology companies, and individual donors.

The NSABP – One Cooperative Group's Perspective

- Research Mission
- Membership
- Funding
- Organizational Structure
- Protocol Development
- Repositories
- Current Cooperative Group Challenges

What is the NSABP?

The NSABP is a Cooperative Group whose research focuses on the treatment and prevention of breast and colorectal cancer.

The group has a more than 40-year history of designing and conducting clinical trials that have changed the way breast and colorectal cancer is treated and prevented.

Several Achievements of the NSABP

NSABP's breast cancer studies led to the establishment of lumpectomy plus radiation over radical mastectomy as the standard surgical treatment for breast cancer.

The NSABP was the first to demonstrate that adjuvant therapy could alter the natural history of breast cancer, increasing survival rates.

The NSABP was the first group to demonstrate on a large scale the preventive effects of the drug tamoxifen in breast cancer.

The NSABP was one of the first groups to demonstrate that adjuvant therapy was effective in the treatment of colorectal cancer.

Examples of Current NSABP Clinical Trials

NSABP B-31

- Phase 3
- Two-arm adjuvant treatment trial evaluating standard therapy (doxorubicin/cyclophosphamide followed by paclitaxel) with and without investigational drug (trastuzumab).
- Accruing with a goal of entering 2700 patients with breast cancer (47% accrued).
- Over 142 participating main centers, branching out to over 500 local centers.

Examples (continued)

NSABP P-2 (STAR)

- Phase 3
- Double-blind prevention trial comparing 5 years of standard therapy (tamoxifen) and investigational drug (raloxifene).
- Accruing with a goal of 19,000 healthy postmenopausal women at risk for developing breast cancer (81% accrued).
- Over 500 participating centers.

Who are NSABP members?

The NSABP has research sites at nearly 200 major medical centers, university hospitals, large oncology practice groups, and HMOs in the United States, Canada, Puerto Rico, Australia, and New Zealand.

These centers diverge further to involve local networks, thereby increasing our reach to 500+ treatment centers.

More than 6000 physicians, nurses, and other medical professionals conduct NSABP treatment and prevention trials.

Where do we get our members?

NSABP physicians recruit individual members locally within their institutions.

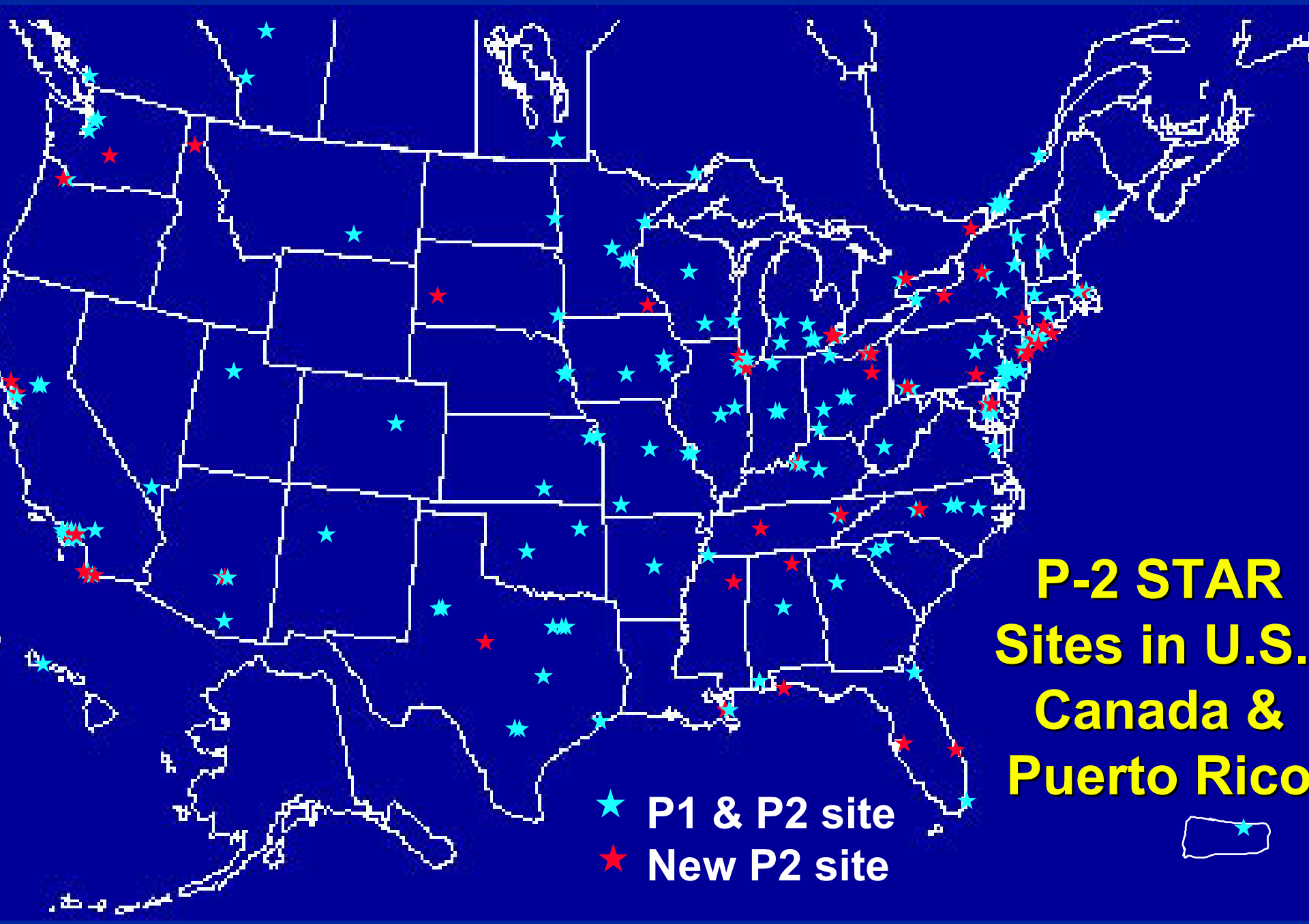
New institutions can be established following an application process when a physician expresses an interest in participating in NSABP trials.

The NSABP headquarters actively promotes its trials at conferences, through professional journals, and by means of its own speaker's bureau to increase awareness of the group's activities.

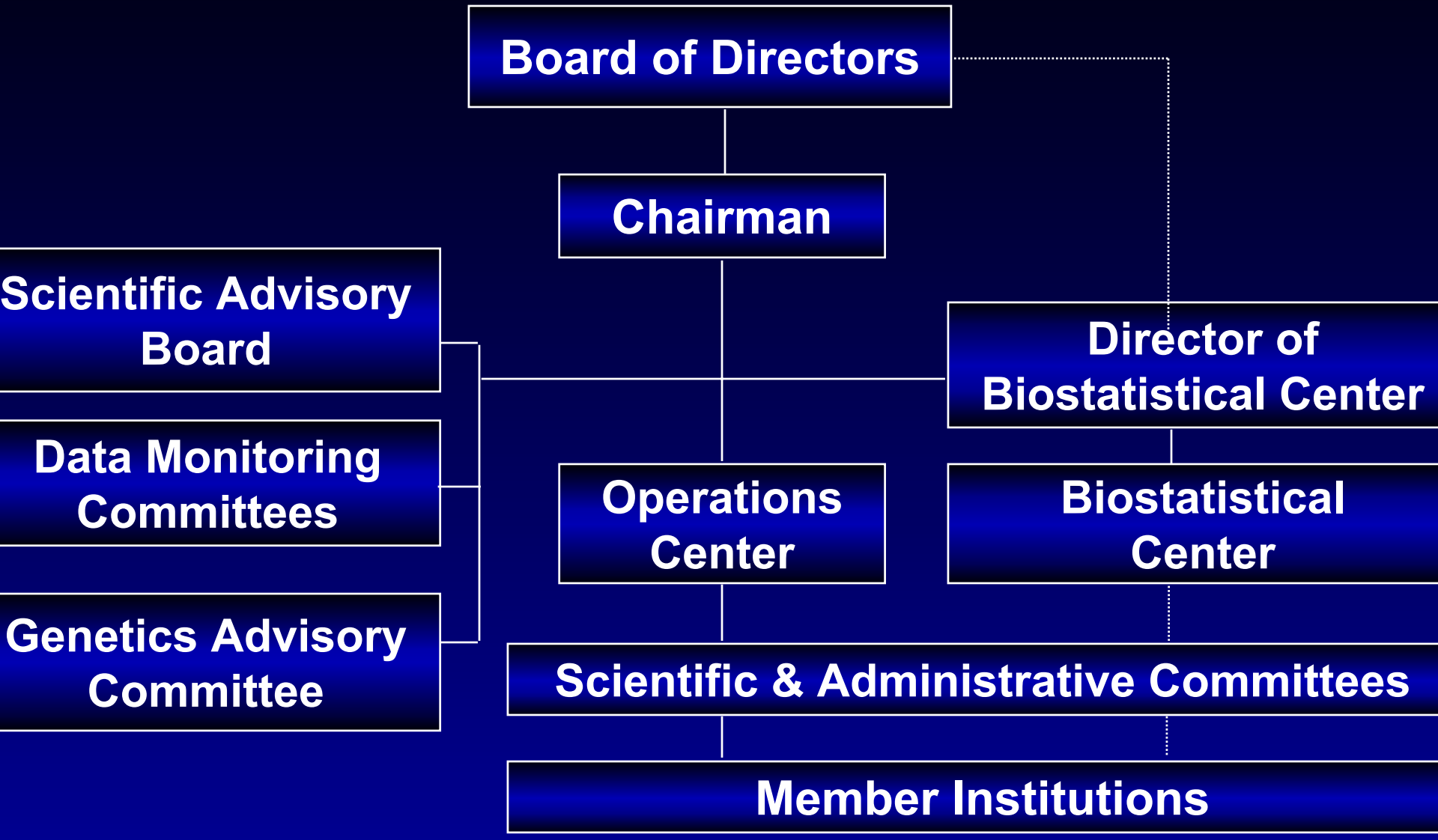
What does NSABP membership require ?

n making application to become an NSABP institution,
he Principal Investigator must, among other things:

- describe the support resources available to assure timely compliance with group administrative and data requirements;
- identify how patients will be recruited and entered on trials (institutions are expected to enter, at a minimum, between 10-28 patients yearly);
- identify pharmacy resources and how handling of investigational drugs will be monitored; and
- document a sufficient accrual record to clinical trials


P-2 STAR
Sites in U.S.
Canada &
Puerto Rico
P1 & P2 site
New P2 site

How is the NSABP organized?



How is a protocol developed?

Initial proposals to address scientific questions generally come from within the group membership, from pharmaceutical companies, or the NCI.

The feasibility of the proposal is discussed at the headquarters level, and then a working group with NSABP members and NSABP Operations and Biostatistical Center staff will develop the scientific questions to be answered and the basic study design.

How is a protocol developed? (continued)

The proposed design is then brought before the respective disease committee (i.e., breast or colorectal committee) to determine interest from NSABP members.

If the committee indicates sufficient interest and support, then a protocol team is established to formulate the clinical trial.

A formal concept is submitted to the NCI for review and approval, and, if approved, protocol development ensues.

Timeline for a Protocol

Protocol development of a large-scale Phase 3 trial takes anywhere from 12-24 months from inception to initiation.

In recent years, trials have become more complex, including components to assess quality of life and correlative studies with blood and tumor specimens.

Timeline (continued)

Studies involving investigational drugs require pharmaceutical company support for supply and distribution of the drug. Cooperative groups encourage the use of the drug distribution system maintained by the NCI.

In addition to the grant funding provided to NSABP members, pharmaceutical funding is often provided to support the direct costs of additional testing or research efforts that are outside standard of care, and the overhead costs for staff support of such efforts.

NSABP Repositories

NSABP Tissue Bank – A collection of over 60,000 annotated breast and colorectal cancer tissue specimens maintained at the NSABP headquarters in Pittsburgh, PA.

NSABP Blood Specimens – A collection of over 30,000 specimens from breast and colon cancer patients that is divided between three facilities in Washington, Texas, and Maryland.

Overseen by Soonmyoung Paik, MD, Director of the NSABP Division of Pathology.

NSABP Repositories (continued)

The samples collected in NSABP trials are of significant value to the research community for the following reasons:

- they are collected from a patient set receiving defined, standardized treatment;
- the stage of the tumor is known and can be linked to a defined set of patient characteristics;
- they are collected and processed in a standardized manner; and
- they can be linked to structured, long-term follow-up information with survival data, in some cases in excess of 20 years.

NSABP Repositories (continued)

Researchers who want to use NSABP samples must submit a proposal for review to the Director of the NSABP Division of Pathology.

They must also provide their own funding for their research.

The NSABP follows a formal review and approval procedure as described on the NSABP Web site at http://www.nsabp.pitt.edu/NSABP_Pathology.htm

Current Issues Affecting Cooperative Groups

The NCI has several major initiatives to accelerate the pace of clinical research and more rapidly answer important research questions. Two of these initiatives involve widening access to trials and streamlining measures:

- CTSU – Cancer Trials Support Unit
- CIRB – Central Institutional Review Board

Goals of the CTSU

- Increase physician and patient access to NCI-sponsored clinical trials
- Streamline and standardize information collection and reporting
- Reduce regulatory/ administrative burden on Cancer Cooperative Groups

Goals of the CTSU (continued)

The system makes NCI-sponsored Phase 3 treatment trials available to qualified oncologists and patients in the United States and Canada.

Doctors who are not affiliated with an NCI-sponsored Cooperative Group must complete an application and credentialing process to become members of the CTSU's national network of investigators.

Benefits of the CTSU are:

- Facilitation of the enrollment of patients on clinical trials and the collection of research data;
- Production of education and training materials (available online);
- Development of a protocol access and referral system to enable patients and network investigators to locate trials of interest and sites where they are being conducted; and
- Provision for centralized auditing, regulatory, and fiscal management support.

Challenges the CTSU presents to Cooperative Groups

The overall effect has been a merger of 10 diverse groups having a similar goal (cancer research), but widely differing procedures and organizational structures.

The Cooperative Groups have had to reorient their independent procedures and database systems to accommodate this more unified approach.

Challenges (continued)

Groups are faced with common problems of limited staff, training requirements, deadlines set by the NCI irrespective of the Group's priorities, and costs to implement new systems.

Cooperative Groups have concerns about data quality, monitoring, and compliance from new investigators unfamiliar with the clinical trial process

The Central Institutional Review Board Initiative

The Central Institutional Review Board (CIRB) Initiative, started in 2000, is a pilot project sponsored by the NCI, in consultation with the DHHS Office of Human Subjects Protections (OHRP).

Created to develop an innovative approach to human subjects protection, the unique feature of the CIRB is its "facilitated review" process that can streamline local IRB review for national multicenter cancer treatment trials.

CIRB Benefits

Local IRBs participating in the pilot will be able to reduce their review workload while still retaining their authority to accept or reject a "facilitated review" on a protocol-by-protocol basis.

Patients and investigators will benefit from the resulting rapid opening and greater availability of new trials.

CIRB Benefits (continued)

The primary goals of the initiative are:

- To improve access to clinical trials for patients and their physicians by enabling local IRBs to rapidly approve NCI sponsored multi-site trials through the use of a facilitated review process.
- To enhance the protection of research participants by providing consistent expert IRB review at the national level before the protocol is distributed to local investigators.
- To collaborate more effectively with local IRBs thus allowing them to focus on the actual conduct of research at their institutions and to educate their staff on the ethical conduct of human research.
- To reduce the administrative burdens on local IRBs and investigators associated with IRB submission.

Challenges the CIRB presents to Cooperative Groups

The overall challenge that the CIRB presents to the Cooperative Groups is procedural, in that the CIRB review process is tied to the NCI review process of protocol projects.

At the current time, the CIRB meets on a monthly schedule and reviews a limited number of protocols. This has resulted in delays in the overall approval process for Cooperative Group trials regarding trial initiations and modifications.

Summary

The overall goal of this presentation has been:

to make others aware of NCI Cooperative Groups and NCI initiatives associated with cancer research, and

to define some of the “alphabet soup” related to NCI Cooperative Groups.

Several Web Sites of Interest:

- NCI http://www.cancer.gov
- NSABP http://www.nsabp.pitt.edu
- CTSU http://www.ctsu.org
- CIRB http://www.ncicirb.org