A National Cancer Clinical Trials System for the 21st Century:

Reinvigorating the NCI Cooperative Group Program

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
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American Cancer Society
C-Change
Centers for Disease Control and Prevention
American Society for Clinical Oncology
Association of American Cancer Institutes

NCI Clinical Trials Cooperative Group Program

- 10 Groups
- 3,100+ institutions
- 14,000+ of investigators
- 25,000+ patients enrolled each year
- Group research has contributed to significant advances in cancer treatment and prevention – detailed in the report

The Cooperative Groups

Cancer and Leukemia Group B (CALGB)
Children's Oncology Group (COG)
Eastern Cooperative Oncology Group (ECOG)
North Central Cancer Treatment Group (NCCTG)
Southwest Oncology Group (SWOG)
American College of Surgeons Oncology Group (ACOSOG)
American College of Radiology Imaging Network (ACRIN)
Gynecologic Oncology Group (GOG)
National Surgical Adjuvant Breast and Bowel Project (NSABP)
Radiation Therapy Oncology Group (RTOG)

Cooperative Group Trials Complement Industry Trials

- Industry trials primarily develop novel therapeutic agents and gain FDA approval for clinical use.
  - R&D efforts entail enormous costs and are critical to progress.
- Cooperative Group trials play a complementary role in advancing science and patient care by addressing questions important to patients but less likely to be top priorities of industry, including:
  - Comparative effectiveness of approved therapies
  - Combining novel agents from different sponsors
  - Therapies for rare diseases
  - Optimal duration, dose of treatment with drugs in clinical use
  - Multimodality therapies
  - Screening and prevention strategies
  - Rehabilitation and quality of life following therapy

Challenges for the Cooperative Group Program

The Cooperative Group Program is at a critical juncture:

- The clinical trials infrastructure has not evolved to adequately incorporate the rapid pace of biomedical discovery.
- Processes are inefficient, with excessive delays.
- Prioritization lacks adequate stringency.
- Government oversight has become extensive and complex.
- Funding is stagnant.
- Industry trials are moving overseas.
- Biomarker-driven selection of appropriate treatment (personalized medicine) will enhance outcomes of trials, but raise costs.

Summary of Committee Recommendations

Goal I. Improve the speed and efficiency of the design, launch, and conduct of clinical trials

Goal II. Incorporate innovative science and trial design into cancer clinical trials

Goal III. Improve the means of prioritization, selection, support, and completion of cancer clinical trials

Goal IV. Incentivize the participation of patients and physicians in clinical trials

Goal I

Improve the speed and efficiency of the design, launch, and conduct of clinical trials

Recommendation 1

NCI should facilitate some consolidation of Cooperative Group front office operations by reviewing and ranking the Groups with defined metrics on a similar timetable and by linking funding to review scores.

- Reduce the number of disease-site Committees among the Cooperative Groups through consolidation, or elimination by peer review.

Recommendation 2

NCI should require and facilitate the consolidation of the Cooperative Groups back office operations and make process improvement in the operational and organizational management of clinical trials a priority.

NCI should consolidate:

- Patient registration
- Audit functions
- Submission of standardized case report forms
- Data collection and management
- Image storage and retrieval
- Training of clinical research associates
- Drug distribution
- Credentialing of sites
- Funding and reimbursement for patient accrual

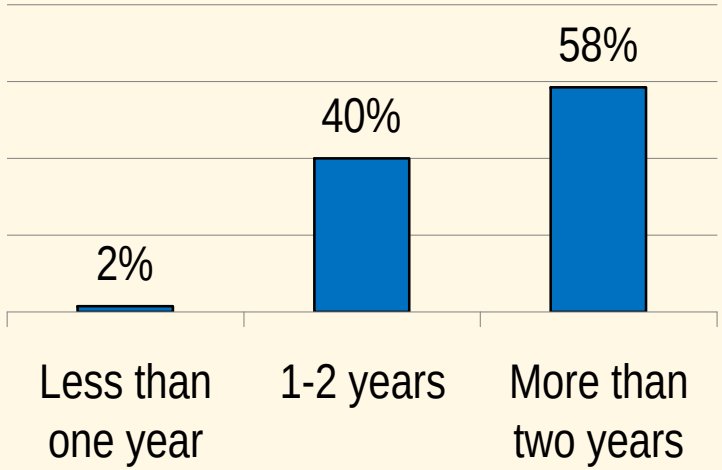
NCI should identify and disseminate best practices

Recommendation 2 (continued)

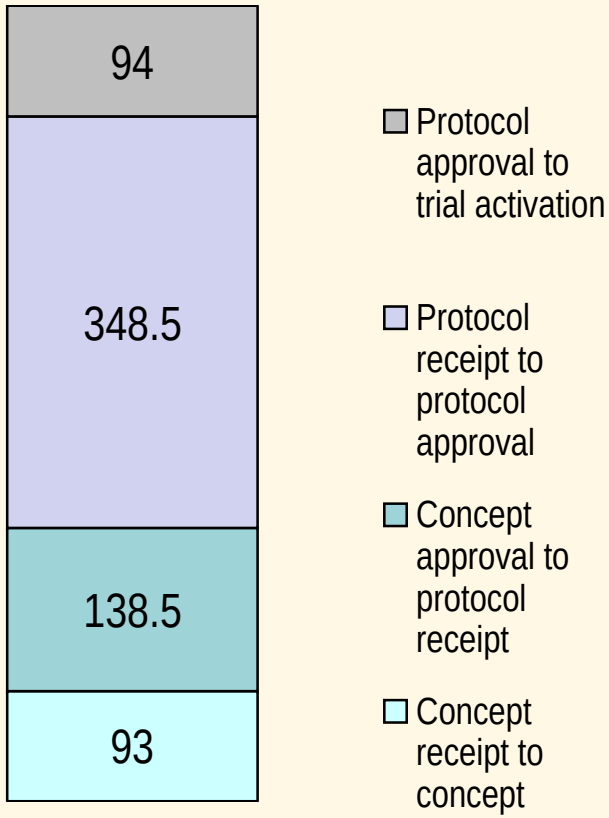
NCI should also coordinate and **streamline protocol development** as recommended in the Operational Efficiency Working Group report.

- A manager assigned to each protocol
- Parallel rather than sequential reviews
- Target metrics: Phase III trials launched in 300 days,
  Phase II trials launched in 250 days
- Conflict resolution by prompt conference, or arbitration
- Rigorous prioritization of proposed clinical trials. The IOM Committee suggests this be done by the newly established Scientific Steering Committees

Time to Trial Activation
Cooperative Group Phase III Trials (2006 – 2008)



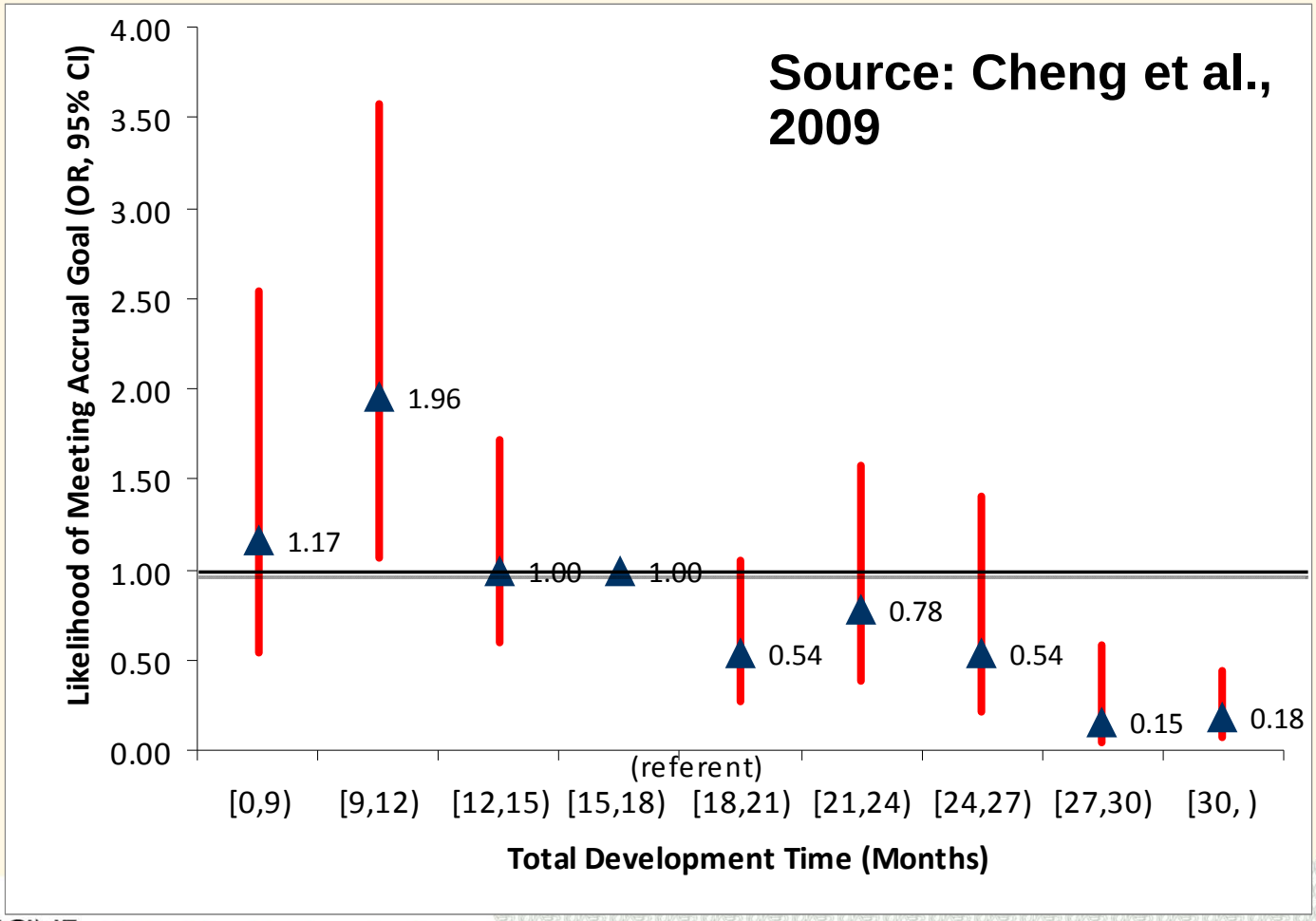
Time to Activation



Median Days per Step

Source: Operational Efficiency Working Group Final Report

More likely to meet accrual goals with development timeline of 9–12 months compared to >27 months



Recommendation 3

HHS should lead a transagency effort to streamline and harmonize government oversight and regulation of cancer clinical trials.

- Reviews should **distinguish** between **major and minor concerns, to reduce recycling and reediting of proposed trials**.
- Federal oversight should be more **flexible for minor amendments**.
- NCI should **coordinate with FDA** for trials involving an IND or IDE.
- FDA should establish **a coordinated Cancer Program** across its centers that regulate oncology products.
- FDA should update regulatory guidelines for **data requirements**.
- OHRP should develop guidance to establish **central IRB authority and accountability**.

Recommendation 4

NCI should take steps to facilitate more collaboration among the various stakeholders in cancer clinical trials.

- Develop standard **licensing** language and **contract templates** in biospecimen-based studies and trials.
- Facilitate more **public-private partnerships** and **precompetitive consortia**.
- Facilitate the development of **hybrid public/private funding** models.
- Implement a **grand challenge competition** to reward significant innovation leading to increased efficiency in clinical trials processes.

Goal II

Incorporate innovative science and trial design into cancer clinical trials

Recommendation 5

NCI should mandate the submission of annotated biospecimens to high-quality, standardized central biorepositories when samples are collected from patients in the course of Cooperative Group trials for their use.

- All data should be considered **precompetitive**, unencumbered by intellectual property restrictions, and be made **widely available**.
- Standardized forms should be used for accompanying clinical data.
- NCI should establish a **national inventory** of samples in central repositories.
- NCI should have a defined **process for access** by researchers that includes a single scientific **peer review linked to funding**.

Recommendation 6

Cooperative Groups should lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies).

Recommendation 7

NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee the development of national unified standards as needed for imaging and biomarker tests.

- Standards are required to ensure quality and comparability.

Goal III

Improve prioritization, selection, support, and completion of cancer clinical trials

Recommendation 8

NCI should reevaluate its role in the clinical trials system.

- NCI should file **more IND applications** for agents to be tested in high-priority trials and provide a leadership role to ensure the success of those studies.
- When NCI does not hold the IND application, the primary focus should be on **facilitating and supporting** high-priority trials, with less emphasis on oversight.
- The newly created **trans-Group Scientific Steering Committees** should provide **peer review** of proposed clinical trials and **impose prioritization**.
- Scientific Steering Committees administered by NCI should deliberate **independently** of NCI staff.

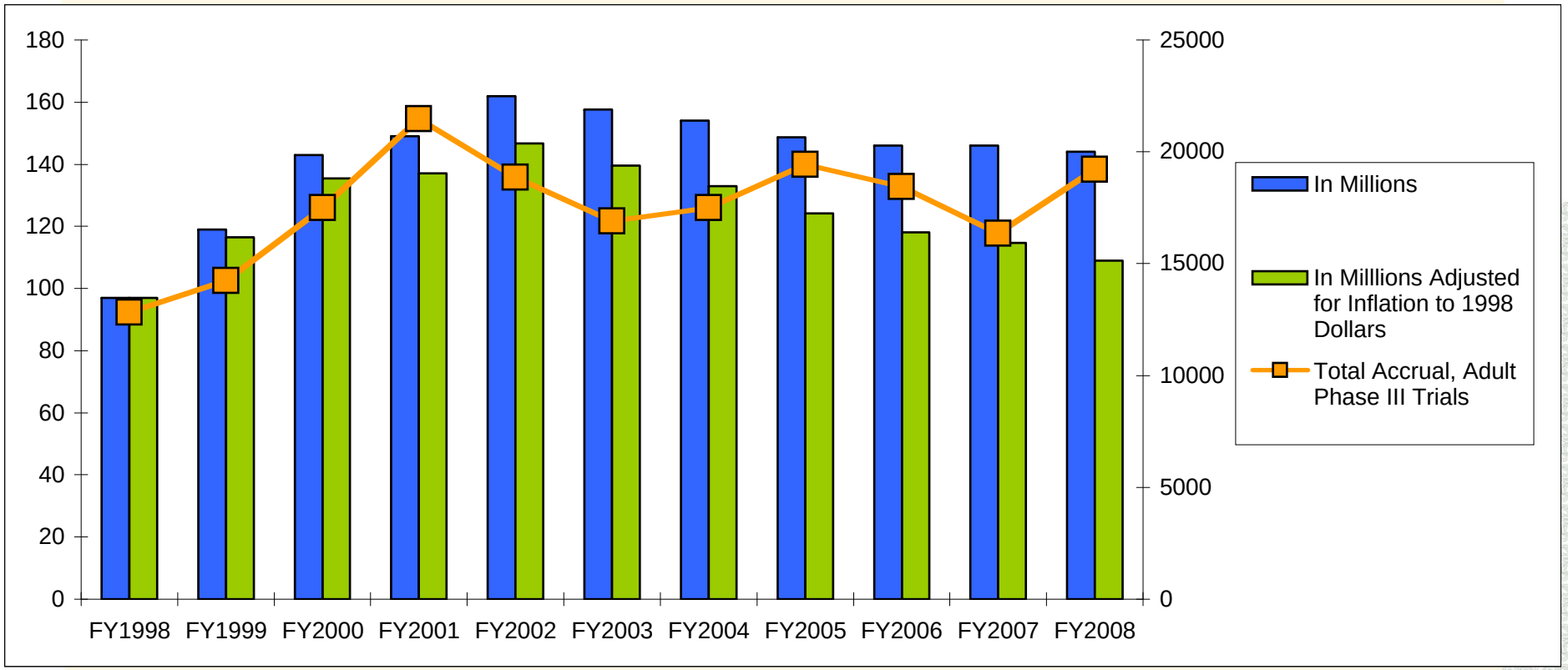
Recommendation 9

NCI, Cooperative Groups, and physicians should take steps to increase the speed, volume, and diversity of patient accrual and to ensure high-quality performance at all sites participating in Cooperative Group trials.

For example, they should:

- Develop **electronic tools** to cue physicians via EMR systems about trials for which a particular patient is eligible.
- Encourage **eligibility criteria** that allow broader patient participation.
- Encourage **enrollment** in high-priority trials, regardless of **origin**.
- **Eliminate** investigators/sites with **low accruals, or inadequate** data management skills or quality.
- Encourage greater participation of **patient advocates** in trial concept development and accrual planning.

Funding for the Cooperative Group Program, FY 1998 – FY 2008 and Total Accrual



Source: NCI, 2009

Recommendation 10

NCI should allocate a larger portion of its research portfolio to the Clinical Trial Cooperative Group Program to ensure that the Program has sufficient resources to achieve its unique mission.

- NCI should increase the **per case reimbursement rate** to adequately fund highly ranked trials.
- **External advisory boards** (e.g. NCAB and BSA) should have a greater role in advising NCI on how it allocates its funds to support a national clinical trials program.
- To ensure sufficient funding for high-priority trials, the **total number of** NCI-funded **trials** undertaken by the Cooperative Groups should be **reduced if adequate funding is not made available** (not the preferred solution).

Goal IV

Incentivize the participation of patients and physicians in clinical trials

Recommendation 11

All stakeholders should work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition.

For example:

- NCI should **recognize and reward** Cooperative Group efforts in Cancer Center Support Grant site visits.
- NCI should provide **funding to sites and trial principal investigators** to cover the time to develop and oversee trials.
- Academic medical centers should develop **policies and metrics** that recognize and reward **clinical and team research** in promotion and tenure decisions.
- NCI should work with a nonprofit foundation to develop a **certification program and registry for clinical investigators**.

Recommendation 12

Health care payment policies should value the care provided to patients in clinical trials and adequately compensate that care.

- For clinical trials approved through NCI-monitored prioritization, there should be consistent payment policies requiring healthcare payors to **cover all patient care costs, except for study-related costs paid for by the manufacturer.** In return, they should not be expected to pay for experimental therapies outside of a clinical trial, unless published evidence justifies off-label use.
- Healthcare payors and providers should work together to **inform patients** about the availability, coverage, and value of clinical trials.
- The AMA should establish **new CPT codes** for offering, enrolling, managing, and following a patient in a clinical trial.
- The U.S. Congress should **amend ERISA** to prohibit health plans from denying (or limiting, or imposing additional conditions on) coverage for routine care in a clinical trial.

Some Key Messages

1. Clinical trials make tremendous contributions to improving cancer care. It is imperative that the processes for designing, opening and completing clinical trials become more efficient and streamlined, with more rigorous prioritization.
2. All stakeholders share the goal of improving patient care. They include clinical investigators, pharma/biotech, government funding and regulatory agencies, patients and their advocates, and health care payors, and each looks at the shared goal through different lenses. They all need to participate and collaborate in implementing these recommendations.

Some Key Messages

3. Clinical trials should place increasing emphasis on innovative design and the use of biomarkers (lab tests and imaging) to target therapy for individual patients (personalized treatment).

4. The value of designing and carrying out clinical trials must be recognized by adequate reimbursement of costs. And the non-experimental costs of care for patients on clinical trials should be paid for by insurance.

To read the report online:

www.nap.edu