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A National Cancer Clinical Trials Network: Recommendations from the Institute of Medicine

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Abstract

Oncology has become one of the most active areas of drug discovery, with more than 800 cancer therapeutics in development. This presents an unprecedented opportunity to improve the outcome for patients with cancer, but also requires an effective and efficient clinical trials network to generate the evidence necessary for regulatory approval and optimal integration of new treatments into clinical care. The Clinical Trials Cooperative Group Program supported by the National Cancer Institute has been instrumental in establishing standards of care in oncology over the last 50 years, but it currently faces numerous challenges that threaten its ability to undertake the large-scale, multi-institutional trials that advance patient care. The Institute of Medicine recently appointed a consensus study committee to assess the organization and operation of the Cooperative Group Program and recommend ways to improve the quality of cancer clinical trials conducted by the Groups and others. The committee developed a set of recommendations, summarized here, that aim to improve the speed and efficiency of trials; incorporate innovative science and trial design; improve prioritization, selection, and support of trials; and increase participation by patients and physicians.

Keywords

cancer clinical trials; Cooperative Group Program; drug development; patient accrual; oncology

Introduction

The opportunity for developing targeted cancer therapies has never been greater than it is today. In recent years, there has been an explosion of data from biomedical research and increased understanding of the molecular underpinnings of cancer, allowing for rational selection of potential drug targets. Oncology has now become one of the most active areas of drug development, with more new cancer drugs entering the market than for any other disease category. But with many new therapies already in the market, and more than 800 cancer therapeutics in development, there is a growing need for a stronger cancer clinical

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trials network to undertake the large-scale, multi-institutional trials that generate the evidence necessary for appropriate clinical use. Industry sponsors play a key role in conducting the trials for Food and Drug Administration (FDA) registration of many new therapies, but publicly sponsored trials also play an essential role, for example by undertaking trials of novel indications, comparing the effectiveness of available therapies in different patient populations, combining novel therapies, and by investigating therapies for less common forms of cancer.

The Clinical Trials Cooperative Group Program, supported by the National Cancer Institute (NCI), has been conducting such trials for more than 50 years. The largest trials network of its kind, the Program involves more than 3,100 institutions and 14,000 investigators who enroll more than 25,000 patients in clinical trials each year. Trials conducted by the Groups have been instrumental in establishing many of the current standards of care for patients with cancer. Just to list a few examples¹: pediatric cancer trials largely carried out by Cooperative Groups over the past four decades have changed childhood cancer cure rates from less than 10 percent to nearly 80%. For adult leukemia, Cooperative Group studies defined the standard care of acute myelocytic leukemia, and demonstrated the efficacy of fludarabine for chronic lymphocytic leukemia, 5-acetytidine for myelodysplastic syndrome, and all-trans retinoic acid for acute promyelocytic leukemia. For breast cancer, landmark trials showed the success of breast conserving treatment with lumpectomy plus radiation instead of radical mastectomy, demonstrated the efficacy of multi-drug chemotherapy and of trastuzumab as adjuvant therapies, and showed that tamoxifen reduced breast cancer incidence by 50% for women at high risk. For stage II colon cancer, adjuvant chemotherapy was shown to improve survival, and the response of advanced colon cancer to chemotherapy was enhanced by addition of bevacizumab. Radiation therapy combined with chemotherapy following surgery improved survival for patients with locally advanced cervical cancer as well as for those with head and neck cancer.

But despite its unique mission and history of accomplishments, the Cooperative Group Program is at a critical juncture, with numerous challenges threatening its ability to conduct innovative trials that benefit patient care. The processes for reviewing trial concepts and protocols prior to launch has become extremely complex and burdensome, with multiple, iterative review steps to select priority trials and ensure that they meet all local, state, and federal regulations (that may conflict with one another). An average of 35% of clinical research costs is now spent on compliance with such regulations (1). The delays caused by repetitive reviews and revisions also have opportunity costs. The science advances while a trial concept languishes in review, and the longer it takes to launch a trial, the less likely it is that the trial will reach the minimum accrual need to achieve meaningful results. About 40% of trials supported by NCI do not reach their accrual goals and are never completed or published (2,3). These uncompleted trials represent a tremendous waste of time, effort, and resources, and are unfair to patients who have participated.

The complexity and cost of trials has also been increasing with the new emphasis on targeted therapies that require biomarker-based stratification of patient populations. But funding for the Program (about 3% of the NCI budget, Figure 1) has been flat for the last decade, and has declined 20% since 2002 when adjusted for inflation. In spite of this declining funding, the number of patients enrolled in Cooperative Group trials has been steady over the last 5 five years (Figure 2). The Program has always relied on a spirit of volunteerism among participating clinicians and institutions, but recent surveys indicate that we are approaching a tipping point at which participation is no longer seen as feasible (4).

¹Many more examples can be found in the IOM report.

All of these factors also contribute to the increasing trend of conducting clinical trials outside of the United States. According to a report by the inspector general of the Department of Health and Human Services (HHS), 80 percent of the drugs approved for sale in 2008 had trials foreign countries, and 78 percent of all subjects who participated in clinical trials were enrolled at foreign sites (5). Cost savings and recruitment efficiencies are cited as the primary drivers of that trend, but assessing therapies within the medical milieu of the U.S. health care system is important to maintain patient access to promising therapies as they develop and to ensure that the findings are relevant to diverse U.S. patient populations.

Recommendations from the Institute of Medicine

Recognizing the importance of the Cooperative Group Program and the challenges it faces, the NCI director, John Niederhuber, asked the Institute of Medicine (IOM) to undertake a study of the program and to generate consensus recommendations on how to improve and strengthen it. The resulting report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the Cooperative Group Program*, put forth 12 recommendations to achieve 4 major goals, as shown in Box 1 (6). Although the committee's charge was focused on cancer, many of the recommendations could have broader implications for trials beyond cancer as well.

Faster, better, more efficient trials

The first 2 recommendations aim to improve the speed and efficiency of Cooperative Group trials, in part through consolidation of some operations and infrastructures. For example, each Cooperative Group devotes significant resources to activities that are defined in the operations management literature as “back office operations” (7). Consolidations of such operations have been quite successful in other industries and organizations, and there is little technical rationale for why these administrative and data management activities must be unique to each group. Consolidation would streamline operations, reduce redundancy, conserve resources, and offer greater consistency across trials.

Each Cooperative Group hosts a number of disease-site committees that focus on cancers originating in various anatomic sites (e.g., breast, brain). Some consolidation of the disease-site committees (“front offices operations”) of the Groups would reduce redundancy and conserve resources while maintaining strong competition for the best trial concepts. This could be achieved through voluntary actions by the Groups or elimination of less successful disease-site committees through the peer review process.

Another key issue addressed in the report is the need for more rigorous prioritization of proposed clinical trials by central Scientific Steering Committees (already in existence), populated by experts in treatment of cancer at the various disease-sites. These committees are charged with identifying trials that are most innovative and most likely to improve patient care. The IOM committee stressed the need to strengthen and streamline the peer review process for trial concepts, with emphasis on scientific strength and opportunity, innovation, feasibility, and the importance to improving patient outcomes.

Combined with increased support for the program and changes made in response to recommendations from the NCI-appointed Operational Efficiency Working Group (8), trials conducted by a consolidated and streamlined Cooperative Group Program should also move more rapidly and efficiently from concept to launch to completion and publication. Trial design, from concept to opening for accrual of patients, must take less than a year, since those requiring a longer time to open are more likely to fail to achieve adequate patient enrollment (2).

But actions by NCI and the Cooperative Group Program will not be sufficient to achieve the goal of faster trials. Other federal agencies that oversee clinical trials also need to make changes to reduce the iterative steps in the current system. The IOM committee recommended that the HHS lead a transagency effort to streamline and harmonize government oversight and regulation of cancer clinical trials. For example, discrepancies between the Common Rule and the Privacy Rule, which are overseen by different offices within HHS, can hinder the approval process for research involving human subjects (9). For large scale, multi-institutional Phase III trials, review by many local institutional review Boards (IRBs) results in further delays and can lead to protocol variations across participating sites, so guidance from the Office for Human Research Protections is needed to encourage and facilitate wider use of the NCI central IRB. Also, all review bodies should distinguish between major review concerns (regarding patient safety and critical scientific flaws, which must be addressed) and minor concerns (which should be considered, but are not obligatory). FDA in particular should update its regulatory guidelines for the minimum data required to establish safety and efficacy of experimental therapies and eliminate requirements for nonessential data, particularly for supplemental applications. For agents already on the market, substantial amounts of safety data already exist. Defining a core set of data elements, along with guidance on how those elements could be modified under various circumstances, would speed the clinical trial process and lead to greater uniformity in data requirements.

Innovative Trials in the Era of Personalized Therapy

One major goal of the IOM committee was to incorporate innovative science and trial designs into cancer clinical trials. Oncology is on the leading edge of the much hoped for transition to personalized medicine. Numerous therapies that target specific molecular changes in tumors are already in clinical use, and many more are in development. But this targeted approach to treatment poses a challenge, as the methodologies of clinical trials must adapt to the new paradigm.

The discovery and analysis of putative biomarkers that can be used to make personalized treatment decisions depends heavily on the collection of and access to high quality, annotated biospecimens. The Cooperative Groups have a history of developing and maintaining biorepositories, but current NCI funding does not adequately support these expensive banking activities, or the retrospective studies that utilize these valuable resources. Moreover, policies and procedures for accessing samples are variable and often burdensome. The IOM committee recommended that NCI implement new funding mechanisms and policies to support the management of central biorepositories, with mandatory inclusion in a national inventory, and the use of specimens in correlative studies. A defined process for research access to samples, with a single scientific peer review linked to funding, would speed the pace of scientific discoveries and clinical advances. In addition, the biomarker data generated from these studies should be considered precompetitive and unencumbered by intellectual property restrictions.

New approaches to trial design are also needed. The ongoing surge in biological knowledge demands increased efforts to develop novel trial methodologies that can take advantage of this knowledge more fully, to improve the efficiency of trials while maintaining the reliability of the results. Innovative trial designs could speed advances in clinical care in numerous ways, and the Cooperative Groups are uniquely positioned to develop and test the feasibility and utility of novel designs. For example, prospective designs that effectively incorporate and test biomarkers are needed, as are better phase II designs to more accurately guide decisions about whether to move into large and costly Phase III trials, which often fail to demonstrate statistically significant benefits of novel therapies. Furthermore, testing all relevant combinations in traditional two-arm trials will be very time-consuming and

prohibitively expensive. Many investigators have proposed novel statistical designs that would enable testing a number of experimental agents in a single trial and would allow more efficient identification of effective and non-effective drugs. For example, multi-arm trials or multi-stage adaptive designs that assess response endpoints during trial accrual in real time and use this information to alter random assignment of experimental drugs might address clinical questions more efficiently, with fewer patients required, and enhanced confidence in the results (6).

The increasing use of biomarkers in clinical trials also necessitates a more consistent approach to the development of standards for biomarker tests, both biomedical imaging and in vitro diagnostics. Critical decisions about patient treatment and conclusions about patient response hinge on the results of imaging and other biomarker tests, and the accuracy and reliability of those tests are affected by many factors. Standards are needed to ensure appropriate and consistent use of new scientific methods and technologies as they develop and mature. For example, the lack of standards for image acquisition and quantification compromises the validity and interpretation of results. The lack of harmonization of methods among different vendors of imaging equipment further compromises the quality and consistency of results. In an effort to improve efficiency, numerous organizations have developed guidelines and proposed standards for biomarker development and use (10).

The IOM committee recommended that NCI work with other relevant agencies, vendors, and investigators to establish a consistent, dynamic process for the development of standards as needed for oncology research. This process should utilize input from experts in both subject matter and standards design, and should incorporate successful approaches used by other standards setting bodies (e.g., the American Society for Testing and Materials, the National Standards Foundation, the National Institute for Standards and Technology, and the International Organization for Standardization.)

Changes by NCI and the Cooperative Groups alone will not suffice to ensure the implementation and success of innovative clinical trials. Effective collaboration among diverse stakeholders is needed, but numerous challenges must be overcome to achieve such cooperation. For example, negotiations to reach contract and licensing agreements to transfer or share materials, data, and intellectual property are complex and can cause lengthy and costly delays in the launch of clinical trials. Standard IP licensing language and contract templates could reduce the delays due to these negotiations and facilitate important new research (11,12).

Effective collaboration among stakeholders will be especially important for combination therapies, which will be crucial for the ultimate success of personalized cancer therapy. Combinations that target multiple key cellular pathways should benefit patients by increasing the efficacy of cancer treatments and reducing the likelihood that resistance will develop, but there has been a reluctance to combine novel agents in the early stages of drug development because of the high risk of failure and the need to demonstrate the safety and efficacy of each agent to the FDA. Preclinical studies indicate that some targeted therapies that work effectively in concert with other agents may not evince a response as a single agent, so combining agents early in development may be essential. This approach is especially problematic if the novel agents in a combination therapy have different sponsors, as this leads to unique challenges in data-sharing, intellectual property, logistics, and marketing. The committee recommended that NCI facilitate a process by which all the key stakeholders (NCI, the National Institutes of Health, FDA, industry, investigators, and patients) can work together to define an effective mechanism for the development of targeted cancer therapies, with particular emphasis on combinations of products.

There are also untapped opportunities for greater collaborations via public-private partnerships, precompetitive consortia, and hybrid funding mechanisms (12–14). Interactions between the cooperative Groups and industry have been limited by a variety of factors, including industry concern about the inefficiencies in the program, the Groups' concern about maintaining independence in study design and execution, and concerns about potential conflicts of interest. However, inadequate government funding of the Cooperative Groups combined with a growing interest by industry to develop new therapeutics and diagnostics for cancer has generated new appeal for developing mutually beneficial ways to work together. For example, some Cooperative Groups have developed a hybrid funding model in which NCI provides funds for fixed infrastructure costs, such as the costs for design, production, conduct, and analysis of clinical trials, while industry funds variable costs, such as per case costs at trials sites, the cost of nonstandard patient care, and the cost of ancillary studies. Similar models for hybrid support of clinical trials are also in use in Canada and the United Kingdom. The NCI should do more to encourage and facilitate the use of appropriate hybrid funding models, in which NCI and industry support clearly defined components of trials that are of mutual interest.

Facilitating Greater Patient Enrollment

Because a critical mass of patients and physicians willing to participate in clinical trials is crucial to the translation of biomedical advances into tangible benefits for patients with cancer, the committee's recommendations sought to facilitate greater patient and physician involvement in clinical trials. Given the central role of Cooperative Group trials in establishing the standards for cancer care, the committee stressed that patients and clinicians who are motivated to participate in publicly sponsored clinical trials should be supported and encouraged to do so.

Ideally, treatment in a clinical trial should be the preferred option for patients who are not cured by standard therapy and for their physicians. Clinical trials provide a standardized protocol and defined treatment plan for these patients, whereas treatment received through usual practice may be highly variable (15). However, participation in cancer clinical trials is not the norm today, for either patients or providers. Only about 3 percent of adults with cancer participate in clinical trials, and many groups are underrepresented in trials, including members of racial and ethnic minorities, the elderly, low-income individuals, and people who reside in rural areas (16). Furthermore, the trend toward targeted therapy and personalized medicine necessitates larger numbers of patients willing to participate in clinical trials, since these trials are increasingly reliant on rare subsets of populations whose cancers bear the relevant biomarker. Without adequate rates of participation by patients and physicians, it is unlikely that important research questions about targeted cancer therapies that have the potential to improve patient outcomes will be answered efficiently and effectively.

Information on clinical trial availability—Surveys indicate that the most important factor affecting accrual is whether a care provider offers participation in a trial to his or her patients. A majority of cancer patients are unaware that participation in a clinical trial is an option, but many would be willing to consider participation if offered (17–19), and physicians remain the primary conduit to patient entry on clinical trials (18). However, information on clinical trial availability often is not easily accessible, and many physicians lack awareness of clinical trials that may be appropriate for their patients. No centralized system currently exists to disseminate clinical trial information to patients and providers, and there are reports that information on the available clinical trial search sites are often inaccurate, outdated, incomplete, or not regionalized (20). Better, user-friendly electronic tools that include information on high-priority trials, that are up-to-date, and that are easily,

widely accessible by both patients and physicians could increase the level of awareness of trials and make it easier for physicians and patients to enroll in the most appropriate studies. Specifically, the committee recommended the development of electronic tools that can cue physicians practicing oncology via electronic medical records systems about trials for which a particular patient is eligible.

Centralized credentialing and auditing—Significant resources are dedicated to credentialing and auditing sites participating in Cooperative Group clinical trials. Each Cooperative Group has its own rules and procedures for credentialing, so for clinical investigators and sites participating in clinical trials from multiple Cooperative Groups, this poses a significant burden to the participating site, the Cooperative Groups, and NCI. Therefore, the committee recommended that NCI establish a centralized credentialing system for clinical investigators and sites that participate in Cooperative Group trials. Having a single process for credentialing sites and investigators could ease administrative burdens and make it easier for physicians to enroll patients in clinical trials. In addition, the committee recommended that Cooperative Groups eliminate investigators and sites with low rates of accrual or a record of inadequate data management skills or quality. These two changes together would improve the efficiency of accrual while maintaining high standards for the participating sites. Centralized credentialing would also facilitate enrollment of patients in high-priority trials regardless of where the trial originates, because more clinical investigators and sites would be credentialed to participate in any Cooperative Group trial.

Support providers—The current system does not foster participation of clinical investigators in publicly sponsored trials. Major barriers include a lack of full reimbursement for the costs of participating in clinical trials and cumbersome regulatory requirements. Participation in clinical trials requires substantial resources and support staff, and clinical investigators who enroll patients in Cooperative Group trials must devote increased time and effort to the endeavor, which is not reflected in current reimbursement policies. The complexity of the protocol, recruitment and selection of study participants, high-intensity visit schedules, protocols that deviate from the standard of care, the complexity and acuity of the patient population, and burden of meeting extensive regulatory requirements all add to the costs of treating patients within a clinical trial setting (21).

The committee emphasized the importance of establishing a mechanism to reimburse physicians for their time, commensurate with the level of work involved with participation in a trial. The report urged the American Medical Association to establish new Current Procedural Terminology codes for offering, enrolling, managing, and following a patient on a clinical trial, and called for enhanced reimbursement of the new codes by the Centers for Medicare & Medicaid Services (CMS), private insurers, and other third-party payors to cover the costs of these activities.

In addition to adequate reimbursement, all stakeholders—including academic medical centers, community practices, professional societies, and NCI—should work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition for scientific accomplishments by promotion and tenure committees. Cooperative Group trials—large-scale, multi-institutional endeavors—require a team approach to research. However, career advancement in the biomedical research field has traditionally focused on individual accomplishment and the current system does not adequately recognize, reward, or support collaborative work. Compounding the problem, clinical investigation is often accorded less value than basic research in consideration of tenure.

If the goal is to have talented individuals embark on a career that includes active design of and participation in clinical trials, this must change. Clinical research is a complex undertaking that requires training, mentoring, and paid time set aside for research to master and apply the skills needed to undertake innovative trials.

The committee recommended several specific actions to better support clinical investigators. First, NCI should work with a nonprofit foundation to develop a certification program and registry that recognizes all research staff (including physicians, nurses, clinical research associates, pharmacists, etc.) for their valuable contributions to the improvement of patient care and treatment via clinical trials. The certification program could also be a component of site credentialing for participation in Cooperative Group trials. Patients may seek out certified physicians, encouraging physicians to become certified and to be more involved in clinical trials.

In addition, NCI should provide funding to principal investigators for clinical trials, to cover the time that they need to develop and oversee approved trials. Similarly, NCI should recognize participation in Cooperative Group trials in the review criteria for a Cancer Center Support Grant (CCSG), as that would acknowledge the importance of patient accrual in these trials and encourage broader participation at those centers. The assessment of a cancer center's funding base, which helps determine the amount of the CCSG award, favors investigator-initiated trials when reimbursement for patient enrollment in Cooperative Group trials is not counted.

Finally, academic medical centers should develop policies and evaluation metrics that recognize and reward clinical and team research in promotion and tenure decisions. The inadequate value given to clinical, team-based research in academic tenure and promotion decisions prevents more robust participation in Cooperative Group trials.

With adequate support and access to information on clinical trial availability, the committee called on physicians to make participation in clinical trials a key component of clinical practice. Physicians should strive to achieve the exemplary attributes of the American Society of Clinical Oncology for academic and community clinical trial sites, which includes high accrual rates of 10 percent or more (22).²

Patient advocates—Although patient advocates have been working with Cooperative Groups since the 1990s, the committee recommended that NCI, Cooperative Groups, and physicians encourage greater participation by patient advocates in the design of clinical trials and in patient recruitment activities. Incorporating patient advocates in the design of clinical trials and in patient recruitment has the potential to hasten accrual because trials that appeal to a broader population may be designed. One potential way to achieve greater participation by patients is through community-based participatory research, in which community-based groups bring community members into the research process as partners to help design studies and disseminate the knowledge gained (23).

Eligibility—Stringent eligibility criteria have excluded many patients from participation in clinical trials, including those with prior cancers and certain prior treatments. There are indications that eligibility criteria are unnecessarily stringent. For example, from 1999 to 2006, the mean number of eligibility criteria increased from 31 to 49 (24), and many cancer patients are ineligible for clinical trials. Since overly stringent eligibility criteria unnecessarily prevent high rates of participation in clinical trials, the committee recommended the development of patient eligibility criteria that allow the broadest possible

²ASCO defines “accrual rate” as the number of patients enrolled in trials annually/number of new patients seen annually.

participation possible. For targeted new drugs, use of tests that measure the targeted biomarker will be important, but beyond that, the adoption of less restrictive eligibility criteria for most studies would permit more rapid accrual and also allow broader generalizations to be made, could better mimic the conditions encountered in medical practice, and could reduce the complexity and costs of clinical trials without compromising patient safety or requiring major increases in sample size (25).

Coverage—Variable and uncertain insurance coverage for participation in clinical trials prevents robust patient and provider participation. The lack of national consensus regarding the financial responsibility for clinical trial-related health care costs has resulted in uneven reimbursement policies, which may hamper patient recruitment and negatively affect evidence-based medicine (26). Lack of adequate coverage is a disincentive to participation by both the patient, who wants to avoid burdensome expenses, and the provider, who needs reimbursement for costs. The committee concluded that it is imperative that coverage policies encourage broader patient enrollment in clinical trials so that care is evidence-based and relevant to the diverse patient population. Therefore, the committee recommended that health care payment policies value the care provided to patients in clinical trials and adequately compensate that care. Health care payors should also work with health care providers to educate patients more effectively about the availability, payment coverage, and value of clinical trials.

Although much of the care provided to patients enrolled in clinical trials is considered routine and would be eligible for reimbursement outside of a trial (27), many health insurance policies generally exclude coverage for participation in clinical trials. The committee recommended that CMS, federal and state health benefits plans, and private health insurers establish consistent payment policies to cover all patient care costs in clinical trials approved through the NCI prioritization mechanism, except for study-related additional costs, which should be borne by the manufacturer. As a quid pro quo, private insurers should be able to eliminate coverage of experimental therapies delivered outside of the clinical trial, but any such limitation in coverage should not affect off-label use that is backed by evidence from clinical trials published in the scientific literature, as evidence-based off-label use constitutes the standard of care for many cancer therapies and is therefore not experimental.

Twenty-three states currently mandate coverage of routine care costs (28), but state laws do not affect the majority of individuals covered by employer-sponsored health plans. Plans affecting about 131 million individuals are primarily regulated by federal law through the provisions of the Employee Retirement Income Security Act of 1974 (ERISA), necessitating federal action to mandate coverage of routine care costs associated with clinical trial participation. A number of Congressional bills have been introduced with provisions to cover routine care costs, including the 21st Century Cancer Access to Life-Saving Early Detection, Research, and Treatment Act, introduced by Senator Edward Kennedy in March 2009, as well as the Access to Cancer Clinical Trials Act of 2009, which was previously introduced in six other legislative sessions.

Hoping to eliminate financial disincentives preventing patients and their physicians enrolling in clinical trials, the IOM committee called on the U.S. Congress to amend ERISA to prohibit health plans from denying coverage for routine care associated with clinical trial participation, reflecting the language of previously introduced bills.

After the committee had completed its report, President Barack Obama signed the Patient Protection and Affordable Care Act (PPACA) (Public Law 111–148), the Senate version of the health care reform bill, into law on March 23, 2010. Included in the PPACA is a

provision that requires coverage of routine care costs for individuals participating in approved clinical trials, to go into effect in 2014. The provision states that a group health plan or health insurance issuer “may not deny (or limit or impose additional conditions on) the coverage of routine patient costs for items and services furnished in connection with participating in the trial.” Approved clinical trials include phase I-IV studies relating to the prevention, detection, or treatment of cancer or other life-threatening diseases or conditions that are either federally funded, under an investigational new drug (IND) application reviewed by the Food and Drug Administration, or a drug that is exempt from having an IND application.

The legislation is intended to apply to ERISA-governed health plans. However, there is uncertainty regarding the number of plans—and therefore individuals—who may be impacted by the clinical trials coverage provision. Plans that were in existence on March 23, 2010 (so-called grandfathered plans) are exempt from some of the provisions of the health care reform bill, provided that they do not lose their grandfathered status by significantly cutting benefits or increasing out-of-pocket spending for consumers (29). According to HHS estimates, plans of large employers have the highest likelihood of remaining grandfathered in 2013 (with estimates of 66% to 33% retaining grandfathered status), while small employers are less likely to retain grandfathered status (estimates of 51% to 20% remaining grandfathered). If grandfathered plans are exempt from the coverage provision, patients with cancer who remain on grandfathered plans may not be guaranteed that their routine costs of care will be covered if they choose to participate in a clinical trial.

Conclusion

The goal of the IOM recommendations was to preserve the historical strengths of the Cooperative Group Program while improving components that are not working as well as they should. Some functions need to be better integrated and supported, and others must be streamlined to eliminate repetitive steps. The new director of NCI has identified reform of the cancer clinical trials system as a top priority (30). But ensuring an effective National Cancer Clinical Trials system that can translate new discoveries into improved patient care in the 21st Century will require changes on the part of numerous stakeholders, including NCI and other federal agencies, academia, industry, foundations, health care insurers, physicians, and patients. Modifying any particular component of the system will not suffice; all participants must reevaluate their combined roles and their contributions to a successful, streamlined process for conducting Cooperative Group clinical trials. Collectively, implementation of the IOM recommendations will lead to the faster approval and adoption of new therapies, new discoveries upon which to base future studies, and the accelerated translation of new knowledge into improved outcomes for patients with cancer.

BOX 1

Summary of the IOM Committee’s Goals and Recommendations

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

1. Review and consolidate some front office operations¹ of the Cooperative Groups on the basis of peer review
2. Consolidate back office operations² of the Cooperative Groups and improve processes
3. Streamline and harmonize government oversight
4. Improve collaboration among stakeholders

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

5. Support and use biorepositories
6. Develop and evaluate novel trial designs
7. Develop standards for new technologies

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

8. Reevaluate the role of NCI in the clinical trials system
9. Increase the accrual volume, diversity, and speed of clinical trials
10. Increase funding for the Cooperative Group Program

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

11. Support clinical investigators
12. Cover the cost of patient care in clinical trials

¹ Front office operations refer primarily to the Cooperative Group scientific committees and statistical offices, which are responsible for activities such as trial design, prioritization, and data analysis.

² Back office operations refer to administrative structures and activities that include such things as data collection and management, data queries and reviews, patient registration, audit functions, case report form processing, image storage and retrieval, drug distribution, credentialing of sites, funding and reimbursement for patient accrual.

Source: IOM, 2010. Reprinted with permission from *A National cancer Clinical Trials System for the 21st Century*, 2010 by the National Academy of Sciences, Courtesy of National Academies Press, Washington, D.C.

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The responsibility for the content of this article rests with the authors and does not necessarily represent the views of the Institute of Medicine or its committees.

Abbreviations

CCSG	Cancer Center Support Grant
CMS	Centers for Medicare & Medicaid Services
ERISA	Employee Retirement Income Security Act of 1974
FDA	Food and Drug Administration
IND	Investigational New Drug
IOM	Institute of Medicine

IRB	Institutional review board
NCI	National Cancer Institute
PPACA	Patient Protection and Affordable Care Act

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Figure 1.

Allocation of the NCI Budget in Fiscal Year 2008. The actual obligations of NCI funds by mechanism are shown, in millions of dollars. The allocation for the NCI Cooperative Group Program represents approximately 3% of the total NCI budget.

Source: <http://www.cancer.gov/aboutnci/servingpeople/snapshot>

Figure 2. Funding for NCI Cooperative Group Program, fiscal years (FY) 1998 to 2008, and total accrual in adult phase III trials during the same time span. Source: Margaret Mooney (NCI), 2010, and IOM, 2010.