The Future of Cancer Clinical Trials Systems – Ongoing Reinvigoration from the Cooperative Group Program to the National Clinical Trial Network –

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Advances in biomedical research have created opportunities for innovative cancer prevention, detection, and treatment. Insights from the molecular mechanisms of disease enable investigators to identify new therapeutic targets and novel agents. A paradigm shift in oncology is on the way, from toxic chemotherapies to highly targeted therapies.

Translation of biomedical discoveries into significant advances in cancer care relies on effective clinical trials systems. Both industry-sponsored trials as well as publicly funded investigations have played different but complementary role to prove improved survival in leukemia, lymphoma, breast cancer, and prostate cancer. However, next generation of research infrastructures to explore the precision medicine may not be easily established.

Recently, the Institute of Medicine (IOM) issued a report to outline necessary, systematic changes for the Clinical Trials Cooperative Group Program (COGs) to more efficiently design, review, and conduct studies. In response to the IOM report, the National Cancer Institute (NCI) has launched the National Clinical Trials Network (NCTN), to facilitate the rapid initiation and completion of cancer clinical trials.

In this review article, the author would like to provide up-to-date information on the new cancer clinical trials system.

Key words: cancer chemotherapy, precision medicine, clinical trial, Cooperative Group Program, National Clinical Trial Network

History of cancer chemotherapy

One in three women and one in two men will develop cancer during their lifetime, and a quarter of all deaths will be attributed to cancer in the developed countries1).

The history of cancer treatment is shaped with successes and failures2).

From William Halsted’s radical mastectomy to Brian Druker’s imatinib, innovative treatments have never been made easily. Sidney Farber’s passion and Mary Lasker’s philanthropy were indispensable to the first successful cancer chemotherapy for childhood leukemia.

Unfortunately, we have learned that the more is not necessarily be the better. Sometimes, disfiguring surgeries and toxic chemotherapies have proven to be worse than natural courses.

Current principles and standards for cancer clinical research

As described in the Declaration of Helsinki, medical progress is based on research that ultimately must include studies involving human subjects. Therefore, current principles and standards have evolved to ensure science, ethics, and quality of cancer clinical research3).

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1. Scientific aspects of cancer clinical research

Clinical research can be a strong source of evidence when medical science is supported by biostatistics.

Observational studies, retrospective and prospective, can be useful to find relationships and to generate hypothesis.

However, clinical trials remain as the final common pathway to address causality, to minimize biases, and to avoid confounding factors.

Optimal designs, depending on the purpose, are important.

Phase I studies of cytotoxic agents, including pharmacokinetics and pharmacodynamics, are focused on mechanism and safety. Intensive monitoring is needed to find dose limiting toxicities (DLT) and the maximum tolerated dose (MTD). The Common Toxicity Criteria for Adverse Events (CTCAE) are often used. RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer patients improve (“respond”), stay the same (“stable”) or worsen (“progression”) during treatments (www.recist.com).

Phase II trials, or proof of concept studies, are important to examine causal relationships, but do not immediately change clinical practice. They may not necessarily use the ultimate clinical endpoint to prove effectiveness, and sometimes use clinically relevant biomarkers to show sufficient activity.

Phase III trials are designed to explore whether an intervention can be effective in real-world settings. A randomized controlled trial (RCT) can be designed when there is equipoise. Blinding and masking are as important as randomization itself. The Consolidated Standards of Reporting Trials (CONSORT) statement should be appreciated.

2. Ethical considerations and human research protections

Clinical research has sometimes provoked profound ethical problems. Although the goal is to improve medical care, the individual participant may or may not directly get benefit.

Thus, clinical study is distinct from clinical practice.

The International Conference on Harmonization (ICH) has published a harmonized regulatory guideline for product registration trials, the Good Clinical Practice (GCP), reflecting principles from the Declaration of Helsinki.

The process of informed consent is an opportunity for a human research subject to make autonomous decisions.

An institutional review board (IRB) or a hospital ethics committee (HEC) evaluates adherence to established ethical guidelines.

An independent data and safety monitoring committee (DSMC or IDMC) helps to determine if the RCT maintains clinical equipoise, or should be terminated.

All human materials including biospecimens are covered by legal and ethical considerations for the collection, storage, use, sharing, and disposal.

3. Quality assurance and research integrity

Quality control (QC) and quality assurance (QA) are mechanisms to systematically prevent errors in data collection, analysis, and report. Depending on the purpose and the available resource, monitoring and auditing will be scheduled for maximizing transparency and accountability.

Research integrity became of public interest as more and more stories, including high profile scientists, have unfolded. Scientific misconduct is defined as fabrication, falsification, or plagiarism in proposal, performance, or report of a research. Questionable research includes such things as failure to retain data, inadequate records, honorary authorship, and premature release of results to the public.

Financial as well as academic conflict of interest (COI) may adversely affect the objectivity of scientific research.

Personalized cancer medicine and targeted therapies

A revolution is under way in the development of cancer therapy.

The key questions for cancer research are: What makes cancer cells different? Why do tumors grow without stopping?

Although damaged chromosomes in some cancer have been recognized back in the 19th century, it was not until the 1980s that scientists finally understood nature of oncogenes, inherited or mutated. As Harold Varmus described when he received Nobel Prize in 1989, cancer is "a distorted
version of our normal selves”.

Now we are living in an era when scientific advancements in genomics, proteomics, and metabolomics are evolving into the personalized medicine \(^7\)〜\(^11\).

1. The science of developing cancer therapy

Most cancer treatments available today are effective in only a minority of patients, probably because of the variability in the molecular abnormalities driving tumor formation. As a result, many patients may be enduring the side effects of costly treatments without deriving any benefit.

To reduce the burden and cost by delivering toxic and ineffective treatments, better understanding of cell death, invasion, and metastasis are hoped for the personalized cancer medicine.

In fact, early success stories, including imatinib for leukemia\(^1\)\(^1\)\(^2\), rituximab for lymphoma\(^1\)\(^2\), and trastuzumab for breast cancer\(^1\)\(^3\), literally opened the door for the targeted therapy. Moreover, once-controversial gefitinib\(^1\)\(^4\)\(^5\), followed by impressive crizotinib\(^1\)\(^6\)\(^7\), re-defined the disease category of non-small cell lung cancer, and guided us into the world of precision medicines and companion diagnostics\(^1\)\(^8\)\(^9\).

Precision medicine need to be based on the discovery, validation, and qualification of biomarkers that can be tested by in vitro diagnostics or through in vivo biomedical imaging. Future treatment decisions are hoped to get benefit from the use of qualified markers and imaging that can predict outcomes of therapy.

However, most diagnostics that are in use today assess a single target. It is widely believed that as technologies mature, diagnostic platforms will become capable of simultaneously examining a large number of potential markers to improve the predictive powers of these tests.

In addition, the decreasing cost of DNA sequencing, in analogous to the “Moore’s Law” in the information technology, making it more feasible to identify the mechanisms underlying cancer. This advance in technology could dramatically change cancer diagnostics and treatments\(^2\)\(^0\).

For example, a group from Harvard recently published the initial result from their “Cancer-paedia” project to find a previously unknown therapeutic target for a rare malignancy, followed by series of investigator-initiated clinical trials\(^2\)\(^1\).

The technologies can also be used to conduct molecular analyses of tissue embedded in paraffin, enabling the large-scale genomic profiling of messenger RNA, the DNA copy number, and focused analysis of mutations on small tissue samples, if they are appropriately collected and liked with the clinical data.

2. Needs for Personalized and Targeted Cancer Trials

Unfortunately, current systems for cancer clinical research have not adjusted themselves fast enough to handle big data coming out of precision medicines, or molecular-profiling-directed therapies. What are the needs for clinical trials to rapidly translate scientific discoveries into public health benefit?

To incorporate innovative technologies or to combine best knowledge for promising treatments, collaboration among stakeholders, with effective and timely communication are necessary. Procedures should be streamlined for rapid planning, approval, and launch of clinical trials\(^2\)\(^2\)\(^2\)\(^3\).

Publicly supported clinical trials systems are needed to complement commercial trials for market approval of products. For well-designed, high-quality trials, robust and standardized systems with adequate resources are necessary.

An efficient and accessible infrastructure would deliver a complete database of trials. Standardized electronic data capturing system (EDCs) as well as publicly accessible tissue repositories could be used in studies.

A consistent and dynamic process to set standardized procedures should qualify new technologies as reliable and reproducible.

To harmonize and synchronize rules and guidelines, government sectors, including regulatory authority, funding agency, as well as health insurance provider, should provide platforms for all the stakeholders to participate from the early stages.

The new guidance will be based on the understanding of science as new paradigms for diagnostics, therapeutics, as well as clinical trials methodologies.

Clinical trial investigators should be recognized and appropriately be supported professionally and
efficiently. For actively participating institutions, adequate reimbursements of cost are also essential for their sustainability.

Patient must be involved in clinical trials broadly. Success should be measured by evaluating patient access to promising therapies. Cost of non-experimental care should be covered when patients are participating in adequately designed, implemented, and conducted trials.

New systems for cancer clinical trials

1. National Clinical Trials Network
On March 20, 2014, the National Cancer Institute (NCI) of the United States has launched a new system, the National Clinical Trials Network (NCTN)²⁴.

The new system is expected to facilitate rapid initiation and completion of cancer clinical trials based on the improved infrastructure, the standardized process to prioritize new studies, the consolidated research groups for improved efficiency, and the implementation of a unified system to protect human research subject.

For example, there are many new features introduced by the NCTN, including:

1. Common IT data management system (Medidata RAVE) for all trials to help development, conduct, and analysis of studies
2. Central Institutional Review Board (CIRB) to cover studies conducted by the entire system
3. Tumor specimen banks and the informatics redesigned to be efficiently integrated to each other

What is NCTN? Why is it important?

2. Cooperative Group Program
NCI started Clinical Trials Cooperative Group Program back in the 1950s to provide publicly funded infrastructure for cancer clinical trials (Figure-1). NCI has been sponsoring the 10 Groups with 3,000 institutions and 14,000 investigators, to

![Figure-1 Structure of Programs (Before)](image-url)
Pharmaceutical companies have been conducting clinical trials to develop new therapeutic agents, and to get market approval. These activities are essential in the progress of cancer treatment. However, since industry may have less incentive to compare different treatments, combine multiple modalities, and explore rare disease, publicly funded clinical trials are also necessary.

In other words, publicly funded trials and industry-sponsored investigations are complimentary to each other.

The accomplishments of the Cooperative Groups are significant. They have developed curative therapies for pediatric cancers and some early-stage cancers in adults. The effective combined modality treatments as well as adjuvant chemotherapies have not been introduced by pharmaceutical industry alone. Also, the Cooperative Groups validated critical markers of diseases, and trained clinical investigators as well as supportive professionals.

However, after five decades, the Cooperative Group Program has been facing challenges. Declining funding, inefficient processes, complex government oversight, and lack of resource may have contributed to the difficulties in translating new approaches for the personalized cancer therapy.

3. The IOM report

Back in 2010, recognizing the importance of publicly funded clinical trials system, the director of NCI requested that the Institute of Medicine (IOM), a part of the National Academy of Science, to develop a recommendation for the new clinical trials system (Figure-2).

The IOM identified the need for an ideal clinical trials system, and analyzed the strength, weakness, opportunities, and threat to the current clinical trials program.

The IOM suggested four goals in their report, “A National Cancer Clinical Trials System for the 21st Century – Reinvigorating the NCI-Cooperative Groups” (Table-1).

1. Improving the speed and efficiency of the design, launch, and conduct of clinical trials
2. Making optimal use of scientific innovations
3. Improving selection, prioritization, support,
and completion of clinical trials
(4) Fostering expanded participation of both patients and physicians.

3.1. Goal 1. Improve the speed and efficiency
To improve the efficiency and reduce the time for designing and launching innovative clinical trials, the new systems will consolidate and streamline front office operations, back office operations, oversight processes, as well as processes for collaboration.  

(1) Consolidate front office operations
To consolidate Cooperative Group front office operations, they will be reviewed and ranked with defined metrics on a similar timetable to get funded.

The focus will be on the quality and the completion of the trial concepts developed, and the record of new investigators.

Committees from different Groups should be organized with a multidisciplinary focus on disease sites to strengthen their productivity scores.

(2) Consolidate back office operations
Administration and data management operations across all of the Cooperative Groups, the back office, will be re-organized to improve clinical trial processes.

Office and personnel should be optimized for data collection, data management, patient registration, audit functions, image storage, drug distribution, credentialing of sites, and funding for patient accrual.

Protocol development processes and trial logistics will be reviewed and streamlined using quality and efficiency metrics.

A common patient registration system, a common remote data capture system, and standardized case report forms should be rapidly developed, adopted, and supported.

(3) Streamline and harmonize government oversight
The government oversight and regulation of cancer clinical trials should be harmonized by a trans-agency effort to eliminate unnecessary repeat, and to focus more on major review concerns (regarding patient safety and critical scientific flaws), rather than minor concerns.

The regulatory authority should establish a coordinated Cancer Program to regulate oncology products, and update regulatory guidelines to establish the experimental therapies (including combinations of products).

The Central Institutional Review Board must be encouraged for wider use and acceptance.

(4) Improve collaboration among stakeholders
To facilitate collaboration among the stakeholders in cancer clinical trials, standard licensing language and contract templates for material and data transfer, including Clinical Trial Agreement (CTA) as well as Clinical Research and Development Agreement (CRADA) need to be updated.

Public-private partnerships and pre-competitive consortia should be created to develop targeted cancer therapies. Ownership of intellectual properties should be protected in biospecimen-based studies and multiple-modalities-combination trials.

Experts in non-cancer fields (e.g. engineering,
3.2. Goal 2. Incorporate innovative science and trial design into cancer clinical trials

Effective incorporation of scientific advances is essential in the progress of cancer treatment. For example, the development of targeted therapy depends on the use of qualified biomarkers. However, when new technologies are adopted, standards to ensure validity and consistency are often lacking.26.

(1) Support and use biorepositories

To develop qualified biomarkers, new clinical trial systems should use standardized central repositories to collect annotated samples from patients in the course of clinical trials.

All data, including biomarker data from serum, tissue, and imaging should be considered precompetitive, unencumbered by intellectual property restrictions, and made widely available.

(2) Develop and Evaluate Novel Trial Designs

Designs of cancer clinical trials are getting more and more complicated as evaluation of diagnostic–therapeutic combination as well as combination therapies make trials fragmented.

Therefore, development and use of innovative and efficient trial designs are critical to speed the progress.

For example, recent technologies, such as the use of adaptive designs, are expected to require fewer patients, need less time, and observe enhanced confidence.

For personalized therapies, prospective clinical trial to randomize patients on the basis of biomarker should be explored. Predictive hypothesis for a biomarker should be tested in the early phase trials.

(3) Develop Standards for New Technologies

Standards are needed to use new scientific methods and technology appropriately and with consistency.

The need for standards will be especially important for breakthrough technologies such as biomedical imaging and biomarkers.

However, the lack of standards could compromise the validity of the results, and the lack of harmonization might compromises the quality and consistency of results.

Therefore, the input of experts in both medical science and standard design should be balanced to develop, publish, and update standards.

3.3. Goal 3. Improve prioritization, selection, support, and completion of cancer clinical trials

Although there are many achievements in the history of the Cooperative Group Program, the current environment is quite challenging for the 50 years old system.

Currently, only about 60% of launched clinical trials have been completed. In addition, the cost for biomarkers, molecular imaging, and information technology are increasing.

Therefore, to make most of the limited resources, and to advance oncology care, streamlined processes are necessary for the prioritization, selection, and support of trials.26.

(1) Reevaluate the role of NCI in the clinical trials system

In the United States, the funding mechanism for the Cooperative Group Program has changed in 1980 from peer-reviewed grants to cooperative agreements with oversight.

IOM recommended NCI to file more investigational new drug (IND) applications, to focus more on facilitating the launch, execution, and completion of trials, and to emphasize less on oversight.

Independent steering committees should be reevaluated to focus on the prioritization of clinical needs and scientific opportunities proposed by the Cooperative Groups, and facilitation of cooperation among Groups.

(2) Increase the speed, volume, and quality of patient accrual

The majority of patients enrolled in clinical trials are from a small percentage of participating sites.

Providing easy-to-access information and adequate case reimbursement would help to align physician and patient incentives.

Eligibility criteria could be less restrictive for most studies to permit more rapid accrual, and to increase generalizability without compromising patient safety.

To ensuring quality at participating sites, collaboration with existing credentialing systems would increase consistency and eliminate burden of re-credentialing.
Patient advocates could facilitate these changes, and provide valuable input to study prioritization, design, confidentiality issues, informed-consent processes, and other factors.

(3) Adequate funding for the clinical trial Cooperative Group Program

Trials with high priority must be adequately funded to move the field forward. To launch more trials than available funding not only compromise the science but also become disincentive to participation.

Although average per case reimbursement has been set at $2,000 since 1999, the median per patient costs are estimated to be from $3,500 to $6,000.

The duties of key research staff, such as physicians, research nurses and clinical research associates are costly in terms of time and resources. Biomedical imaging and other biomarker tests must also be obtained through other support mechanisms.

The allocation of NCI funds among the competing needs is a major challenge.

Even in the absence of overall funding, launching fewer but higher-priority trials could increase per case reimbursements to trial sites.

Greater input from the broad expertise and experience would be helpful to ensure the most rational distribution of funds across the major NCI programs, as long as they are not involved in the oversight of individual trials.

3.4. Goal 4. Incentivize the participation of physicians and patients in cancer clinical trials

Current indications suggest that both for physicians and for participation, participation in clinical trials is the exception rather than the routine.

For clinical investigators, regulatory burdens, academic procedures, and concerns about reimbursement make it unrealistic to expect most clinicians to participate in trials.

Patients may decline participation if coverage of costs in clinical trials is not consistent among health care providers.

(1) Support clinical investigators

The current system does not adequately recognize, reward, or support collaborative work, since career advancement in oncology has traditionally focused on individual accomplishment. In addition, clinical investigation is often considered to be less valuable than either basic research or patient care.

IOM encouraged all stakeholders, including academic medical centers, community practices, professional societies, and NCI, to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition.

Funding should be provided to site and trial principal investigators to cover the time that they need to develop and oversee approved trials.

Academic medical centers should develop evaluation metrics to recognize and reward clinical trials and registries for improving patient care and treatment.

(2) Cover the cost of patient care in clinical trials

Traditionally, healthcare insurers have not covered experimental therapies. However, much of the basic care provided to cancer patients is similar whether the patient is participating in trial or not.

No insurers would like to pay for ineffective, harmful, and/or illegal procedures, but they want treatments for cancer care to be evidence based. Therefore, it is important for coverage policies to encourage rather than deter patient enrollment in trials.

Ideally, insurers should be able to eliminate coverage of experimental therapies delivered outside of the clinical trial setting. Of course, any such limitation in coverage should not affect off-label indications backed by evidence from clinical trials published in the scientific literature, as off-label use constitutes the standard of care for many cancer therapies and is therefore not experimental.

Education for patients must be more effective about the availability, payment coverage, and value of clinical trials.

4. Potential Risks of Replacing the Program

There are some concerns for replacing the program with proven track record of success.

The Cooperative Groups are unique ecosystems, each with its own culture and style. Despite their differences, the groups share many characteristics that provide the essential infrastructure for their many successes in the face of chronic underfunding.

Since NCTN reduced the number of groups and
trials to increase per patient resources, the knowledge might fade over time with less mentoring, limited career opportunities, and more pressures for performance metrics.

However, patients with cancer will benefit greatly from robust cancer clinical trials systems if they deliver practice-changing results.

Future of cancer drug discovery

Previously, any scientific advance could lead to a dedicated effort throughout the pharmaceutical industry to discover molecules for a new, better treatment.

Pharmaceutical companies were eager to be first to learn of the basic science discoveries made in the government-sponsored academic laboratories. This is no longer true.

With a clear eye on stock price, shareholder value and perceptions, pharmaceutical industry has to focused more on finances.

If the trials take too long, the risks are too great. In addition, if the precision medicine leads to the fragmentation of diagnosis, the cost will increase.

What this means is that the investors of Wall Street and the financial managers of the industry could be deciding which diseases to treat.

Since the pharmaceutical industry is still the only source of new drugs, there needs to be incentives. Tax incentives, exclusive marketing licenses, and, of course, publicly supported clinical trial systems.

Value-based competition in health care

Throughout the economy, competition among rivals is the most powerful force to drive improvements in the quality and cost of products and services.

However, competition is failing in health care, at least so far.

Physicians are taught that competition promotes self-interested behavior, and that it compromises patient care.

The force of competition is actually strong in health care, but less-than-ideal incentives are driving predictable, but undesirable, result of rising costs.

Therefore, the nature of health care delivery needed to be strategically transformed from the cost–based pricing to the value–based incentives.

This new paradigm in cancer clinical trials systems, first ignited in the United States, would eventually transform Japan as well as the rest of the world into the value-based competition.

When all the stakeholders get together to share respect for science, gratefulness for care, and hope for research, major improvements in cancer care could occur from within the system, without the need for government–led reform.

References


