

C-Change Clinical Trials Team RECOMMENDATIONS TO ENHANCE THE PUBLIC CLINICAL TRIAL SYSTEM

PURPOSE

In April 2002, C-Change (formerly the National Dialogue on Cancer, NDC) convened a conference of a Clinical Trials Team to look at the existing national clinical trials system and explore ways to optimize patient accrual. Participants in this national conference included key clinical trials opinion leaders from industry, community-based networks, academic centers, cooperative groups, the National Cancer Institute (NCI) and the patient advocacy community. It was quickly recognized that significant frustration existed on the part of academic oncology leadership, clinician scientists and within the private sector regarding the NCI process that is currently required for concept review, protocol development and eventual trial implementation. To address these concerns, a smaller subcommittee* was formed, chaired by Ronald B. Herberman, and including John Niederhuber, Robert Comis, Collier Smyth, Charles Balch, and Emilie Tierney. The subcommittee was charged with developing recommendations to enhance the public clinical trial system and to reduce or eliminate unnecessary or duplicative processes. To more fully understand the current processes and their rationale, the subcommittee held a follow-up meeting with the Cancer Therapy Evaluation Program (CTEP) staff and Connie Curran in Washington, D.C. on February 6, 2004. What follows is a summation of these meetings and a series of recommendations by the Clinical Trials Team.

OVERVIEW

The Clinical Trials Team recognizes that the pharmaceutical industry is the major force for drug development in the world. It is estimated that over 450 compounds are in development at the present time. Many of these compounds represent unique molecular approaches to cancer therapy based upon the recent explosion in the understanding of cancer biology.

Under the regulations governing the use of investigational new drugs, the development process is considered a continuum from early preclinical and clinical studies through submission of a marketing application and additional studies in other indications undertaken after approval of an NDA. The clinical component of the process mandates all new drugs proceed through the defined phases of development, including Phase I trials designed to establish a dose and schedule with acceptable toxicity; Phase II disease-oriented efficacy testing; and ultimately a Phase III study which compares the new approach to the accepted standard of care. Although some agents receive "accelerated approval" from the FDA based on encouraging Phase II results, accelerated approval is actually a "review status" which represents an FDA promise to approve a drug IF the company meets the defined requirements set by the FDA as a result of "pre-study" meetings between FDA and the company. Ultimately, full approval is generally based upon the results of Phase III studies

In the course of a drug's development, the initial (commercial) Investigational New Drug (IND) application is generally filed by the individual company after completion of preclinical testing. Only after the application is accepted is the sponsor allowed to proceed with the clinical phases of the development process through the regulatory system. Companies perform the initial trials intended to support product registration under their own IND, but as a drug proceeds through development, the NCI, individual

investigators, or the NCI-sponsored cooperative groups may receive corporate permission to cross-file and hold their own INDs to support expanded programs of evaluation and investigator-initiated trials.

The role of the NCI in clinical trials research, including evaluation of many of the drugs developed by industry, is vital, and members of the Clinical Trials Team of C-Change acknowledge the support of the Institute in keeping clinical research and clinical trials as a high funding priority. Despite this tremendous support, the current process involved in bringing forward a new trial concept to an activated clinical trial protocol is admittedly slow and frustrating to both the PI-investigator and the NCI. A careful and thoughtful consideration of the current review process indicates a need for change on all fronts.

A major role of the NCI relates to the holding of the INDs for most investigational drugs studied by the NCI-sponsored cooperative groups. Although the cooperative group system is rarely engaged in the performance of Phase III registration trials intended to support a New Drug Application (NDA) or Biologic License Application (BLA), the cooperative group system is often engaged in important trials upon which supplemental NDA (sNDA) and BLA filings are based. These studies are generated through the interaction of key opinion leaders based in cancer centers throughout the country, working within the cooperative groups or cancer center structure, often together with researchers based in industry or the government. All trials that are performed under an NCI-sponsored IND require approval. In addition, all trials that involve more than 100 patients require full CTEP review.

In those cooperative group studies where the NCI holds the IND, through its relationship with industry, the NCI is considered the “sponsor;” alternatively, when the IND is held by a cooperative group, or other organization, they are considered the “sponsor” in the eyes of the FDA. The sponsor is defined as an individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial and, by rule, assumes the responsibility for ensuring compliance with the regulations governing the conduct of research involving human subjects.

In the instances in which a cooperative group, or other organization, holds the IND, and assumes the role of sponsor and investigator, there is a dual review process for the study, which includes full review and approval by both Federal agencies—the NCI and the FDA. This dual review process can significantly affect the time to final protocol approval and study activation. Also, the uncertainty with regard to study design and execution issues as they relate to supplemental NDA filing may be a disincentive for industry to seek partners within the cooperative group and cancer center structure. It should be noted that there are extensive data indicating that processes and procedures within the cooperative groups contribute substantially to delay in initiating these phase III trials quite independent of delays associated with federal review, which do not comply with industry expectations for speed or efficiency. This may be further disincentive for industry to work with the groups.

Further improvements in the existing review and initiation processes to increase the enthusiastic participation of academic investigators and private industry in this essential phase of drug development are urgently needed. The Clinical Trials Team concluded from these meetings and numerous discussions that the current process at CTEP and in Cooperative Groups operations offices is at risk of being a major disincentive to investigators. As a result, this is likely to interfere with the ability to accelerate development of innovative clinical studies and to enhance patient participation in such studies in order to achieve the goal of providing more effective treatment for patients with cancer.

In reviewing these issues with colleagues at NCI-CTEP, the following categories of clinical trials currently require full CTEP review from concept to implementation.

All clinical trials involving investigational agent(s) for which CTEP holds the IND.

Clinical trials generated by investigators participating in CTEP-funded inter-institutional consortia or international consortia

Cooperative group trials that have not had specific NIH peer review, and trials involving more than 100 patients.

Cooperative group phase III trials.

It became clear from the discussion that CTEP does not review most cooperative group phase I or II trials and similarly does not become involved in the review of the large majority of clinical trials taking place at NCI-designated cancer centers. Unless CTEP is asked to hold the IND, it is not involved in the review of investigator-initiated trials or trials that are part of the SPORE program.

Nevertheless, there are many clinical trials that involve CTEP review and approval before implementation and thus there is a definite need to improve the process by which the involved parties (faculty PI's, cooperative group investigators, industry PI's, FDA and NCI) work together in a timely fashion to accomplish the process of review. The Clinical Trials Team subcommittee acknowledged that there are important strengths inherent in the current CTEP review process. These include:

- Independent committee with a national needs perspective;
- Uniquely extensive experience with a wide range of clinical trials;
- Members are free of conflict of interest;
- Members have access to unpublished clinical data;
- Members have access to plans for other clinical trials under development;
- Members often have access to privileged industry data;
- Review process is built around weekly meetings and set time lines for decisions.

RECOMMENDATIONS

Therefore, it seems prudent to enhance the current CTEP review process rather than make any major change in the requirements. To accomplish this objective, the Clinical Trials Team proposes the following recommendations.

1. Investigators responsible for submission of a trial concept to NCI/CTEP should involve CTEP staff early in the process of concept design, prior to concept submission. This pre-submission conferencing with an assigned CTEP member(s) should result in a concept application that is optimally prepared for rapid review.
2. When the concept is reviewed at CTEP but requires a revision or response by the investigator, there will be an agreed-to rapid response time for the investigator.
3. The current double and sequential review of protocols by CTEP, NCI and by the FDA should be eliminated as follows:

For all Phase III trials funded by NCI, whether CTEP or another entity holds the IND, for which special FDA review is required because of NDA or sNDA filing or other important licensing issues, CTEP should coordinate a rapid meeting of all involved parties (NCI, Cooperative Group, industry, and FDA) within 3 weeks of approval of a fully developed concept by CTEP. This meeting should resolve any issues regarding the concept and agree on timelines and identify responsible principles from each organization.

It seems essential that a fully developed concept (including rationale, patient population, supporting data, statistical design and analysis plan) be provided in order for these entities to engage in a meaningful and binding discussion of the proposal.

It is encouraging that the FDA has indicated a willingness to participate in such meetings and respond to the proposal. Typically, they participate in such detailed discussions in formal end of Phase II meetings scheduled more than 6 weeks in advance and with the provision of detailed documents. However, the FDA is exhibiting significant flexibility in being willing to meet within 2-3 weeks notice, with the sponsor and involved entities supplying only the concept document for the trial and any specific questions the parties want FDA to address/discuss at the meeting.

For their part, FDA has not only agreed to discuss and attempt to resolve any major design issues at this meeting, but also agreed to grant a Special Protocol Assessment (SPA) when the final protocol is submitted. This essentially creates a binding agreement with regard to the trial.

It should be noted that there has been some encouraging experience gained recently with this recommended process, which has led to a truncated time to agreement and protocol development by all involved parties. This has been very appealing to industry collaborators in the two instances where these procedures have been utilized in 2004.

Implicit in this recommendation is that the agreement reached would represent an agreed upon understanding that the concept, design and execution framework for the study was sufficient to proceed to full protocol development and approval, and that the study may be employed for registration submission.

4. The Clinical Trials team proposes that a greater emphasis be placed on providing clinical investigators with a professional staff trained to assist in the writing of concepts and protocols. Such assistance on a full-time basis would have a major impact on meeting timelines and decreasing turn around times during the review process. Too often the bottleneck is at the level of the over committed and understaffed investigator.
5. The Clinical Trials Team recommends that FDA review and approval processes be streamlined to facilitate new drug development to the maximal extent possible, while continuing its necessary regulatory role to assure the safety and efficacy of drugs marketed for the treatment of cancer. Ongoing dialogue involving clinical trial investigators, FDA, NCI and the pharmaceutical industry should continue to focus on ways to expedite new cancer drug development and the mechanisms by which multiple agents can be simultaneously and appropriately tested on patients' tumors, using acceptable endpoints while ensuring public safety.
6. Finally, The clinical Trials Team urges the Office for Human Research Protections (OHRP) and other HHS agencies to take concrete steps to reduce duplication and delay in connection with review of trials by local IRBs. At present, clinical trials that have already received scientific review by central review authorities in the cooperative groups and otherwise are frequently subject to additional review by local IRBs, which may involve up to 60 to 90 days of unnecessary delay. Clearer direction from OHRP and HHS specifying which review functions may be forgone by local IRBs could streamline the process significantly and reduce current burdens on clinical research.

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