REGULATORY FOCUS

FDA's Oncology Clinical Trial Makeover

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Recent communication by FDA affirming its support for modernized oncology clinical trial conduct, manifested in four guidance documents addressing adolescents, conduct of First-in-Human (FIH) expansion cohorts, the use of placebo/maintenance of the study blind and master protocols. This article provides an overview of new FDA guidances related to oncology drug development and a review of pilot programs aiding faster access to new, innovative treatments without increasing risk to patients.

Introduction

To reshape and modernize cancer research, in 2018, the US Food and Drug Administration (FDA) released four guidance documents related to oncology drug development. The announcement of the Complex Innovative Designs Pilot Meeting Program further supports the goal of advancing medical product development and encouraging pioneering innovations in clinical trial design. Additionally, two pilot programs, sponsored by the Oncology Center of Excellence, directly support efficient development of cancer therapies.

Cancer: Statistics and Milestones

In the US, cancer is the second most common cause of death behind cardiovascular disease. Breast, lung and bronchus, prostate and colorectal

cancers account for almost 50 percent of all new cancer cases in the US.[1] It is projected there will be an estimated 1.7 million new cancer cases and more than 600,000 cancer deaths in the US alone in 2018.[2,3] Globally, these numbers climb to 18 million and nine million, respectively.[4]

The oldest evidence of cancer can be found in fossilized bones, human mummies in Egypt and written about in ancient manuscripts. The oldest descriptions of cancer date back to about 3000 BC, found in a papyrus part of an Egyptian textbook on trauma surgery describing the cauterization of eight cases of tumors or ulcers of the breast.[5] The word "cancer" was first introduced by Hippocrates (Greek physician) as the terms "carcinos" and "carcinoma," which, in Greek, refers to "crab."

From the Halsted mastectomy, used in 1882 as radical treatment for breast cancer, to hormonal therapies introduced in the 1940s, to CAR-T cell-based products as the first gene therapies in 2017[,6,7] much progress has been made in cancer research and treatment over the decades. However, many cancers still have no curative treatment.

Reshaping Oncology Clinical Trials

Over the last century, it has been established that drug development is a long and costly process. There is an extremely limited success rate for drug candidates from their discovered in the research lab to be finally approved for human use. Scientific advances for a range of targeted therapies beyond chemotherapy require new trial design approaches. Accordingly, FDA recently released four guidance documents aimed at increasing efficiency in the drug development process to potentially supporting faster access for patients while maintaining subject safety during clinical trials. These guidances outline:

1. Considerations for the inclusion of adolescent patients in adult oncology clinical trials.[8]
2. Expansion cohorts: use in first-in-human clinical trials to expedite development of oncology drugs and biologics.[9]
3. Hematologic malignancy and oncology disease: considerations for use of placebos and blinding in randomized controlled clinical trials for drug product development.[10]
4. Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics.[11]

In a blog released following the guidance on including adolescents[12] and the first-in-human expansion cohorts,[13] FDA Commissioner Scott Gottlieb indicated that further guidance on topics including master clinical trial protocols, efficient trial design strategy, adaptive trial designs and use of innovative endpoints such as minimal residual disease for hematologic cancers will be addressed.[14] FDA subsequently released various guidance documents.

This article provides a general overview on the above four guidance documents, followed by a discussion of the FDA's pilot initiatives.

Inclusion of Adolescents in Adult Trials

This guidance document[15] provides advice on including adolescents—defined by the guidance as ages 12 to 17—in adult oncology clinical trials to address two key issues for this demographic group:

1. declining enrollment with increasing age in pediatric clinical trials due to lack of interest and off-label use
2. delayed access—often several years—due to exclusion from adult trials

The age-related declining enrollment of adolescent patients in clinical trials was noted in a 2017 publication by Chuk, et al.[16] The authors noted that only 10-15% of adolescents ages 15-19 with cancer participate in clinical trials. Generally, due to the types of cancer appearing in the pediatric population compared to that in the adult population, makes it clear that a separation between pediatric and adult trials is sensible. However, the adolescent population has a higher incidence of cancers commonly observed in the adult population. Examples include soft tissue and bone sarcomas, central nervous system tumors, leukemias and lymphomas. Since the cutoff for adult clinical trials is 18 years of age, adolescent patients cannot participate in clinical trials relevant to their cancer immediately, and sometimes not until several years after New Drug Application (NDA) approval of the drug when pediatric trials are initiated.

To solve this conundrum, FDA proposes adolescents should be eligible to enroll in adult oncology clinical trials when the histology and biologic and/or drug molecular target is relevant to adult and adolescent patients.[17] The guidance highlights the requirement to conform with 21 CFR 50.50 and 21 CFR 50.52 (both Code of Federal Regulations) describing safeguards for children in clinical trials. Criteria for including adolescents in adult oncology trials include:

- First-in-human trials: generally, after adult pharmacokinetics and toxicity have been established.
- First-in-human trials: restricted to relapsed or refractory adolescents with no curative action.
- Later stage allows for simultaneous enrollment to adults.
- Dosing is determined by whether adults are dosed according to body size (weight or surface area).
    - If according to body size, the same rule should be followed for adolescents as for adults.
    - If fixed dose, a distinction of dose level should be drawn between subjects to avoid overexposure—generally the cutoff is 40kg (body weight of a 12-year-old).
- Long-term follow-up: abnormalities in growth or fertility issues may not be able to be observed in a standard trial so sponsors should allow for the appropriate long-term follow-up as appropriate for the age group.

The current draft guidance should be applied when including adolescents in adult trials and supports earlier access of this patient population to effective therapies. Open questions requiring further clarification include the timing of FDA-sponsor communication and whether this inclusion would satisfy requirements under the Pediatric Research Equity Act and alignment with international regulatory requirements.

Similarly, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research both find that the inclusion of pediatric patients in adult oncology clinical trials is feasible with an appropriate clinical trial design. Gore, et al (2017)[18] discuss recommendations for two trial scenarios:

1. Early-stage trial (dose, safety, pharmacokinetics) in a variety of tumors

   Recommendation: use staged enrollment by first including 12-17-year-old patients, followed by younger age groups (6-11 at first) once initial safety and toxicity data is available.

2. Later phase trial (efficacy) in specific disease spanning adult and pediatric populations

   Recommendation: age range should reflect disease age range. However, trials for diseases spanning pediatric and adult age ranges should include patients 12-17 years.

Generally, adult protocols allowing for inclusion of pediatric patients should include pediatric oncologists as investigators, be reviewed by a central institutional review board and/or include pediatric expertise, include pediatric centers experienced in drug development and may require special pediatric-friendly formulations to further mitigate risks. Rapid advances in drug development research, science and technology support the automatic inclusion of pediatrics to allow faster access to new innovative treatments for this population as long as appropriate safeguards are in place.

First-in-Human Expansion Cohorts

The First-in-Human (FIH) trials with multiple expansion cohorts aims at expediting medical product development by seamlessly moving from the Phase I safety and potentially effective dose determination, to additional cohorts with objectives typically investigated in Phase II.[19] Due to their continuous nature, these trials are commonly called “seamless trials.” FDA defines an FIH multiple expansion cohort as an “FIH trial with a single protocol with an initial dose-escalating phase that also contains three or more additional patient cohorts with cohort-specific objectives.” The additional objectives can include the assessment of anti-tumor activity, alternative doses or schedules, establishment of dose or schedule in combination with another therapy, or evaluation of predictive biomarkers.

This expedited trial design poses several challenges due to the rapid enrollment of larger numbers of subjects and treatment with medical products with unknown efficacy and minimal characterization of the toxicity profile. They are:

- infrastructure necessary to efficiently disseminate evolving information to all stakeholders in the trial
- exposure of subjects to potentially suboptimal or toxic doses
- enrolling more subjects than necessary
- missing interpretations due to ongoing data collection and analysis

Using this trial design requires justification that potential benefits outweigh risks and should be limited to serious diseases without an available curative treatment. FDA expects the investigational product would qualify for breakthrough therapy designation. The sponsor should provide a scientific rationale for the inclusion of each cohort and the guidance document provides considerations specific to various cohort objectives.

FDA advises safety monitoring should follow a systematic approach to ensuring rapid communication of safety events and that an independent safety assessment committee or an independent data monitoring committee should be established due to the complexity of this type of trial. The sponsor also should provide cumulative safety information to the institutional review board/independent ethics committee to support fulfilling the board's/committee's continued review requirements. The guidance document provides further recommendations regarding informed consent and protocol content.

FDA strongly encourages sponsors to discuss their plans in a pre-IND meeting. If protocol amendments substantively affect safety or scope, the sponsor should notify the FDA project manager 48 hours before submitting the protocol amendment. Although protocol amendments generally can proceed, FDA advises submission at least 30 days before activation unless the amendments are necessary to ensure patient safety. In the latter case, changes should be implemented immediately. Also, a teleconference can be requested by either sponsor or FDA within 30 days of submission to discuss the amendments.

The aim is to avoid costly delays between the end of one trial and the start of the next trial. It is hoped that the data collected in the FIH cohort extension trial will provide the basis for regulatory decision-making for marketing approval.

Placebo Control and Blinding in Clinical Trials

A placebo-controlled, double-blind randomized trial design is a common standard for reducing the likelihood of bias, differential patient dropout and bias in assessment of outcomes. However, this design may pose practical and ethical issues in trials for the development of treatments for malignant hematologic and oncologic disease.[20]

Due to the characteristics and/or toxicity profile of some active treatments, it might be possible for patients and/or investigators to infer placebo use. Placebo use also poses an ethical issue if a treatment already is available for the oncologic disease. Therefore, FDA recommends using placebo only in specific situations, such as when surveillance is standard of care and with certain trial design features such as in an add-on to standard of care. The use of an active control is preferable if approved treatment is available. The sponsor should provide a detailed rationale and justification if placebo use is considered, particularly if invasive procedures are required.

Additional challenges are posed by maintaining the blind after the occurrence of severe adverse events due to the possibility of incorrect management of adverse events. FDA recommends unblinding patients when an adverse event suspected to be related to the experimental treatment occurs and management would involve products with substantial toxicity and/or invasive procedures.

Also, maintaining the blind after disease progresses or recurs could delay the subject's subsequent treatment with available therapies and/or the entry into other clinical trials. FDA recommends unblinding the subject at the time of either documented disease progression or recurrence, unless there is no available treatment.

The informed consent must notify the subject of potential risks and disadvantages if the protocol calls for maintaining the blind in either of these situations. A detailed justification also will be necessary.

Master Protocols

Similar to the FIH cohort expansion trial design, master protocols combine multiple studies and/or sub-studies under one coordinated overall structure to increase efficiency in drug development, but at a later stage[21] FDA recommends the recommended Phase II dose be established before conduct of the master protocol. The guidance defines a master protocol as "a protocol designed with multiple sub-studies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes with the overall trial structure."[22]

Examples of master protocols include:

- Basket trial design: a single drug or drug combination is tested in a single-arm design to evaluate activity in different populations. A response seen in a sub-study may lead to expansion, which may generate data supporting marketing approval.
- Umbrella trial design: multiple investigations treatments (single drug or drug combinations) are administered to a single disease population. These trials can be a randomized controlled trial where the control arm should be standard of care for the target population.

- Complex trial design: combining features of basket and umbrella trials, the complex design might evaluate multiple investigational drugs (drug combinations) in multiple tumors or populations.

For master protocols including a standard of care control arm, sponsors should suspend patient enrollment if standard of care changes during conduct of a randomized controlled study until appropriate updates have been made to the protocol, informed consent and statistical analysis plan.

For master protocols evaluating concomitant administration of two or more investigational drugs, a dose-finding stage may be included if the recommended Phase II dose has not been established. However, safety data for a minimum of six treated patients at the proposed dose must be available before trial start. The sponsor also should provide a strong rationale for the use of the combination rather than the single product, and the study plan should provide the approach for determining each individual investigational product's contribution to any effect.

The document also provides guidance on biomarker development but recommends sponsors should discuss the development plans as early as possible with FDA. Due to the complexity of master protocols, it is pertinent to have a sound safety monitoring plan with appropriate reporting structures in place to ensure the safety of study participants. An independent safety assessment committee or independent data monitoring committee should be instituted with the constitution and responsibilities described in the IND. The complexity of master protocols warrants a more frequent safety assessment. Continued monitoring by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) should be ensured and all necessary updates to the ICF are submitted to the IRB/IEC and potentially to the IND if needed.

The master protocol should contain information and the charter for a blinded independent radiologic review committee (tumor-based assessment) and an independent data monitoring committee (monitor efficacy results) if the results from one or more sub-studies are intended to form the basis for marketing approval.

To provide the appropriate regulatory support, FDA strongly recommends the master protocol should be the only trial conducted under an IND and sponsors should discuss the master protocol at a pre-IND meeting. The meeting request and future amendments need to be clearly identified as relating to a master protocol and sponsors should inform the FDA about upcoming amendments 48 hours before submission.

Although master protocols provide many advantages, it is important to keep in mind that additional time and resources may be needed to plan and coordinate agreements on trial design, operations and governance with all parties at the outset. However, once established, the potentially shared trial infrastructure and assessment of multiple questions under one protocol can greatly increase the efficiency of drug development. Woodcock and LaVange (2017)[23] argue that

master protocols can support a fast progression of new innovations from the laboratory to clinical evaluation and that coordination of research efforts is inevitable with the development of more precise drug targets. Various master protocol trials are analyzed in the publication. The guidance also provides examples.

FDA Pilot Initiatives

Complex Innovative Design Pilot Meeting Program

On 29 August 2018, FDA announced the Complex Innovative Design Pilot Meeting Program (CID), which provides additional opportunities for sponsors of drugs and biologics to meet with FDA to discuss novel and innovative complex trial designs.[24] Examples of CIDs include:

- "seamless" trial design
- operating characteristics assessed by modeling and simulation
- biomarker-enriched populations
- complex adaptive trials
- Bayesian models
- synthetic control arms
- other novel designs

Sponsors may request to participate in the program on a rolling basis through 30 June 2022. The pilot will run until fall 2023. Only those requests received by the last day of each quarter of the fiscal year will be considered for the following quarter. Meeting-granted and -denied decisions and notifications will be made within 45 days after the quarterly closing date. Requests should be submitted electronically to the pre-IND/IND. Participation in the program provides for an initial meeting to discuss the trial design and a follow-up meeting on the same trial within 120 days. To qualify, FDA will consider the following:

- Innovative features of the trial design, particularly whether the innovation may provide advantages over alternative approaches. Initial priority will be given to trial designs for which:
  - analytically derived properties (e.g., type I error) may not be feasible
  - simulations are necessary to determine operating characteristics
- Therapeutic need (i.e., therapies being developed for use in disease areas where there are no or limited treatments).

It should be noted that FIH trials are specifically excluded.[25]

This new pilot aims to stimulate innovation when developing clinical trial designs by providing necessary earlier and intense feedback from FDA. The discussions are proposed to advance late stage drug development with efficient clinical trials. As a condition of participation, the sponsor must agree FDA can publish the protocol used in the pilot program even if the products under

investigation have not yet received regulatory approval. This transparency is intended to maximize lessons learned and provide a blueprint to inform future complex trial designs that may cause some sponsors to hesitate to participate due to proprietary information concerns.

FDA Oncology Center of Excellence Initiatives

FDA's Oncology Center of Excellence (OCE)[26] was established in 2016 to leverage the combined skills and expertise of agency regulatory scientists and reviewers. The OCE aims to expedite more efficient product development for oncology and hematology medical products. In 2017, the OCE supported approval of 16 new drugs and biologics license applications and 30 supplemental applications.[27] The OCE supports a number of programs, including two pilots:

- Real-time Oncology Review Pilot Program (RTOR)[28]
- Assessment Aid Pilot Project[29]

The RTOR supports the development of an efficient review process to ensure availability of safe and effective treatments as early as possible, while ensuring the review team workload remains feasible.[30] This pilot is only available for supplemental new drugs or biologic license applications and various eligibility criteria apply. A sponsor may apply to participate in the pilot program when top-line results from the pivotal study are available. The advantage of participating in the pilot is that FDA can review data much earlier during the development program, in real-time, and before an approval application has been submitted. The first step is the submission of top-line data from which FDA staff will determine eligibility to participate. Subsequently, once accepted, the sponsor can send pre-submission data two to four weeks after data lock and the decision to apply for approval. FDA will start the data review to assess sufficiency and integrity to provide feedback to the participant regarding the most effective data analysis to address key regulatory questions.

The Assessment Aid Pilot Project is a voluntary submission to facilitate assessment of new drugs and biologics license applications with the aim to focus FDA's review while increasing efficiency and consistency.[31] Interested applicants should submit a notification of interest to FDA and the assessment aid template will be made available to the sponsor during the investigational new drug stage. The applicant will add its position statement after top-line data are received and submit to FDA at the time of regulatory filing. Applicants also participating in the RTOR can submit their position before or at the time of regulatory filing. FDA's review time will add its position, focused on whether FDA agrees with the applicant and information on any additional findings/analysis. This pilot project is open to all oncology medical products. This new format allows for a more focused FDA assessment and a more dynamic review process compared to FDA's multidisciplinary review document.

Neither of these pilots has a definitive ending date. However, an analysis will be conducted after each CDER Office of Hematology and Oncology Products review division has completed the pilot.

Conclusion

Cancer is the second most common cause of death in the US, which has led to cancer trials being among the most active areas of product development. Recent communication by FDA affirmed its support for modernized oncology clinical trial conduct, which has now been manifested in the four guidance documents addressing adolescents, conduct of FIH expansion cohorts, the use of placebo/maintenance of the study blind and master protocols. FDA Commissioner Scott Gottlieb indicated further guidance, with the aim to support efficient development of safe drug products to treat oncology disease, will be forthcoming. The pilot program to support complex innovative trials and various programs is available from FDA's Oncology Center of Excellence to support product development and marketing applications. Eligible applicants should evaluate the use of these opportunities to engage FDA earlier in the trial design process, accelerate their drug development programs, and facilitate the time to complete studies needed to support their new drug or biologics license applications. The increasing speed of innovation and growing scientific insight into cancer biology both demand the implementation of modern complex trial designs for efficient safety and efficacy evaluation of new treatment and to allow faster access for all appropriate patient populations.

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Cite as: Mann P, Messmer K and Pelloso L. “FDA’s Oncology Clinical Trial Makeover.” Regulatory Focus. February 2019. Regulatory Affairs Professionals Society.