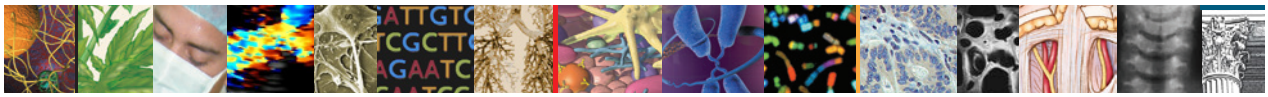

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Perspective

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Seamless Oncology-Drug Development

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For more than half a century, the clinical development of anticancer drugs has followed a predictable and orderly set of sequential stages: phase 1 trials were designed to determine the drug's safety, tolerability, and dose; phase 2 trials then explored the drug's activity in a variety of cancers; and phase 3 trials compared the new drug with existing treatments and served as the basis for regulatory approval. Advances in our understanding of cancer biology in the past decade have led to both development of more effective drugs and improved patient selection made possible by early biomarker discovery and companion diagnostic development. Desire for early access to transformative new anticancer drugs has resulted in increased demand for patient entry into first-in-human trials, as well as calls for expediting the drug development and approval process. The three distinct sequential phases of drug development have therefore become increasingly blurred.

In 2011, Merck initiated a first-in-human trial to determine the safety and recommended dosage of pembrolizumab, a monoclonal antibody that blocks the interaction between the programmed cell death 1 receptor and its ligands, in patients with advanced solid tumors (ClinicalTrials.gov number, NCT01295827). When impressive response rates and durations of response were observed early in the trial, particularly in patients with metastatic melanoma or non–small-cell lung cancer, the sample size was rapidly increased. Cohorts were added to assess efficacy in these two patient populations and to evaluate alternative dosing regimens and candidate predictive biomarkers — a move that resulted in the enrollment of more than 1200 patients in the trial.

Just 3 years after this trial was initiated, data from a cohort of 173 patients served as the primary evidence supporting the initial accelerated approval for the use of pembrolizumab in melanoma. Subsequent data from this trial have been used to support accelerated approval in non–small-cell lung cancer, as well as approval of a companion diagnostic test.

Given this drug development program's efficiency and ultimate success with regard to several indications, many drug companies have since forgone the conventional three sequential phases of drug development and opted for a seamless approach of adding cohorts to a first-in-human trial to investigate doses and activity in a variety of cancers. We have identified more than 40 active commercial investigational new drug

Questions Regarding the Design of Large First-in-Human Cancer Trials.

- Is there a compelling rationale for including multiple expansion cohorts?
- Is the sample-size range consistent with the stated objectives and end points?
- Is there an appropriate statistical analysis plan for all stated end points?
- Are the eligibility criteria appropriately tailored to the expansion cohorts?
- Is there a defined end to the trial, in terms of both efficacy and futility?
- Is there a system in place to communicate with all investigators in a timely fashion?
- Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
- If the trial may be used for regulatory approval, is there an independent oversight committee?
- If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

(IND) applications for large first-in-human oncology trials that are using this seamless strategy. Although the pembrolizumab example illustrates a successful model of seamless drug development aimed at enhanced efficiency, multiple stakeholders who strongly support expedited development and approval of transformative anticancer drugs — including clinical investigators, institutional review board (IRB) members, biostatisticians, pharmaceutical companies, patient advocates, and regulators — have expressed concerns about the rapid proliferation of first-in-human trials enrolling hundreds or even thousands of patients.

Our mutual concerns (see box), which were publicly discussed at the 2015 Accelerating Anticancer Agent Development and Validation workshop and the 2015 Friends [of Cancer Research]–Brookings Conference on Clinical Cancer Research, relate primarily to standard elements of clinical trial design that are routinely found in sequential-phase drug development but have been lacking in a number of trials with expansion-cohort designs.[1,2] For example, all clinical trials should have clearly stated objectives, with a design and statistical analysis plan capable of achieving those goals. For trials that intend to enroll multiple expansion cohorts, that means prospectively providing a rationale for the definition, number, and sample size of the expansion cohorts. It also means that patient eligibility criteria for expansion cohorts should be explicitly defined by investigators and reviewed by IRBs and regulators. And the informed consent should accurately reflect what is known about the drug at the time a patient enrolls — which, in turn, requires updating of informed consent as the trial progresses, not only to reflect new safety data, as is already standard practice, but also to incorporate important evolving efficacy data.

First-in-human trials with expansion cohorts may encompass an entire drug development program in a single trial, and potentially important regulatory interactions and protections may therefore be missing. Without delineation of the drug development phases, standard guidance meetings between the sponsor and the Food and Drug Administration (FDA), such as the meetings held at the end of phase 2 and before the initiation of a phase 3 trial to discuss late-phase development and a registration strategy, may not occur.[3] For trials with expansion cohorts of patients with several types of cancer, regulatory oversight within the FDA may rest with a disease-specific oncology team that will not be responsible for the ultimate review of the drug's marketing application. Although a larger-than-usual safety database derived from the multiple cohorts may be available at the time of initial drug approval, it may be difficult to characterize the drug's toxicity profile because of the lack of a control group. Finally, data from trials involving a single treatment group may be inadequate to support regulatory approvals or reimbursement in some countries, so global access to the drug might be delayed or limited.

Given the potential for greater efficiency afforded by seamless expansion-cohort designs and the potential risks involved in such trials, additional patient safeguards are necessary. We propose that the FDA's "breakthrough therapy" designation be considered as a mechanism of identifying drugs with sufficient early evidence of efficacy to justify a seamless development program.[4] Drugs may receive a breakthrough designation when preliminary clinical evidence indicates a substantial improvement over available therapy in terms of a clinically significant end point. This designation leads to far more intensive, real-time interaction with the FDA throughout the course of drug development, which would ensure a high level of regulatory oversight and frequent, timely communication between sponsors and regulators from all disciplines. Limiting use of seamless designs to designated breakthrough therapies could thus address many concerns that have arisen regarding such development programs.

The use of an independent data and safety monitoring committee whose role is to review clinical trial data and make recommendations regarding changes to the trial's conduct may also provide important quality control. That a trial being conducted to support potential regulatory approval warrants independent oversight is not a new concept, nor is it intended to be burdensome. In a multiple-expansion-cohort trial, such a committee would take scheduled pauses to review safety and efficacy data from existing cohorts, advise investigators about the addition or closure of cohorts, provide external transparency, and ensure the trial's statistical integrity.

We believe that the desire to provide earlier access to highly effective drugs should encourage further use of seamless expansion-cohort trials, particularly as drugs with unprecedented levels of efficacy advance into clinical trials. The type of attention to patient protections afforded by conventional, phased trial designs can be incorporated into this approach through more careful selection of the drugs to be studied in this fashion, greater attention to the statistical rationale and analysis plan for additional cohorts, establishment of external oversight committees, and more frequent, real-time communication among sponsors, investigators, IRBs, regulators, and patients. These concerns and potential solutions to address them will be the topic of a session on regulatory science and policy at the annual meeting of the American Association for Cancer Research (April 16–20, 2016) and will be addressed in further detail in guidance to industry currently being drafted by the FDA Office of Hematology and Oncology Products.[5]

An audio interview with Alice Shaw is available at NEJM.org

Even as we strive to provide earlier access to highly effective anticancer agents, we cannot abandon our commitment to well-designed, well-conducted clinical trials. Such studies are the only way to obtain the high-quality efficacy and safety data that will enable clinicians to counsel patients about a drug's risks and benefits, permit patients to make informed choices about their treatment, and ultimately facilitate widespread global access to highly effective new anticancer agents through regulatory approval and reimbursement.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. American Association for Cancer Research. Accelerating Anticancer Agent Development and Validation Workshop, Bethesda, MD, May 6–8, 2015 (http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=64#.VwPLmOnsbGt).
2. 2015 Friends–Brookings Conference on Clinical Cancer Research, Washington, DC, November 17, 2015 (http://www.focr.org/events/2015-friends-brookings-conference-clinical-cancer-research).
3. Electronic Code of Federal Regulations (e-CFR), Title 21, Section 312.47. Washington, DC: Government Printing Office (http://www.ecfr.gov/cgi-bin/text-idx?SID=8eef990f93702d038cbd4bb7c32df143&mc=true&node=se21.5.312_147&rgn=div8).
4. Guidance for industry: expedited programs for serious conditions — drugs and biologics. Silver Spring, MD: Food and Drug Administration, May 2014 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf).
5. Session detail: American Association for Cancer Research annual meeting, New Orleans, April 16–20, 2016 (http://www.abstractsonline.com/plan/ViewSession.aspx?sKey=4b13301d-c6e8-45af-985d-993fa57123cc&mKey=%7b1D10D749-4B6A-4AB3-BCD4-F80FB1922267%7d).

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Will Precision Medicine Move Us beyond Race?

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Health care providers have long struggled with the utility of race in the prescribing and dosing of medications. It is widely accepted that self-identified race often correlates with geographical ancestry, that geographical ancestry is a major determinant of genomic variation, and that genomic variation can influence reactions to drugs. The challenge for clinicians, however, is that self-identified race does not predict the genotype or drug response of an individual patient. Prescribing medications on the basis of race oversimplifies the complexities and interplay of ancestry, health, disease, and drug response. Eventually, precision medicine may revolutionize our