Background
Improving the biomedical innovation ecosystem in the United States will require stakeholders to address challenges throughout all stages of product development. Early funding and venture capital investment, modern approaches to translational science and clinical trial designs, reforms in regulatory approaches, and improvements to post-market application and evidence generation of new medical products all involve unique issues and challenges in providing patients with the best possible treatments. This is especially true for disease areas with small patient populations or for investigational therapies targeting highly specific subgroups within a larger patient population. For the growing range of medical product development opportunities in these areas, the traditional process of moving promising discoveries from bench to bedside may be too inflexible and inefficient to support the development of new treatments.

A number of recent collaborative efforts have sought to address some of the challenges in this process: pre-competitive consortia are tackling industry data standardization and streamlined clinical trial administrative issues, the U.S. Food and Drug Administration (FDA) is applying new tools like Breakthrough Therapy Designations to speed the approval process for drugs that represent a considerable advance over current standard of care, and a national post-market data collection infrastructure to expand clinical evidence on product safety and effectiveness is becoming a reality. Addressing challenges within the design of clinical trials themselves, however, still remains an area ripe for identifying new ways to ethically and efficiently leverage patient populations in the trial process. Clinical trialists and regulatory scientists both must focus considerable effort on re-examining the scientific issues underpinning the old paradigm in order to arrive at nimble, adaptive clinical trial designs that are responsive to the evidence being accrued, the needs of specific patient groups, and the safety and efficacy requirements of regulators.

In traditional clinical trials, key trial parameters such as sample size, study eligibility criteria, and randomization ratio are determined in advance and fixed throughout the trial. Fixed randomized controlled trials remain the gold standard in clinical drug development; however, there is growing interest in innovative trial designs with the potential to increase the efficiency of the development process. Adaptive trial designs differ from conventional clinical trials in that they allow for modifications to ongoing trials based on accumulating data. Trial modifications are preplanned and made based on the results of interim analyses that use accumulating data to learn about the efficacy of the treatment throughout the trial. The flexibility of adaptive trial designs hold the promise of producing the evidence needed for regulatory approval in a smaller and shorter clinical trial. Their potential to streamline the drug development process is greatest in more complicated trial settings that aim to answer multiple questions during a single trial. The FDA has encouraged the use of adaptive designs, and in 2010 FDA issued draft Guidance for Industry1 regarding adaptive trial designs in drug development programs to inform sponsors of the regulatory implications of adaptive clinical trials.

Adaptive clinical trials may modify different aspects of the trial, including stopping early due to futility or efficacy, sample size re-estimation, or population or treatment selection. The use of simple adaptive trial designs, such as early stopping for futility, has increased during the last decade and such designs are

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now used in about 20 percent of clinical trials.\(^2\) Other, more complex types of study adaptations have much lower industry adoption rates, but may hold additional promise for improving the efficiency and success rates of clinical trials.

Complex adaptive features have already had some success in phase II studies, notably the BATTLE lung cancer\(^3\) and I-SPY 2 breast cancer\(^4\) trials. These trials use outcome adaptive randomized designs to assess and identify promising biomarker-drug combinations during a single trial. Both trials use accumulating data to learn what therapies are most beneficial for patients with specific biomarker signatures. As the trials progress and more learning occurs, the randomization probabilities are modified and patients are more likely to be assigned to drug therapies predicted to be most effective for their specific biomarker. The hope is that information gained from these trials can be used to design more efficient, targeted phase III confirmatory trials.

Adaptive clinical trials like BATTLE and I-SPY demonstrate the potential for adaptive designs to result in more efficient learning during the exploratory disease setting.\(^5\) Adaptive clinical trials like BATTLE and I-SPY demonstrate the potential for adaptive designs to result in more efficient learning during the exploratory disease setting. A key design feature of interest to FDA is the use of an intermediate endpoint for the interim analysis upon which the initial approval decision is based, with efficacy subsequently demonstrated with respect to a validated long-term clinical outcome.\(^5\) This workshop will explore frequentist and Bayesian approaches to adaptive designs that take into account the results from the assessment of both the intermediate and long-term clinical outcomes and the relationship between the two, potentially informed by the use of external data sources.

Workshop Objectives and Overview
Under a cooperative agreement with FDA, the Engelberg Center for Health Care Reform at the Brookings Institution is convening an expert workshop to facilitate discussion regarding the use of adaptive designs for accelerated approval in a curative disease setting. A key design feature of interest to FDA is the use of an intermediate endpoint for the interim analysis upon which the initial approval decision is based, with efficacy subsequently demonstrated with respect to a validated long-term clinical outcome.\(^5\) This workshop will explore frequentist and Bayesian approaches to adaptive designs that take into account the results from the assessment of both the intermediate and long-term clinical outcomes and the relationship between the two, potentially informed by the use of external data sources.

Workshop participants were invited to submit adaptive models for discussion. The appended models will be considered and compared with respect to their statistical properties as described in greater detail below (Session II). The discussion will also address operational considerations for the successful implementation of the submitted designs (Session III). Please note that this expert workshop is intended to inform FDA’s thinking on this topic but does not constitute a federal advisory committee and will not be making formal recommendations. Please also note that all materials included in this docket are confidential and for discussion purposes, and should not be distributed more broadly.

Session IIa: Statistical Considerations for the Design of Adaptive Trials – Understanding the Tradeoffs in the Proposed Designs
This session is the first of a two-part discussion regarding statistical considerations that arise in designing an adaptive clinical trial for accelerated approval in the curative disease setting. Discussion in this session will include the following topics:

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When designing a trial with prospectively planned adaptations, the potential impact of the adaptations on the operating characteristics of the trial design should be evaluated during the planning stage. Evaluating the statistical performance of the design involves studying the operating characteristics of the design under different scenarios using trial simulations or a set of statistical assumptions. What statistical assumptions are used to evaluate each design’s statistical properties and how sensitive are the statistical inferences to variations in these assumptions?

Frequent interim analyses during the trial may affect the Type I error rate and increase the risk of a false positive conclusion. How do the proposed designs demonstrate preservation of the Type I error rate, and what are the relative strengths of their approaches?

Confirmatory clinical trials must have sufficient statistical power to demonstrate treatment efficacy; however, additional statistical power often implies a larger sample size and longer study duration. One of the key benefits of adaptive designs is that they are more flexible and investigators can modify trial parameters, including the sample size, as more information is learned about a trial’s statistical power and other characteristics. How do the proposed trial designs optimize across these trial dimensions and how do these design decisions impact their potential efficiency gains? What are the potential downsides to their approaches?

This session is a continuation of the discussion in Session IIa regarding adaptive clinical trial design considerations, with a focus on providing statistically valid and reliable evidence for assessing treatment efficacy and safety. Discussion in this session will include the following topics:

A key feature of designs for accelerated approval in the curative disease setting is the use of an intermediate endpoint (in the case of neo-adjuvant breast cancer trials, pathologic complete response or pCR) to support accelerated approval. Efficacy for the long-term clinical outcome of interest (event free survival or EFS) must also be demonstrated in the same trial or in another study for full approval to be granted. It has been shown that irrespective of the treatment received, patients who achieve pCR are likely to have longer EFS compared to patients who do not achieve pCR; however, the relationship between the two endpoints in assessing a treatment effect over an existing treatment is unknown. How do the proposed adaptive designs considered here differ in terms of how they obtain sufficient statistical power to demonstrate a treatment effect for both pCR and EFS endpoints? What assumptions about the relationship between pCR and EFS do the proposed designs use to inform trial adaptations and provide evidence for approval decisions? What are the advantages and disadvantages of each approach?

Adaptive designs may combine data from multiple stages or trials to obtain an estimate of the overall treatment effect for FDA approval. Treatment effect estimates are also used during the trial to make interim decisions. How do the proposed designs account for statistical bias that may have been introduced during the trial and ensure the validity of their statistical inferences?

Confirmatory clinical trials must provide sufficient evidence of a treatment’s clinical benefit and safety relative to the standard of care to obtain FDA approval. How can—and should—clinical trial simulations be used to assess a design’s statistical characteristics and inferences, and provide evidence for the approval decision?

Session III: Operational Considerations for the Successful Implementation of Adaptive Trials
The complexity of adaptive trials when compared to traditional, fixed parameter trials means that adaptive trials are often more complicated to plan and implement. This session will focus on the logistical and procedural issues associated with conducting adaptive clinical trials. Discussion in this session will include the following topics:
The complexity of adaptive clinical trials varies. A key component that affects trial design complexity, and potentially its feasibility, is the number and type of interim analyses and adaptations. How do the potential benefits of the trial adaptations in each of the proposed designs compare to the effort required to successfully implement each design?

Trial adaptations, particularly those that require interim analyses of unblinded data from the trial, have the potential to introduce bias into a clinical trial. What is the potential for information leakage in each of the proposed designs, and how might the planned adaptations be designed and implemented to limit threats to trial integrity?

Patient recruitment is a challenge in many clinical trials. The adaptive trial design may impact patients’ willingness to enroll in the trial. What potential impact may the proposed adaptive designs have on patient enrollment? How should the trial adaptations be designed and communicated to encourage sufficient patient enrollment?