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FDA's Expedited Approval Programs: Evidentiary Standards, Regulatory Trade-offs, and Potential Improvements

Short title: FDA's Expedited Approval Programs

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Abstract

The United States Food and Drug Administration (FDA) has several regulatory programs and pathways to expedite the development and approval of therapeutic agents aimed at treating serious or life-debilitating conditions. A common feature of these programs is the regulatory flexibility, which allows for a customized approval approach that enables market authorization on the basis of less rigorous evidence, in exchange for requiring postmarket evidence generation. An increasing share of drugs approved by the FDA in recent years are associated with expedited programs. In this paper, we provide an overview of the evidentiary standards required by FDA's expedited development and approval programs, summarize the findings of the recent academic literature demonstrating some of the limitations of these programs, and outline potential opportunities to address these limitations. Recent evidence suggests that therapeutic agents in the FDA's expedited programs are approved on the basis of fewer and smaller studies that may lack comparator groups and random allocation, and rather than focusing on clinical outcomes for study endpoints, rely instead on surrogate markers of disease. Once on the market, agents receiving expedited approvals are often quickly incorporated into clinical practice and evidence generated in the postmarketing period may not necessarily address the evidentiary limitations at the time of market entry. Furthermore, not all pathways require additional postmarketing studies. Evidence suggests that drugs in expedited approval programs are associated with a greater likelihood that FDA will take a safety action following market entry. There are several opportunities to improve the timeliness, information value, and validity of the pre- and postapproval studies of drugs receiving expedited approvals. When use of nonrandomized and uncontrolled studies cannot be avoided prior to market entry, randomized trials should be mandatory in the postapproval period, unless there are strong justifications for not carrying out such studies. In the premarket period, validity of the surrogate markers can be improved by more rigorously evaluating their correlation with patient-relevant clinical outcomes. Opportunities to reduce the duration, complexity, and cost of postmarketing randomized trials

should not compromise their validity and instead incorporate pragmatic ‘real-world’ design elements. Despite recent enthusiasm for widely using real world evidence, adaptive designs, and pragmatic trials in the regulatory setting, caution is warranted until large scale empirical evaluations demonstrate their validity compared to more traditional trial designs.

Keywords: Food and Drug Administration, Pharmaceutical Regulation, Drug Policy, Expedited Approval, Postmarketing

Introduction

In the United States, the Food and Drug Administration (FDA) is responsible for ensuring that new therapeutic agents are safe and effective. FDA's review of applications for new drugs and biologics (hereafter, novel therapeutic agents) is guided by the Federal Food, Drug, and Cosmetic Act, which requires that manufacturers submit data from 'adequate and well-controlled' investigations to determine efficacy.¹ In particular, FDA guidance suggests that drug manufacturers submit at least two trials, often referred to as 'pivotal trials', that provide independent evidence of efficacy.² Although the traditional 10-month review process is designed to prevent unsafe or ineffective drugs from entering the market, FDA faces continual pressure to accelerate the regulatory review and approval of new drugs, in order to promote innovation and provide patients with serious life threatening conditions access to new therapeutic agents as quickly as possible.

Over the past 30 years, the US Congress and FDA have introduced four programs (*Fast Track* designation, *Accelerated Approval* pathway, *Priority Review* designation, and *Breakthrough Therapy* designation) that aim to expedite the approval process for certain agents that address an 'unmet medical needs in the treatment of a serious or life-threatening condition' (Figure 1).³ Since their inception, there has been a significant increase in the number of therapeutic agents qualifying for FDA's expedited development and review programs.⁴ However, evidence suggests that these programs introduce flexible approval standards that can lead to products being approved on the basis of fewer or less robust studies,⁵ and are associated with greater likelihood that the FDA will take a safety-related action after the agent has been approved for use.⁶

Although a recent study provided an overview of common methodological challenges encountered in pivotal clinical trials supporting expedited regulatory approvals,⁷ different

methodological and regulatory factors influence the validity of studies conducted in the pre- and postapproval periods. In this paper, we first provide an overview of the evidentiary standards required by FDA’s expedited development and review programs for therapeutic agents and summarize the findings of the recent academic literature demonstrating some of the limitations of these programs. We then outline potential opportunities to address these limitations both in the pre-and-postapproval setting.

Expedited programs: evidentiary standards

FDA has four programs that are intended to ‘facilitate and expedite’ the development and review of therapeutic agents that have a potential advantage over existing treatments or are the first available treatment for a serious disease (**Box 1**).³ While certain programs, such as *Priority Review*, do not formally change evidentiary standards,³ others allow agents to be approved at earlier stages or based on less rigorous testing, which can have important implications for patients, physicians, payers, and policy makers.^{4,5} In addition, FDA’s policy for requiring postmarketing studies varies by program.

Box 1. The expedited development and review programs at the US Food and Drug Administration
<i>Fast Track</i>
In 1988, FDA formalized the <i>Fast Track</i> designation, which now allows therapeutic agents to be approved based on a single phase 2 study if the agent is ‘intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition.’ ³ According to FDA, <i>Fast Track</i> designation can be requested by drug sponsors with or after an IND, ‘ideally, no later than the pre-BLA or pre-NDA meeting’. ³ When an agent receives fast track designation, it can still be eligible for <i>Accelerated Approval</i> and <i>Priority Review</i> . ³ Between 1987 and 2014, 144 (19%) of approved therapeutics had a fast track designation. ⁴
<i>Priority Review</i>
In 1992, under the Prescription Drug User Fee Act, FDA established a two-tiered system of review times. A drug can receive a <i>Priority Review</i> designation if it ‘treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.’ ³ Although <i>Priority Review</i> does not formally change evidentiary standards, it establishes that that the FDA deadline to make a decision is within six months of submission. During the review process, priority designation is made at the time of original NDA, BLA, or efficacy supplement filing. ³ However, priority review does not guarantee that a novel therapeutic will be approved. Nearly one in five (18

or 96, 18.8%) novel therapeutics approved by the FDA after multiple review cycles between 2001 and 2011 had a *Priority Review* status.⁸ Since 1992, *Priority Review* has been the most common expedited approval program (331 of 774 [43%] of new drugs).⁴

Accelerated Approval

In 1992, FDA also instituted the *Accelerated Approval* program, which allows for the expedited (6 months) approval of novel therapeutics that treat serious or life-threatening diseases.⁹ Under the *Accelerated Approval* program, marketing approval is granted based on pivotal trials that use surrogate markers, which are biomarkers or intermediate endpoints that are ‘reasonably likely’ to predict patient-relevant outcomes, such as mortality and morbidity, as primary endpoints.⁹ However, once an agent has been approved, drug sponsors are then required to conduct postmarketing trials to describe and verify clinical benefit. Generally, drug sponsors are expected to discuss potential accelerated review agents with the FDA review division during development.³ Approximately 10% of the new drugs approved by the FDA since 1992 have been evaluated through the *Accelerated Approval* program.^{4,5}

Breakthrough Therapy

In 2012, FDA introduced the *Breakthrough Therapy* designation, which allows drugs that treat serious diseases to be approved based on preliminary clinical evidence suggesting substantial improvement over available therapies on clinically significant endpoints.³ However, breakthrough drugs must eventually be approved or rejected under normal FDA approval standards.³ Breakthrough requests are submitted with or after IND, ‘ideally, no later than the end-of-phase 2 meeting’.³ *Fast Track* and *Breakthrough Therapy* designation drugs are generally approved within 60 calendar days of receipt of request.³ To date, there has been limited evaluation of agents receiving *Breakthrough Therapy* designation.

BLA = Biologic License Application; FDA = Food and Drug Administration; IND = Investigational New Drug Application; NDA = New Drug Application

Issues and potential solutions in the premarketing period

Studies have shown that recent regulatory flexibility has resulted in approvals based on single, nonrandomized, or uncontrolled pivotal trials without patient-relevant outcomes or adequate participation of the elderly and racial or ethnic minorities.^{5,10} Considering that postapproval studies of the same therapeutic agents for the same indications are not always carried out,¹¹⁻¹³ trials that support the approval of an agent may be the only source of available evidence. The perceptions of the potential treatment benefits of new agents may therefore rely on the results from pivotal trials that are used to inform approval. However, the use of a single trial or multiple less rigorous trials to inform marketing decisions involves certain trade-offs, particularly risking making erroneous inferences about the long term clinical effect of a new treatment.

Single pivotal trials

Instead of the regular requirement of at least two ‘adequate and well-controlled’ investigations to determine efficacy,¹ novel therapeutic agents receiving fast track approvals can be approved based on a single phase 2 trial.³ Similarly, most accelerated approvals are supported by a single study at the time of market entry.⁵ The findings from an individual, potentially spurious, study may provide inaccurate information about the safety and efficacy of a therapeutic agent.

According to a large empirical evaluation, initially observed effect estimates typically become smaller as additional trials are performed.¹⁴ Furthermore, findings from single studies may be less reliable if their sample sizes are small: previous assessments have shown that small trials are associated with substantially exaggerated treatment effects.^{15,16} For instance, trials with sample sizes ranging from less than 50 to 999 were found to have statistically significantly larger treatment effect estimates than trials of 1000 patients or more.¹⁶ While some of these findings could be explained by the fact that small trials with non-statistically significant findings may be more likely to go unpublished than larger trials with non-statistically significant findings and that small studies need larger effect sizes to be statistically significant, these concerns may still apply to the drug approval process. For instance, it is possible that drug sponsors only submit individual trials with the largest treatment effects to the FDA.

Currently, drug sponsors are not required to conduct postmarketing trials to describe and verify the clinical benefit of their products receiving *Fast Track* approval. However, such trials are essential to ensure that the treatment effect observed in single pivotal trials are confirmed in adequately powered evaluations. According to a recent review of randomized trials published after market entry for all novel therapeutic agents approved for 123 indications by the FDA between 2005 and 2012 on the basis of limited evidence, only 6 of 33 (18.2%) indications approved on the basis of a single trial had at least one randomized, controlled, double-blind study using a clinical outcome for the primary endpoint that showed superior efficacy.¹⁷

Although postmarketing studies are required in the *Accelerated Approval* pathway, they are often delayed or terminated.¹³ Even when postapproval trials are completed, they often have similar design deficits as pivotal studies.^{13, 17, 18} In particular, postapproval studies for *Accelerated Approval* drugs are commonly nonrandomized and instead of evaluating accelerated approval agents versus comparators, postapproval studies generally include them as background therapies.¹⁸ This may suggest that agents receiving accelerated approval quickly become part of standard treatment, despite the fact that they often lack robust pre-and-postapproval evidence.¹⁸

Randomized controlled trials

Evidence suggests that pivotal trials of therapeutic agents approved through the *Accelerated Approval* pathway are less likely to be randomized.⁵ Rigorous randomized controlled trials are often considered the gold-standard when it comes to evaluating the efficacy of a new drug.¹⁹ The process of randomly assigning subjects to different intervention groups helps ensure that the findings are a result of the intervention instead of systematic differences that may exist between groups. There are numerous concerns about the validity of treatment effect estimates from nonrandomized study designs. Empirical studies have shown repeatedly that the estimated treatment effects from nonrandomized studies tend to be larger compared to those from randomized controlled trials.²⁰⁻²² However, randomization may be inappropriate if the intervention is designed to prevent certain rare events or if they target a serious condition without any licensed treatments and well-estimated outcomes.²³ Furthermore, patients and clinicians may also refuse to participate in randomized controlled trials of already-approved agents.

Between 2005 and 2012, over half of the pivotal trials for novel therapeutics approved through the *Accelerated Approval* pathway were single-arm trials.⁵ A comparator group (e.g., active or placebo) is often considered an essential part of the scientific method, used to determine

whether the observed results are actually attributable to the safety and efficacy of a treatment. When novel therapeutics are compared to a control arm, it is easier to determine whether the drugs are behaving as one would expect from previous knowledge and experience. However, when evaluating a new drug, one of the primary goals is to demonstrate a clinical benefit while limiting the number of patients who may be exposed to a treatment without clear evidence of effectiveness. While randomized controlled trials provide the most reliable information about the effect of a treatment, it may not always be possible to allocate patients to multiple groups. For instance, when drugs that target extremely rare indications or unmet medical needs are being evaluated, there may not be any existing comparator options. However, when only one treatment is being evaluated in a trial, it can be difficult to determine whether outcomes or adverse events are due to the treatment, disease, or a specific patient characteristics.

In order to rely on the evidence from nonrandomized and/or single-arm trials, it will be necessary to establish a framework to specify the circumstances under which these study designs can be accepted for the approval of novel therapeutics (**Table 1**). If single-arm studies are utilized, manufacturers should consider multiple sources of historical control data and ensure that the patients enrolled in single-arm studies are comparable to patients in historical studies. Furthermore, FDA, researchers, clinicians, and research consumers should be cautious when interpreting the findings from single-arm studies. When the results from single-arm studies are used to guide the approval of novel therapeutics, it should be clearly communicated that nonrandomized and uncontrolled study designs do not always allow for causal interpretations.²⁴ Instead, nonrandomized trials can be used to complement the interpretation of randomized trials. Although it may not always be feasible to enroll an adequate number of patients for all randomized trials of agents targeting rare conditions within a reasonable period of time,²⁵ approximately one in three clinical trials supporting rare cancer drug approvals between December 1987 and May 2011 were randomized.²⁶ This could suggest that randomized

controlled trials are a realistic design for evaluating the efficacy and safety of drugs for rare indications.²⁶⁻²⁹ Various frameworks for designing randomized trials in settings where large-scale clinical trials may not be typically feasible have been proposed.^{27, 29} While there may be proper justification for nonrandomized trials in exceptional circumstances, manufacturers may need to perform randomized trials in other stages of the disease or in different disease settings. For instance, when drugs receive accelerated approval, postapproval trials could be conducted in less advanced stages of the disease than the initial approval.³⁰

Surrogate markers

FDA licenses certain therapeutics based solely on the evidence of their effects on surrogate markers, which include laboratory measurements, physical signs, or intermediate outcomes.³¹ Between 2005 and 2015, 95% of the pivotal trials for novel therapeutics approved under the *Accelerated Approval* pathway had a surrogate marker as the primary trial endpoint.⁵

Unlike patient-relevant outcomes, which reflect how patients feel or function or how long they survive, surrogate markers can accumulate more quickly which can help shorten the duration, size, and total cost of pivotal efficacy trials.³¹⁻³³ While many patient-relevant outcomes are discrete, surrogate markers are often continuous and repeatedly measured. This can provide trials with more statistical power to detect potential treatment effects.³⁴ These are desirable characteristics for sponsors and patients seeking new treatments, as well as for regulators who face pressure to shorten testing and review times. There are also important ethical reasons that may justify the use of a surrogate marker. For new treatments targeting serious conditions with alternative therapies, it may not be feasible to perform long-term studies with patient-relevant end points.

While there are successful examples of approved drugs based on established surrogate markers (i.e., HIV RNA for AIDS drugs), the role of surrogate markers in guiding patient care and health policy remains uncertain and concerning.³⁵⁻³⁹ The *Accelerated Approval* pathway distinguishes between established surrogate markers and those that are only ‘reasonably likely’ to predict clinical benefit.³ Therapeutic agents granted accelerated approval can therefore receive marketing authorization on the basis of less established surrogates.

Indeed, surrogate markers do not always provide the same clinical answers as final patient-relevant outcomes.³⁸ A surrogate marker may not be valid if the treatment effect on the surrogate does not correspond to the treatment effect on the final outcome, if there is no consistent association between the surrogate and final outcome across multiple studies, and if there is no biological plausibility of relation between the surrogate and final outcome.³¹ Furthermore, surrogate markers generally overestimate the treatment effect of interventions.^{38, 40} Recently, a meta-epidemiological study of trials from high impact medical journals found that surrogate primary outcomes are more likely to have larger treatment effects than trials reporting final patient-relevant primary outcomes.³⁸

There are also concerns related to the validation of surrogate markers. In oncology, most trial-level validation studies of surrogate markers use only a subset of all available trials and report low correlations with survival.⁴¹ Such methodological issues may pose significant challenges for regulators. For example, in 2008, bevacizumab (Avastin; Roche/Genentech) gained accelerated approval for metastatic breast cancer based on pivotal trial evidence suggesting that it could improve progression free survival.⁴² However, the metastatic breast cancer indication of this drug was later withdrawn after multiple randomized trials found that bevacizumab did not improve overall survival.⁴³

Numerous steps should be considered before promoting the broader use of surrogate markers. In the United States, there is a need for an independent evaluation and validation of currently used and candidate surrogate markers (**Table 1**). At a minimum, FDA may need to enhance their enforcement of formal empirical verification of surrogate markers. This can help establish the performance of a surrogate marker and inform whether certain surrogate markers should continue to be used as a substitute of treatment benefit. An FDA advisory committee may be necessary to examine why the same surrogate markers for the same drugs do not always replicate exactly in postapproval studies.

Recently, Ciani and colleagues outlined a three-step framework that can be used to validate and use surrogate-based evidence for health care decision making.³¹ The first step in the process is to establish the level of evidence (e.g., level 1 (highest): randomized controlled trial evidence; level 2: epidemiological/observational study evidence; level 3: biological plausibility of relation between surrogate and patient relevant outcome). The second step is to assess the strength of association between the surrogate and final outcome. Although numerous approaches exist, the most reliable method is to perform a meta-analysis using patient-level data from all randomized controlled trials. The final step involves ‘predicting and quantifying the relation between the surrogate and the final outcome, and between the observed effect on the surrogate and the expected effect on the final outcome.’³¹ Without a systematic effort to consider, evaluate, and report on the predictive value of commonly used surrogate measures, their incorporation in regulatory decisions will continue to spark controversy.

Patient heterogeneity

In order for evidence from pivotal trials to inform decisions in clinical practice, it is essential that the patients participating in these trials reflect the population of patients that are expected to ultimately use the novel therapeutic agent.¹⁰ Since 1998, FDA has taken measures aimed at

improving and ensuring the representativeness of patients participating in clinical trials. With the ‘demographic rule’, FDA required drug makers to report the age, sex, and race of clinical trial participants in their annual reports to the agency.⁴⁴ In 2013, FDA released a report describing the demographic characteristics of participants in trials of drugs and devices approved in 2011.⁴⁵ In 2015, FDA published an investigation on the representativeness of clinical trials supporting drugs approved between 2010 and 2012.⁴⁶ In the same year, FDA piloted the “Drug Trials Snapshot” website, which provides data about participants included in trials that supported the FDA approval of new therapeutic agents (e.g., potential subgroup differences across sex, race, and age groups).⁴⁷ However, a recent independent evaluation of the demographic characteristics of patients participating in pivotal trials for all novel therapeutics approved by the FDA between 2011 and 2013 found that black and Hispanic patients were underrepresented.¹⁰ Overall, white patients accounted for almost 80% of pivotal trial participants and the proportion of black and Hispanic patients was far less than their representation in the general population.¹⁰

Although previous analyses have not explored differences by approval pathway, trial population heterogeneity is important to consider as trials continue to become smaller. For example, pivotal trials for products approved through the *Accelerated Approval* pathway have statistically significantly smaller sample sizes than non-accelerated approval drugs.⁵ With smaller pivotal trials, the ability to understand potential differences across demographic subgroups will become more difficult.

While women and older populations, historically underrepresented in clinical research, appear to be better represented in pivotal drug trials over the last 20 years, even greater research participation from minority populations will require a concerted effort by both public and private stakeholders, taking into account the barriers and facilitators of participation.⁴⁸

Issues and potential solutions in the postmarketing period

The approval of novel therapeutics based on less robust evidence highlights the need for required postmarketing trials and rigorous surveillance to monitor drug efficacy and safety after market introduction.

Postmarketing Requirements

In 2006, the Institute of Medicine Report on the Future of Drug Safety recommended that the FDA adopt a ‘lifecycle’ evaluation approach.^{49, 50} Under a lifecycle evaluation approach, certain agents can be approved based on potentially less robust clinical evidence with the assumption that their safety and efficacy will be continuously evaluated after approval.¹⁷ Prior to 2007, FDA generally could only request that manufacturers voluntarily ‘commit’ to performing postmarketing studies or trials (i.e., ‘postmarketing commitments’).⁵¹ However, since the Food and Drug Administration Amendments Act (FDAAA) in 2007, FDA has had the authority to require manufacturers to complete certain postmarketing studies and trials after therapeutics receive approval (i.e., postmarketing requirements).⁵¹ There are currently four separate authorities under which FDA can require drug manufacturers to perform postmarketing studies or clinical trial (**Box 2**).

Box 2. Food and Drug Administration Postmarketing Requirement Authorities
<i>Accelerated Approval</i> postmarketing requirements: FDA can require postmarketing studies or clinical trials to verify efficacy for accelerated approval drugs approved on the basis of surrogate or intermediate endpoints ‘reasonably likely’ to predict clinical benefit. ³
<i>Pediatric Research Equity Act (PREA)</i> postmarketing requirements: FDA can approve therapeutics if they have been tested in adults; however, certain postmarket pediatric studies, evaluating the same drug for the same indication for which they are approved in adults, may be deferred. ⁵⁰
<i>Animal Efficacy Rule</i> postmarketing requirements: In situations where it is unethical to conduct trials using human subjects, therapeutics can be approved exclusively based on animal studies, but postmarketing studies in humans may still be required. ⁵⁰
Food and Drug Administration Amendments Act (FDAAA) postmarketing requirements: FDA has the authority to require studies that assess known serious risks, signs of serious risks, or unexpected serious risks related to the use of a drug. ^{52, 53}

While postmarketing requirements can provide important new evidence on the safety and efficacy of approved drugs, there have been growing concerns about the fulfillment and monitoring of required postmarketing studies.^{11, 12, 18} An analysis of both postmarketing commitments and postmarketing requirements from 2007 to 2011 found that 40% of the required studies had not started in 2011.¹¹ In a more recently study of 614 postapproval requirements and commitments imposed in 2009 and 2010, approximately 20% of postapproval studies had not been started after 5 to 6 years.¹² According to an evaluation of 24 indications for 22 drugs granted ‘conditional’ accelerated approval by the FDA between 2009 and 2013, only 42% had efficacy confirmed in postapproval trials within 3 years of approval.¹³

Findings from required studies are an important source of postapproval clinical information and can lead to regulatory actions, which can help guide payers, physicians, and patients. For approximately half of the postmarketing requirements fulfilled in fiscal year 2014, ‘FDA required sponsors to make labeling changes and/or take other actions to ensure the safety of their drugs’.⁵³

Postmarket safety actions

With evidence that the majority of drugs qualify for expedited pathways and that pivotal trials are often small, short, and evaluate surrogate markers,^{4, 5} it is possible that expedited development or review can lead to increased risk from safety issues in the postmarketing period. According to a recent evaluation, one third of the 222 novel therapeutics approved between 2001 through 2010 required that the FDA take a postmarket safety action, with accelerated approval therapeutics having significantly higher rates.⁶ In a separate study, drugs approved through expedited development and regulatory review pathways between 1997 and 2016 were associated with increased safety related label changes after approval.⁵⁴ In particular, expedited pathway drugs had a 40% higher rate of changes to boxed warnings and contraindications compared with

nonexpedited pathway drugs.⁵⁴ In a study of new small molecule drugs submitted, approved, and launched between 1997 and 2009, drugs approved with a *Priority Review* were 3.51 times more likely to receive a post-marketing boxed warning.⁵⁵

Moving forward, requirements for postapproval trials should be enhanced (**Table 1**).

Investigators should conduct postapproval trials that have adequate sample sizes, follow-up durations, and design characteristics. Furthermore, FDA should continue to ensure that sponsors complete postmarketing requirements in order to provide additional information about the safety, efficacy, and optimal use of a new drug.⁵⁶ Useful measures to assist in study accrual and completion in the postmarket setting include the addition of study sites or plans to conduct the confirmatory study in countries where the drug may not yet be commercially available. Moreover, measures that would ensure timely completion of the confirmatory studies after accelerated approval is granted should be part of the development plan.

Although the FDA's Sentinel Initiative, which combines administrative claims and clinical data, allows for the detection of postmarket safety events using multiple data sources, additional collaboration between FDA and other stakeholders will be necessary to 'develop and maintain an effective system for detecting postmarket safety events'.⁶ This is particularly critical for accelerated approval drugs, which have been associated with a greater likelihood that FDA will take a safety action in the postmarketing period.

Future outlook

Recent proposals for FDA reform, including the 21st Century Cures Act, have called for the use of nontraditional study designs and evidence from real world non-clinical trial data sources (i.e., real world evidence [RWE]) to further speed up the drug approval process.^{57, 58} Recently, Dr. Scott Gottlieb, the FDA commissioner, made remarks to the National Academy of Sciences

outlining that ‘advancing the adoption of RWE in support of its programs remains a top priority.’⁵⁹ Dr. Gottlieb further outlined that RWE may be ‘especially relevant in settings like rare disease or other unmet medical needs, where it can be hard to enroll patients in clinical trials.’⁵⁹ Moving forward, it will be important to monitor how the FDA will be using RWE in drug approval. So far, FDA’s definition of RWE has been aligned with the use of pragmatic trials in actual clinical practice.⁶⁰

Pragmatic clinical trial designs

Pragmatic clinical trials are ‘designed for the primary purpose of informing decision-making regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.’⁶¹ The key feature differentiating traditional ‘exploratory’ or ‘mechanistic’ trials from their more ‘pragmatic’ counterparts is the degree to which they reflect real-world settings. Relative to traditional designs, pragmatic clinical trials often impose fewer restrictions on participant and investigator selection, and treatment delivery and follow-up.⁶² Accordingly, such designs tend to better reflect care delivered in actual clinical practice, generating generalizable – externally valid – findings.⁶³⁻⁶⁵

Pragmatic clinical trials can also improve the efficiency of evaluations without sacrificing on their validity. These practical designs allow for embedding random allocation of treatments in high-quality observational studies or integrated data systems such as existing population cohorts, disease registries, or electronic health records. For example, an existing observational cohort of patients with stable, chronic disease can serve as an efficient infrastructure to conduct multiple randomized trials of novel therapeutic agents.^{66, 67} Existing disease registries, observational cohorts, or electronic health records can also facilitate reliable data collection.⁶⁸ For example, objective long-term outcomes can be captured in administrative claims or reliable electronic data networks currently under development as part of the National Patient-Centered Clinical

Research Network, an initiative of the Patient-Centered Outcomes Research Institute (PCORI).⁶⁹

Therefore, combining elements of randomized and nonrandomized studies in such hybrid designs can allow internally valid evaluation of treatment effects in large numbers of people at low cost with long periods of follow up (**Box 3**).

Box 3. Combining elements of randomized and non-randomized studies

Randomized trials embedded in observational data collection systems have gained in popularity in recent years. For example, the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA) was conceived as a platform to conduct of multiple randomized controlled trials of interventions among cancer survivors.⁷⁰ In an earlier example, researchers in Sweden conducted the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial to evaluate whether thrombus aspiration reduces mortality in an already existing observational registry, maximizing the number of trial participants while minimizing – and even eliminating – some of the most complex, time consuming, and costly elements of traditional trial designs such as recruitment, follow-up and data collection.^{71, 72}

Despite recent enthusiasm for more widespread use of pragmatic clinical trials in development and regulatory decision making,⁷³ key features of such designs may preclude their use in pivotal trials supporting regulatory decisions. Currently, clinical trials conducted on investigational new drugs are subject to FDA regulations with limited prospect for relaxing restrictions on participant and investigator selection, informed consent practices, and protocol-driven follow-up mechanisms.⁷⁴ However, the suitability of pragmatic clinical trials when fulfilling postmarketing commitments and requirements of already-approved products should be carefully investigated. As the FDA comes under repeated scrutiny for its oversight and enforcement of postmarketing studies,¹² pragmatic clinical trials can help with effectively and efficiently addressing questions that are unanswered at the time of approval.

Adaptive trials

Recently, the FDA has started to encourage the use of adaptive or innovated clinical trial designs. In 2010, FDA issued guidance that designated an adaptive design clinical study as:

“...a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are performed at prospectively planned timepoints within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing.”⁷⁵

Considering the costly and time-consuming nature of drug development, adaptive trials have the potential to increase the flexibility and efficiency of the drug development process. Ideally, the modifications and adaptations in adaptive trials should be pre-planned and based on the data provided in the study. However, changes to eligibility criteria, study dose, treatment duration, diagnostic procedures, randomization, study design, study hypotheses, data monitoring and interim analyses, and statistical analysis plans can have a big impact of study validity and integrity.

Adaptive trials may require greater statistical expertise during the design, conduct, and analysis than in a traditionally-designed randomized controlled trial. According to a recently survey,⁷⁶ the attitudes towards adaptive trials are inconsistent. Biostatisticians, in particular, are not as optimistic about the validity and potential conclusions that can be drawn from adaptive trials.⁷⁶ Further empirical investigations are needed before establishing a formal role for the use of adaptive trial designs in drug development and approval.

While efforts are underway to ensure the internal validity of findings obtained from adaptive trial designs when compared to traditional ‘mechanical’ trial designs, significant opportunities exist to lower the cost and complexity of randomized trials without compromising their validity.

Conclusions

As the number of novel therapeutic agents included in expedited approval pathways and programs has increased, there are several opportunities for improving the timeliness and information value of clinical trials conducted for regulatory purposes. In recent years, an increasing number of agents have entered the United States market on the basis of a single pivotal trial and trials using surrogate markers as primary endpoints or employing non-randomized or uncontrolled designs. Moving forward, clear regulatory guidance is necessary to identify the circumstances in which the use of surrogate markers is warranted. Efforts are needed to evaluate and reach consensus on the predictive validity of current and future surrogate markers. In cases where agents are approved on the basis of single-arm trials, randomized controlled trials should be required in the postmarketing period, unless there are strong justifications, from an ethical or feasibility perspective, for not carrying out such studies. In parallel, introducing elements of pragmatic (real-world) designs into randomized trials, especially in the postmarketing setting, can help with reducing the complexity, and hence cost, of such studies, which play a pivotal role in evaluating the effectiveness of newly marketed agents in the real world. Although RWE, adaptive designs, and pragmatic trials hold great promise, caution is warranted until empirical studies demonstrate the validity of such designs as compared to traditional, protocol-driven randomized controlled trials.

Declaration of conflicting interest

In the past 36 months, Dr. Wallach has received support through Stanford and Yale from the Laura and Arnold Foundation to support the Meta-Research Innovation Center at Stanford and the Collaboration on Research Integrity and Transparency at Yale. Dr. Ross has received research support through Yale University from Johnson and Johnson to develop methods of clinical trial data sharing, from Medtronic, Inc. and the Food and Drug Administration (FDA) to develop methods for postmarket surveillance of medical devices (U01FD004585), from the Food and Drug Administration to establish Yale-Mayo Clinic Center for Excellence in

Regulatory Science and Innovation (CERSI) program (U01FD005938), from the Blue Cross Blue Shield Association to better understand medical technology evaluation, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting (HHS-500-2013-13018I), from the Agency for Healthcare Research and Quality (R01HS022882), from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) (R01HS025164), and from the Laura and John Arnold Foundation to establish the Good Pharma Scorecard at Bioethics International and to establish the Collaboration for Research Integrity and Transparency (CRIT) at Yale. Dr. Naci has no conflicts to declare.

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Table 1. Recommendations to improve the design and analyses of clinical trials	
Area	Investigators and regulators should:
<i>Single-arm trials</i>	Identify the circumstances where the use of single-arm trials may be warranted
	When use is justified, consider multiple sources of historical control data
	Ensure the comparability between patients in single-arm studies and potential historical controls
	Provide cautious (non-causal) interpretations of the findings from single-arm studies
	Ensure postmarketing evidence generation requirements include randomized controlled trials
<i>Trial outcomes</i>	Rely on surrogate markers that have been validated or validate surrogate markers using a three-step process ³¹
	Enhance the process to evaluate and report on the validity of currently used and candidate surrogate markers
	Ensure that patients and physicians understand how to interpret the results from trials with surrogate markers
	Require postmarketing trials that incorporate patient-relevant, clinical outcomes
<i>Accrual and complexity</i>	Consider the addition of study sites or plans to conduct confirmatory studies in countries where certain agents may not yet be commercially available
	Introduce elements of pragmatic ('real-world') designs and use routinely available data sources to reduce the complexity of postmarketing randomized trials
<i>Adaptive trials</i>	Ensure that modifications and adaptations are pre-planned and based on the data provided in the study
	Interpret findings obtained from adaptive trials with caution until empirical evaluations confirm their validity

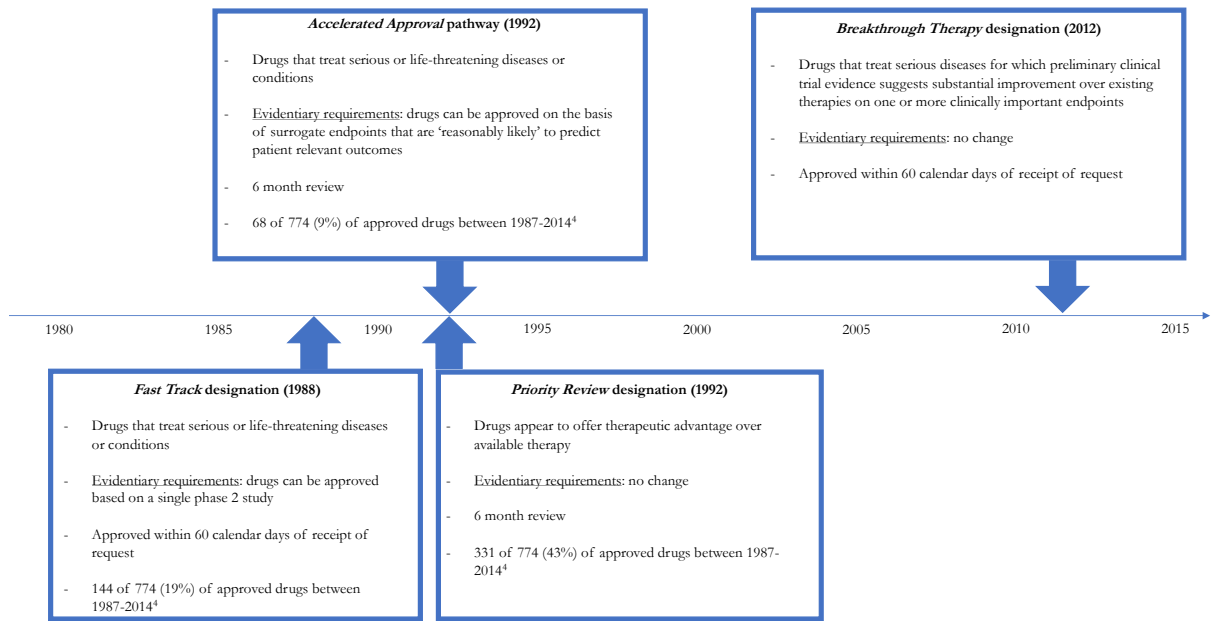


Figure 1. Expedited development and review programs and their evidentiary standards

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