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The FDA Should Not Mandate Comparative-Effectiveness Trials

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Over the next few years, legislation to fund the Food and Drug Administration (FDA) is going to be up for authorization by Congress. The Prescription Drug User Fee Act (PDUFA), the Medical Device User Fee Act, a user-fee program for generic drugs, follow-on biologics, and reauthorized pediatric exclusivity are all among the measures likely to be combined into one massive piece of FDA legislation. This sweeping bill will become a vehicle for the passage of many other drug-related measures. Consumer groups are pushing for a new drug approval mandate that would require drug companies to conduct "comparative effectiveness" trials to win FDA approval for new medicines. Proponents of this policy argue that new drugs should have to prove superior to older medicines to gain marketing approval. These requirements would add a major hurdle to the development and approval of new medicines, adding significant time and cost. Equally important, the proposed mandates are unnecessary. In situations where differences in the efficacy of two medicines could have important medical implications, the FDA already uses its considerable authority to require head-to-head comparisons between drugs. In situations where this sort of comparative data is important to guide cost-effective medical choices, drug companies are doing these trials on their own prerogative to secure insurance coverage and placement on formularies. Moreover, if such an FDA mandate were adopted, the resulting studies would likely be "noninferiority trials," which are unlikely to conclusively show whether a new medicine is indeed more effective than an existing alternative.

Next year, Congress will reauthorize legislation that helps fund the FDA drug-review program. The PDUFA requires drug companies to pay user fees to help defray some of the FDA's cost of reviewing applications. Consumer groups are making a hard push in Washington to use this fifth iteration of the PDUFA to add new requirements to the drug approval process. In particular, they want Congress to mandate that

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Key points in this *Outlook*:

- Consumer groups are pushing to add a step to the FDA drug approval process: "comparator" trials, which test a new drug against the current standard treatment.
- But these trials are already being conducted in important cases. A new FDA approval requirement would slow down the drug approval process elsewhere.
- Achieving the goal consumer groups want—safer and more cost-effective drugs—requires innovation in clinical trial design, not a congressional mandate.

drug companies undertake "comparative effectiveness" studies prior to the approval of a new drug.

These comparator trials would involve drug companies running clinical trials, prior to FDA approval, that pit their new medicines against current drugs. The ostensible goal is to require sponsors to prove that their new drug is better than a currently used medicine. Proponents argue that mandatory comparator trials would yield information that can improve prescribing decisions by steering patients to the most cost-effective treatment. They say such a scheme would lower health care costs by identifying when newer, and presumably more expensive, medicines are little better than cheaper, generic alternatives.

It is a simple, if not seductive, pitch: new medicines should demonstrate that they offer clear advantages over older, often cheaper drugs. But it fails to take into account the costs this requirement would impose, the weakness of the clinical information it would ultimately generate, and the existing regulatory authorities and market forces that already compel drug companies to undertake these "active comparator" trials when the information that can be generated is important to clinical decision making.

The Last Push for a New Mandate and Its Aftermath

When this debate surfaced during the last reauthorization of the PDUFA, the FDA's senior career staff made a convincing case against it. They quietly argued that a law requiring the FDA to mandate comparator trials could get in the way of the agency's mission of determining safety and effectiveness. They worried that such a mandate would force drug makers to use clinical trial designs that make baseline evaluations of safety and efficacy more difficult.

Advocates for comparative effectiveness subsequently turned their attention instead to postmarketing surveillance: collecting comparative data from the real-world use of medical products. This was the early genesis of a political movement for government funding of comparative-effectiveness research (CER).

The stimulus package[1] passed in February 2009 allocated $1.1 billion for CER to three federal health agencies.[2] President Barack Obama's signature health legislation, the Patient Protection and Affordable Care Act, provided an additional $3 billion and created a nonprofit Patient-Centered Outcomes Research Institute to identify research priorities and commission studies.[3]

Notwithstanding these legislative victories, advocates for government-sponsored CER are looking again to the FDA requirements. They want to use the new drug approval process to advance their agenda. This *Outlook* lays out some of the faults with this policy scheme.

The New, New Case for FDA-Mandated Comparator Trials

Proponents of this agenda laid out their reasoning in a series of prominent opinion articles. A September 2009 editorial published in the *New England Journal of Medicine* stated the argument this way: "If the FDA label were required to indicate what is and is not known about a product's superiority to other treatments, then clinicians, patients, and payers would be less willing to pay more for a new treatment without proof that it improved health outcomes."[4]

An editorial published in the *Journal of the American Medical Association* in March 2010 framed the argument similarly: "The current FDA standards for approval fail to assess whether newly approved drugs and devices are less efficacious or less well-tolerated than existing alternatives. This raises the possibility that patients may be harmed by receiving a newly approved treatment instead of an alternative with established efficacy and safety. . . . With effective marketing, patients may receive a new treatment instead of a more efficacious older treatment, thereby potentially subjecting patients to excess risk of poor outcomes. In addition, excess costs are likely to be generated by the often higher costs of new treatments and the need for additional treatments that may have been avoided."[5]

Others proponents go further. They argue that the FDA should require that new drugs prove superior to existing medicines before they can win regulatory approval.[6]

Policy Arguments Fall Short

The drive to add a comparative-trial mandate to the FDA drug approval process resurfaces each time the PDUFA is up for reauthorization.[7] The PDUFA legislation provides an attractive vehicle for these sorts of political efforts. Proponents of these policy proposals take some of their cues from Europe. Comparative trials are already encouraged as part of some European drug submissions, not only for some of the same clinical

reasons that the FDA sometimes already requires these studies be performed for US drug submissions, but also for economic reasons—to help guide European government payers. To these ends, the European equivalent of the FDA, the European Medicines Agency, stated in a 2004 guidance document that, when possible, trials with both active-comparator and placebo-controlled groups should be performed.[8] This European experience provides some of the impetus for similar proposals here in the United States.

The cynical view of these European policies holds that the real intention is to cut health care costs by delaying the approval and coverage of new drugs. The requirement for comparative data also provides European government health systems an additional point of negotiation when they haggle with drug companies over the pricing of new drugs. It is noteworthy that drug reviewers both in the United States and Europe privately concede that the resulting comparative trials are often small, and therefore not statistically rigorous enough to yield firm results because the trials are "underpowered." As a result, the information from the comparator trials often does not factor heavily in regulators' baseline decisions about the safety and efficacy of a new medicine.

For these and many other reasons, the rationale for requiring comparative trials prior to granting a new drug FDA approval falls short on some key policy assumptions.

First, the FDA already exercises its considerable authority to require these trials when this information is needed for making regulatory decisions and guiding sound clinical choices.[9] For example, the FDA has traditionally required comparator trials when it believes that the approval of a new medicine that is less effective than current therapies could create risk to patients. This happens in diseases for which the absolute efficacy of drugs is one of the key considerations in prescribing decisions. One example is the approval of anti-infective drugs. The FDA typically requires that new antibiotics prove as good as existing treatments before they can be approved. Another situation where the FDA typically requires this sort of comparative data is in the approval of drugs to prevent the rejection of transplanted organs.

In most of these cases, the FDA requires drug makers to undertake noninferiority trials to prove that their new medicine is equivalent to current drugs. Noninferiority trials are intended to show that a new treatment is at least as good as a current standard of care. In a noninferiority trial, the new drug cannot differ from the existing treatment by more than a specified margin, called the "delta." The FDA asks for noninferiority studies because superiority studies (where a new drug is proved better than an older treatment) would be unfeasible due to their enormous size. In many cases, sponsors would not be able to recruit enough eligible patients for superiority trials.

Market forces are requiring drug companies to prove that their drugs are better than existing medicines. More companies are doing comparator trials voluntarily.

Second, an FDA mandate for generating comparative data before approval is unlikely to yield the kind of prescribing information that proponents envision. Consumer advocates mostly talk about the need to show that a new drug is better than its cheaper alternatives. To these ends, they have in mind superiority trials. But they misjudge the cost and difficulty of conducting superiority trials.[10] Superiority trials require an enormous number of study subjects to discern clinically meaningful differences between two drugs. These trials can require tens of thousands of patients when two closely matched drugs are being compared. If the FDA were to require comparative data before approval, it would inevitably require drug makers to pursue noninferiority studies instead because of the sheer impracticality of running superiority trials.

A study recently published in the journal *Nature Reviews Drug Discovery* laid out the implications of running studies to determine if one drug is superior to its closest alternative. The analysis showed how the size of a clinical trial can explode when trying to prove whether one drug is superior to a second, active therapy. The analysis reinforces the claim that, given a mandate for comparative data, practical considerations will lead to the performance of noninferiority studies.

The analysis also shows that, even making fairly conservative assumptions (that a new compound is being developed for an indication where the expected placebo response rate is around 70 percent, the anticipated cure rate of current drugs is around 80 percent, and the cure rate of a new drug falls between 78 percent

and 85 percent), demonstrating the efficacy of the new drug in a placebo trial would require the enrollment of six hundred patients in a pivotal study. This is true even if the new drug's expected cure rate is 80 percent (in other words, if the new drug is no better than the standard of care). By contrast, demonstrating the noninferiority of the same compound would require 3,100 to 12,600 patients depending on the chosen delta or margin.

Superiority trials become even more burdensome. Even assuming the new drug is significantly better than the current standard of care (a cure rate of 83 percent for the new drug, versus 80 percent for the old medicine), showing the superiority of the new drug would require a trial of 5,300 patients. But assuming, more realistically, that the two drugs are more closely matched (a cure rate of 81 percent for the new drug versus 80 percent for the older one—a small, but still clinically meaningful, difference), a trial to show its superiority would require 49,000 patients. Such a difference in cure rates, while small, could still be clinically significant. Yet it could be impossible to demonstrate this superiority in any reasonably sized, premarket clinical trial.

In some clinical indications, demonstrating superiority may be scientifically impossible, at least at equivalent doses of a drug. This is particularly true when the experimental drug exerts its pharmacological effect through the same mode of action as the compound it is being compared to.[11] For all these and other reasons, if a comparative mandate were added to the FDA approval process, the vast majority of trials the FDA would require would be noninferiority studies. But as mentioned, these noninferiority trials have their own important shortcomings.

The greatest difficulty with noninferiority trials relates to the issue of "assay sensitivity"—the ability of a specific clinical trial to demonstrate a difference between two treatments if such a difference actually exists. A trial that successfully demonstrates superiority has simultaneously demonstrated assay sensitivity. However, a noninferiority trial that successfully finds the effects of the treatments to be similar has demonstrated no such thing. A well-run noninferiority trial that correctly demonstrates the treatments to be similar cannot be distinguished, on the basis of the data alone, from a poorly executed trial that fails to find a true difference. In other words, in a noninferiority trial, the lack of a difference between two drugs could be due to both drugs being equally effective. Or it could be the result of both drugs being equally ineffective.

As a result, a noninferiority trial must rely on an assumption of assay sensitivity based on elements that are not part of the trial's data. These elements might include the quality-control procedures put into place to ensure the trial's integrity or the reputation of the investigators who conduct the study.[12] Regulators try to make sure that sponsors control for these kinds of factors, since problems with them can reduce assay sensitivity. As a result, noninferiority trials rely on an element of faith. Factors such as poor compliance with the study medication, poor diagnostic criteria, excessive variability in how the primary outcome is measured, and bias in how the results are assessed can all impact the reliability of studies and confound their results.

These are not the only challenges with noninferiority trials. Determining the suitable noninferiority margin is also difficult.[13] There are two approaches. Both have shortcomings.

We need to develop better models for doing clinical trials that are specifically geared toward generating comparative data.

The first approach is to specify the equivalence margin based on what is presumed to be the minimally important therapeutic benefit of a given drug. However, this is clearly subjective. This approach can allow the equivalence margin to be set wide enough to allow harmful treatments to be judged noninferior. To avoid this, the equivalence margin is often chosen with reference to the effect of the active control in historical placebo-controlled trials. But sometimes this data comparing the active control to the placebo does not exist.

Even when it does, the result can still be confounded. When the equivalence margin is chosen based on data from past placebo trials, there is some basis to claim that a positive noninferiority trial implies that the new treatment is superior to the placebo. However, this claim requires an assumption that the effect of the active control in the current trial is similar to its effect in the historical trials, and there are plenty of reasons why this assumption is not always true.[14]

Finally, although noninferiority trials have smaller sample sizes than actively controlled superiority trials, noninferiority trials can have considerably larger sample

sizes than placebo-controlled studies. This is because the equivalence margin is often much smaller than the treatment difference that placebo-controlled trials are powered to detect. In addition, the sample size of a noninferiority trial is very sensitive to the assumed effect of the new treatment relative to the active control. The sample size can be much larger if the two drugs are assumed to be equivalent than if the new drug is slightly more effective than the comparator medicine (the active control).[15] But in most cases, drug developers are working off conservative assumptions. So the aim is to power these studies to assume that the two treatments exert similar effects.

For all these reasons, noninferiority trials are typically more subject to imprecision and bias than placebo-controlled efficacy studies. It is no wonder drug regulators prefer to make decisions based on placebo-controlled trials whenever possible.

Third, in situations when comparator trials can help inform the decision to use an expensive new medicine over a cheaper and seemingly similar alternative, the mandate for comparative data may be superfluous and unnecessary. This is especially true when a new and expensive medicine seems closely matched to a much cheaper, often generic alternative. In these cases, drug companies already take on the enormous investment in preapproval superiority trials to gain market access for their new drugs. Payers are becoming increasingly aggressive at implementing tiered formularies that sharply increase copayments for many newer, more expensive drugs, and taking other steps to drive generic substitution. The time to market for a new drug is no longer defined by its time to licensing by the FDA, but by its time to reimbursement. Increasingly, the market success of a new drug is driven less by conventional marketing efforts than by the ability to demonstrate added therapeutic value to patients and payers. Similar to the regulatory process, reimbursement decisions are often taken by expert committees and are increasingly based on sophisticated methodology.[16]

As a result, drug makers are compelled by market forces to develop data showing that their new drugs are superior to older, less expensive medicines if they hope to secure favorable reimbursement terms. These market forces are also driving drug makers to curtail a growing number of development programs when a new compound is not expected to provide clear evidence of superiority to existing treatments.[17] In cases where drug makers undertake comparative trials to help secure reimbursement, they are doing the studies before approval and submitting them as part of their FDA files so they have the information available at the time of approval. In some cases, they try to get the information into drug labels so they can promote it.

There are some notable, recent examples where drug makers undertook very large and costly superiority studies to meet the economic prerogatives of an increasingly competitive drug market. Among them is the experience with a new class of antiplatelet drugs used to prevent heart attacks and complications from coronary angioplasty. These new drugs have been compared to the current standard of care, Plavix, in enormous trials undertaken by drug makers.

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Plavix is soon going off patent and will be available as an inexpensive, generic medicine. Drug makers developing alternatives to Plavix recognize the need to prove that their new medicines are not simply noninferior to the standard of care but superior to it to justify a premium price over the soon-to-be generic alternative. To these ends, the new antiplatelet drug Brilinta was compared to Plavix in a trial that involved 18,624 patients hospitalized with acute coronary syndrome during a median treatment of nine months.[18] Another new antiplatelet drug, Effient, was studied in several significant trials. The largest of these studies enrolled 13,608 patients and compared its effects to the blood-thinning effects of Plavix in patients with a threatened heart attack or an actual heart attack and about to undergo coronary angioplasty.[19]

Trials of this size are mammoth economic investments, not only to the drug makers but also to broader society. Each patient enrolled in a pivotal study adds more than $30,000 to the cost of the trial. It also takes these patients away from other studies that they might have enrolled in. These costs get baked into the eventual retail price of the new drug charged to consumers.

But the bottom line is that market forces are requiring drug companies to prove that their drugs are better than existing medicines. More companies are doing comparator trials voluntarily.

In fact, today the rate of inclusion of comparative data in applications submitted to the FDA mirrors the experience of European regulators, even though Europe has a more explicit policy to encourage this data to be developed before approval. A recent review of the approval packages for new molecular entities (NMEs) approved between January 1, 2007, and December 31, 2008, shows that 40.5 percent (seventeen out of forty-two) of approval packages contained an active comparator trial that evaluated the drug's efficacy. The same survey found that 31 percent of approved NMEs (thirteen out of forty-two) included these active comparator data in the resulting drug label.[20] A more recent study looked at 197 NMEs approved by the FDA between 2000 and 2010. It found for the NMEs for which alternative treatment options existed that 70 percent had data from active comparator studies available at the time of FDA approval.[21]

By comparison, the European Union has enjoyed a largely similar rate of inclusion of comparator data, despite regulatory mandates for it. A survey of drugs approved in the European Union between 1999 and 2005 found that 48 percent of new drugs had been studied in comparison with existing medicines at the time of approval.[22] The same study found that, in total, 153 pivotal trials were based on active controls over the same time period. The objective of only fifteen (10 percent) of these was to show superiority to the standard of care.[23]

Market forces will likely continue to drive the conduct of more active comparator studies. This raises the question: why is it necessary to mandate that these trials be conducted as part of the FDA approval process? To the contrary, there are compelling reasons why this mandate would fail to achieve the practical goals envisioned by proponents, while adding significantly to the cost of new drugs. It could actually weaken the information available about drug safety and efficacy by leading to the use of noninferiority studies in lieu of placebo trials.

Clinical Arguments Fall Short

Even if proponents of adding a new mandate to the FDA drug approval process were right on the economic and policy arguments, they would still be wrong on their clinical rationale.

For one thing, premarket comparator trials are unlikely to yield clinical information that can help patients make true head-to-head comparisons of new drugs. Conducting a trial to discern differences between two active compounds (two drugs that both work to treat a given condition) can require large and long studies to ferret out small differences. Even if a very large study can discern these kinds of small differences in relative efficacy, determining whether they lead to a benefit in long-term clinical outcomes can require a study so long and large as to be impractical.

Premarket comparator studies are also often suboptimal for making regulatory decisions. The clearest way to discern the risks and benefits of a new drug is a placebo trial. As noted, noninferiority studies, and similar constructs, have inherent design flaws that make them less reliable. In some cases, we have to depend on these kinds of studies because we have no alternative—for example, because of ethical or practical concerns. But placebo trials remain the gold standard for determining a drug's baseline safety and effectiveness.

Finally, in many cases, even superiority studies would be unlikely to answer the clinically relevant question. For example, for antidepressant or blood pressure medicines, there is a significant heterogeneity in patients' responses to different compounds. It is less important to establish that one compound is superior to another than to merely establish that a new compound is effective for a particular condition and a certain subgroup of patients. In clinical practice, patients often try many similar drugs until they find one that works best for them. So the absolute efficacy of a compound is not the operative question. The most important question is whether a compound can provide some benefit, and whether it exerts its effects differently than other compounds. This is precisely because a patient may not respond well to one drug but may have a robust response to a different but similar one. It is true even among drugs in the same class.

Better Opportunities to Pursue Comparative Data in FDA Trials

All this does not mean that there are no more opportunities to generate reliable information about the relative efficacy of different drugs, and to develop this data in the context of their FDA registration trials. But the most efficient approaches to developing this evidence will likely require innovation in how clinical trials are conducted. We need to develop better models for doing

clinical trials that are specifically geared toward generating comparative data.

For example, some have proposed novel approaches to the design of drug trials that would reduce the length of time that patients receive a placebo. Under this approach, the trial would begin with patients being randomized in the conventional way to receive either the new drug or a placebo. After a certain period of time, the experimental drug would be given to the patients on the placebo. This design allows for the primary assessment of efficacy and safety of the new drug, with secondary assessment of efficacy and safety compared to the standard of care.[24]

Other approaches could use adaptive clinical-trial designs. In these trials, the way patients are treated changes over the course of the study based on scientific feedback, such as how patients are responding to a particular drug. Adaptive trials allow researchers to more easily compare different treatment strategies and to focus on the drugs that are proving the most promising. Our current approach to designing and running trials inhibits adaptation because of the requirement to prespecify all possible study outcomes. This, in turn, requires a more rigid study design.[25]

Consumer groups often insist on these rigid statistical approaches. They insist that drug companies should be held to a high statistical bar even in settings like cancer, where consumer advocates increasingly advocate randomized, placebo trials where the FDA previously permitted nonrandomized or single-arm studies. This is ironic because these are some of the same groups that support the comparative mandate that would lead to studies that are inherently less reliable than placebo trials. Of course, some proponents of these new mandates would square this contradiction by arguing that the comparative trials should merely supplement the placebo trials as part of the FDA approval package. But that proposition is so impractical as to be a nonstarter. If drug companies are forced to develop comparative-effectiveness data prior to FDA approval, in the vast majority of cases they simply will not be able to simultaneously run placebo and active comparator trials because of the costs. Ultimately, sponsors will invest in fewer drugs, and there will be fewer research dollars available for developing new medicines.

Conclusion

The decisions of regulators to approve a new drug, and of private health plans to cover it, are increasingly made in a similar time frame. Both public and private payers are often dependent on the FDA approval package for making their decisions. So it is understandable that they want more power to influence the clinical trials conducted for regulatory filing.[26] In both the United States and Europe, for the first time, government health care payers (such as Medicare in the case of the United States) are acquiring explicit political mandates to interact with drug regulatory authorities.

The evolution of this trend is contributing to pressure on the FDA's approval requirements. Payers have long wanted higher bars to the approval of new medicines, and more data that they can use to inform their business decisions to cover a new drug. Consumer advocates have taken up this cause. The most expedient way for these groups to get drug companies to generate more comparative data is to demand they be developed prior to FDA approval. A far more honest way to achieve these same ends would be for payers to take on the role of requiring these data prior to, or shortly after, they agree to pay for a new drug. To the degree that payers make this kind of information a prerequisite to coverage in certain crowded drug classes, sponsors have shown they will respond to these market forces by undertaking investment in the requisite trials.

In many cases, the market already demands that a new drug show that it is superior to an older, often cheaper alternative. Drug companies routinely pursue superiority trials to secure reimbursement when their drugs are destined to compete with ostensibly similar but cheaper alternatives. In other cases, where public health prerogatives obligate new drugs to prove equal to or better than existing medicines, the FDA already uses its considerable latitude to demand noninferiority trials, and in some rarer cases, superiority trials.

In short, comparative trials are already getting done where it most counts. If the FDA were forced to mandate comparator trials, we would probably end up with a plethora of weakly powered noninferiority studies. These clinical trials would be far less suitable than today's standards for establishing the baseline safety and effectiveness of new medicines.

Notes

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