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A Modern System for Approving the Cures of the Future

By Edward Hudgins

Summary

- FDA's drug certification process, which relies heavily on randomized clinical trials, stifles new drug creation and adds years of delays and billions of dollars in costs to the drug development process.
- Use of real-world data is driving cutting-edge drug research.
- A Free to Choose Medicine track would allow patients to access drugs still in clinical trials and would collect real-world data in a Tradeoff Evaluation Drug Database, helping patients make informed treatment choices, speeding up certification and spurring innovation.

Executive Summary

The world should be entering a golden age of medicine, but the Food and Drug Administration's (FDA) antiquated process for certifying the safety and efficacy of new treatments could significantly delay that future, limiting innovation and unnecessarily harming millions of patients in the process.

All Americans desire access to drugs that are safe and effective, but they also want timely and affordable drugs. However, a report by the Tufts Center for the Study of Drug Development found it takes on average more than a decade—at a total cost of $2.9 billion (including the cost of failed drugs)—to bring a new drug from research labs to market, where patients can access these life-saving or life-improving treatments.[1] Much of those resources are consumed by years of FDA-mandated tests allegedly meant to certify the efficacy of medicines that have already been determined to be safe.

While FDA bureaucrats slow-walk the approval of new pharmaceuticals, millions of Americans suffer or even die waiting for promising treatments to be made available. Many of those patients left in anguish rightly ask, "Isn't there a better way?" The answer is unequivocally, "Yes!"

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[1] Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansenc, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics*, Volume 47, May 2016, pp. 20–33, https://www.sciencedirect.com/science/article/abs/pii/S0167629616000291

The Free to Choose Medicine (FTCM) model would offer the developers of new drugs that have passed safety tests and at least one efficacy trial the option of making them available to patients. Patients have a right to take responsibility, in consultation with their doctors, for their own health and to accept informed risk in order to preserve or enhance their own lives by accessing such new drugs and biologics. Currently, only the few thousand patients who are permitted to participate in drug trials have that opportunity.

FTCM would also create a system for determining efficacy that, at minimum, would supplement FDA's use of statistical analyses generated using data from randomized, controlled clinical trials. Under FTCM, a Tradeoff Evaluation Drug Database (TEDD) would be created. Information about patients, including their genetic data, relevant biomarkers, and clinical treatment results from the use of drugs on FTCM tracks, would be logged into TEDD, with patient privacy strictly guarded. This database would be accessible to the public and researchers alike and would give patients and physicians a fuller understanding of all their treatment options in a way that is currently impossible to achieve.

In the past decade, real-world data, which are used as evidence to determine the efficacy of medical treatments, have increasingly been used to gain insights of practical value. Relying on such observational data is now recognized, even by FDA, as the cutting edge in medical research. On the issue, FTCM was ahead of its time, highlighting the importance of such data as early as 2007.[2]

This *Policy Brief* argues an FTCM approach, by collecting real-world data on the effects of new drugs, would provide more patients with access to potentially life-saving drugs, and it would do so much faster and more efficiently than the current FDA system. By providing observational data in real time to drug developers, FTCM would allow less-efficacious drugs to fail faster, weeding out poorly performing drugs in a shorter period and revealing more quickly which drugs are likely to work well.

By expediating these processes, the overall cost and time associated with drug development would be reduced markedly. This would create more opportunities—especially for smaller, innovative researchers—to develop breakthrough drugs and methods by which to demonstrate their efficacy.

This paper will consider the following:

1. Limits of Clinical Trials

Once considered the "gold standard" by which any drug should be reviewed, the randomized clinical trial approach has significant and widely recognized shortcomings. Adopted in federal law in 1962, decades before the computer and internet revolution offered other possibilities for efficacy certification, the FDA clinical trial mandate is in serious need of modernization.

[2] An early addition of Bartley J. Madden's book, *Free to Choose Medicine*, was translated into Japanese in 2007, and in 2014, Japan adopted FTCM for its regenerative treatments. See Edward Hudgins, "Free to Choose Medicine in Japan: A Model for America," *Policy Brief*, The Heartland Institute, June 2018, https://www.heartland.org/_template-assets/documents/publications/61418_ JapanFTCM1.pdf

2. Tradeoff Evaluation Drug Database

The Tradeoff Evaluation Drug Database system for collecting real-world data, an innovative aspect of FTCM, would provide to patients and doctors access to information crucial to their treatment choices. It would also give drug developers information and data that would help them create new drugs. This model would enable the developer of the new drugs and other biopharmaceutical companies to make better decisions about how and when to allocate research and development funds, thereby improving the output of the biopharmaceutical industry.

3. Off-Label Uses of Drugs

The prescription of drugs by physicians and use of drugs by patients for purposes not certified by FDA reveals how real-world data have been used for decades to help best serve patient needs.

4. FDA's Adverse Event Reporting System for Updating Labels

FDA already uses a data collection system similar to TEDD to keep labeling information for drugs up to date. FDA has supplemented this effort through its Sentinel Initiative.

5. The Real-World Data and Evidence Revolution

Reliance on real-world data and the development of innovative ways to discover the efficacy of medical products are on the cutting edge of medical research. TEDD would shorten expensive, years-long clinical trials, and it would justify the creation of a modern "Observational Approval" certification designation for new drugs, an option offered in addition to certification that's based only on clinical trial results.

6. Medical Device Information Consortium and NESTcc Database

Currently, perhaps the best attempt to utilize real-world data and evidence is the new Medical Device Information Consortium, which aims to benefit patients by advancing medical device regulatory science. Most notable is the consortium's NESTcc system, which would document patient experiences with devices in a TEDD-like database.

7. The Case for TEDD

Now, more than ever, Americans need Free to Choose Medicine, which depends on the implementation of TEDD. The FDA has created a variety of approaches to make its regulatory process faster, but these changes (e.g., breakthrough designation) are only marginal changes that leave in place the system's current structure, which depends on extremely expensive (in terms of both time and money) randomized control trials. It is time for a paradigm change utilizing real-world data to save patients' lives, reduce health care costs, and expedite the availability of superior medical treatments.

1. Limits of Clinical Trials

An antiquated 1962 law, as well as subsequent regulatory reforms, require FDA to certify the safety and efficacy of new drugs and medical devices before they can be marketed to patients in America.[3] Researchers usually spend several years creating and doing preliminary tests on new, potentially effective drugs. The FDA-mandated certification process then normally begins with drug developers, manufacturers, or sponsors submitting what they hope will be an effective medication for Phase I basic safety tests. Next, drugs deemed safe and promising are approved for Phase II randomized clinical trials, which are used to determine a trial drug's general efficacy and potential side effects. The randomized control trials of Phase III are much more extensive than Phase II, to better gauge safety, proper dosing, and efficacy.

AN ANTIQUATED 1962 LAW, AS WELL AS SUBSEQUENT REGULATORY REFORMS, REQUIRE FDA TO CERTIFY THE SAFETY AND EFFICACY OF NEW DRUGS AND MEDICAL DEVICES BEFORE THEY CAN BE MARKETED TO PATIENTS IN AMERICA.

During the randomized clinical trials usually required in Phases II and III, one group of patients receives the medication under review while the other group receives placebos or the current standard of care treatment. Better treatment results for the group receiving the new drug are used as evidence of the drug's effectiveness.

The criteria by which patients are chosen to participate in these trials are often tightly controlled to minimize the number of factors that might cause patients' health to improve or worsen. After the three phases are complete, which together often last longer than 10 years, manufacturers can submit a "New Drug Application" to FDA, which then decides whether to approve the product for use by the public.[4]

These randomized clinical trials are considered by some to be the "gold standard" because of their statistical rigor. While there are most certainly benefits to this 1962 model, there are also significant costs, including that many patients end up suffering unnecessarily. Some even die. The longer the trial periods for ultimately approved drugs in this status quo approach, the greater the toll paid by society and the patients waiting for a drug to be approved.

A closer look at these trials highlights other shortcomings. First, the highly selective nature of the trials is a drawback. For example, a drug's sponsor might exclude men under the age of 50, smokers, diabetics, and those who drink more than one glass of wine or beer per night. Such criteria limit who can be included in clinical tests, in order to help statisticians

[3] Public Law 87-781, October 10, 1962, p. 780, https://www.govinfo.gov/content/pkg/STATUTE-76/pdf/STATUTE-76-Pg780.pdf; also see "Kefauver-Harris Amendments Revolutionized Drug Development," FDA Consumer Health Information, October 1992, https://www.gvsu.edu/cms4/asset/ F51281F0-00AF-E25A-5BF632E8D4A243C7/kefauver-harris_amendments.fda.thalidomide.pdf

[4] Bartley J. Madden, *Free to Choose Medicine*, Third Edition (Arlington Heights, IL: The Heartland Institute, 2017), p. 20.

analyze data. However, real-world patients differ from the highly controlled clinical test group, which is why observational data of real-world patients is extraordinarily useful.

Second, attaining the most complete picture of the efficacy of a medication often requires numerous clinical trials, all with different parameters and varying patient criteria. This might be a rigorous approach, but the more data that are sought, the more trials that are necessary, thereby slowing the trial phases and making drug approval more expensive.

Third, as has been noted, in these clinical trials, only one group of participants is given the new medication. The other group unknowingly receives placebos, which means many of the patients in a trial do not benefit from trial participation. This raises some important ethical and practical questions. Indeed, the 1964 Declaration of Helsinki on "Ethical Principles for Medical Research Involving Human Subjects" has been wrestling with this issue for decades.[5] If a patient has a debilitating or life-threatening ailment, giving him or her a placebo, as opposed to a drug that might help, is arguably immoral. Testers always struggle with this dilemma. Further, when trials are limited to patients with milder cases of an ailment, patients with advanced cases of the ailment are sacrificed for statistical purity, which might benefit analysts but certainly does not benefit those excluded.

Fourth, FDA's "compassionate use" option is often promoted as a solution for seriously ill patients who are not chosen for clinical trials, but that option presents immense difficulties for physicians and patients, who are required to spend countless hours devoted only to completing applications and filling out paperwork. Additionally, such patients often are very ill and cannot wait years for a product to clear all clinical trials, meaning they are much more seriously ill than the average patient participating in clinical trials. Pharmaceutical sponsors are typically wary of providing drugs for those seeking to pursue the compassionate use option, because they fear that if patient health does not improve, this failure would be considered by FDA as a black mark against the efficacy of the product, even if those patients' ailments are much more advanced or severe than those facing the trial participants.

ONE OF THE PRIMARY PROBLEMS WITH RELYING ON HYPER-CONTROLLED CLINICAL TRIALS CAN BE PROPERLY PUT IN CONTEXT BY UNDERSTANDING THE DIFFERENCES BETWEEN STUDYING A TIGER IN THE ZOO VERSUS A TIGER IN THE WILD.

One of the primary problems with relying on hyper-controlled clinical trials can be properly put in context by understanding the differences between studying a tiger in the zoo versus a tiger in the wild. Just as researchers learn more about the tiger living in nature than the tiger in

[5] Antonia-Sophie Skierka and Karin B. Michels, "Ethical principles and placebo-controlled trials – interpretation and implementation of the Declaration of Helsinki's placebo paragraph in medical research," *BMC Medical Ethics*, Volume 19, Issue No. 24, March 15, 2018, https://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-018-0262-9

captivity, pharmaceutical researchers can learn more in the long term by studying drugs used by people in real-world settings, rather than in a clinical trial zoo that relies on testing models from the previous century.

The modern tools revolutionizing medical research today didn't exist in 1962, when lawmakers first mandated FDA certification. In that bygone era, computers were huge, slow, prohibitively costly, and not accessible to individuals. Detailed medical data collection was primitive. Modern diagnostic tools such as MRI machines and IBM's Watson supercomputer, which uses artificial intelligence to analyze data, did not exist. The internet had not yet been created. The human genome had not been sequenced, either, and genetic engineering was still decades away from being developed.

TODAY'S OUTDATED FDA METHODS FOR CERTIFICATION FAIL TO ADEQUATELY LEVERAGE THE AMAZING TECHNOLOGICAL ADVANCEMENTS MADE IN RECENT DECADES IN MEDICINE.

Today's outdated FDA methods for certification fail to adequately leverage the amazing technological advancements made in recent decades in medicine.

2. Tradeoff Evaluation Drug Database

An alternative to the current slow and costly FDA drug certification system is the Free to Choose Medicine (FTCM) model.[6] Under FTCM, after a new drug passes the FDA Phase I safety tests and at least one Phase II efficacy trial, the developer could petition to have an FTCM committee permit the new treatment to become available on the FTCM track. These drugs would be offered provisionally and ultimately be required to receive FDA approval.

Under this model, patients, in consultation with their physicians, could choose to use promising drugs under FTCM or choose the status quo: relying solely on drugs that have already been approved by FDA or waiting for promising drugs to complete lengthy FDA certification.

The FTCM approach echoes and perfects the 1992 "parallel track" established to allow patients suffering from AIDS/HIV to access medications still undergoing Phase II or Phase III efficacy trials.[7] The drug stavudine was approved in 1992 for use on the parallel track. By the time it had received final FDA certification, about three years after the parallel track had been utilized, about 12,000 individuals had already accessed that life-saving medication.[8]

[6] *Ibid.*

[7] Edward Hudgins, "How Extending the AIDS Drug Access Model to Other Diseases Would Save Lives," *Policy Brief*, The Heartland Institute, February 2019, https://www.heartland.org/_template-assets/documents/publications/ParallelTrackPB.pdf

[8] Robert Anderson *et al*., "Design and Implementation of the Stavudine Parallel Track Program," *The Journal of Infectious Diseases*, Volume 171, Supplement 2, March 1995, pp. S118–S122, https://www.

Some critics of the regulatory change that created the parallel track worried it might draw patients away from traditional clinical trials, undermining their validity in the process. A revolutionary part of FTCM that would avoid that perceived problem is the Tradeoff Evaluation Drug Database.

With the TEDD database in operation, patients accessing medications on the FTCM track would have their personal details—age, gender, health history, genetic data, etc.—and their experience with the trial medication recorded by their doctor in the TEDD database, which would include significant privacy protections.

The high-quality information entered into TEDD would be observational data—"real-world data"—that would allow the drug's sponsor, researchers, physicians, and patients to judge which drugs are most promising and efficacious and in which circumstances (e.g., certain subgroups of patients may do especially well or poorly). It would also allow less-promising drugs to be quickly removed, saving patients from experiencing unnecessary pain and suffering. In other words, manufacturers would "fail fast and fail forward," discovering more quickly which new drugs don't work or have limited uses so they could move on to more promising drugs.

The FTCM model would allow drug manufacturers to continue holding traditional clinical trials and use whatever mix of methods seem best to them to certify efficacy. FDA would analyze TEDD data, and the drugs with benefits that outweigh their adverse effects would be granted a new form of FDA approval: "Observational Approval."

Drug manufacturers would then be allowed to charge patients for the drugs used on the FTCM track, permitting smaller but more nimble and innovative researchers to develop new drugs. Currently, smaller companies and many medium-size entities simply cannot afford the $2.9 billion cost it often takes to bring a product from lab to market.

THE FTCM MODEL WOULD ALLOW DRUG MANUFACTURERS TO CONTINUE HOLDING TRADITIONAL CLINICAL TRIALS AND USE WHATEVER MIX OF METHODS SEEM BEST TO THEM TO CERTIFY EFFICACY.

Receipt of Observational Approval would be a huge incentive for insurance companies to choose to reimburse the cost of drugs on the FTCM track. If an FTCM drug is deemed superior to an existing approved drug and has a lower price, it is in the insurance company's economic interest to reimburse patients who purchase these drugs.

Under the FTCM model, manufacturers would be incentivized to keep prices down because extremely high prices would make it difficult to attract patients to use drugs on the FTCM track. In particular, smaller biopharmaceutical companies lacking the financial resources of larger companies would be motivated to use the FTCM track to quickly demonstrate a new drug's treatment results. Breakthrough treatment results would greatly help them raise

jstor.org/ stable/30133583?seq=1#page_scan_tab_contents

much-needed capital to accelerate the development of their pipeline of other potential breakthrough drugs.

TEDD would also encourage the development of innovative ways to demonstrate the efficacy of medicines. Indeed, in recent years, researchers, physicians, patients, and even FDA have increasingly recognized the importance of real-world data, which can, at minimum, be used to supplement randomized clinical trials.

3. Off-Label Uses of Drugs

The pervasive off-label use of drugs serves as an example of how real-world information about a drug's effectiveness can be gathered and utilized.[9] FDA certifies the safety and efficacy of drugs for certain uses. The approved drug's manufacturer is limited to advertising and promoting a product for the FDA-approved use only. But FDA does not dictate which medications physicians must prescribe to patients for particular ailments. This means physicians can prescribe patients FDA-approved medications as part of treatments FDA has not tested or certified.

A 2006 study of a group of commonly used drugs revealed 21 percent were used off-label.[10] Another study's authors found 36 percent of medications used in intensive care units were for off-label uses.[11]

Similarly, physicians sometimes judge a medication only approved for use in one class of patients—elderly patients, for example—works in different doses for other patients. Or they determine that a medication used for one purpose has clinical success in treatment of other ailments. Such findings are often discussed at conferences and in medical journals, alerting physicians to non-FDA-approved uses.

Despite many examples of physicians using drugs for off-label uses, many drug manufacturers have chosen not to seek FDA approval to bring off-label uses "on-label." The primary reason this has occurred is that the FDA certification process for such expanded approval can be extremely costly and time-consuming.

One of the best examples of a non-FDA-approved off-label use is the practice of physicians prescribing aspirin to prevent heart attacks. For years, physicians had been prescribing aspirin for this purpose, even though aspirin manufacturers could not advertise the apparent life-saving benefits of their product until 1998, when FDA approved the use of aspirin as a treatment for

[9] Christopher M. Wittich, Christopher M. Burkle, and William L. Lanier, "Ten Common Questions (and Their Answers) About Off-label Drug Use," *Mayo Clinic Proceedings*, Volume 87, Issue 10, October 2012, pp. 982–990, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/#bib13

[10] S.S. Shah, M. Hall, and D.M. Goodman, "Off-label drug use in hospitalized children," *Arch Pediatric Adolescence Medicine*, Volume 161, Issue 3, 2007, pp. 282–290, https://www.ncbi.nlm.nih.gov/pubmed/17339510

[11] Ishaq Lat *et al.*, "Off-label medication use in adult critical care patients," *Journal of Critical Care*, Volume 26, Issue 1, February 2011, pp. 89–94, https://www.sciencedirect.com/science/article/pii/S0883944110001759?via%3Dihub

heart attacks.[12] In 2014, FDA denied a petition to allow aspirin's on-label use in other cases.[13]

Insurance companies typically choose not to cover the cost of expensive drugs prescribed by physicians for off-label uses, but there have been exceptions, because insurers know that if a drug will likely help a patient avoid future medical bills, it's in their best interest to cover that medication.

In 2008, Medicare rules were somewhat liberalized to allow the system to reimburse off-label uses in more instances. If the federal government, through Medicare, is reimbursing for uses of drugs that FDA has not certified, this certainly calls into question FDA's limitations on off-label communications and highlights FDA's effort to guard its regulatory power.[14]

4. FDA's Adverse Event Reporting System for Updating Labels

When a new drug is approved by FDA to go on the market, not every important detail about its effects on real-world patients is known. Delaying patient access until researchers identify all effects occurring in every conceivable circumstance would add years to the already long certification process. A much more efficient and comprehensive system would rely on real-world data.

For decades, FDA has been tracking after-market experiences with drugs and then periodically updating product labeling, which is crucial for physicians, patients, and researchers alike. The latest iteration of a tracking system, created in 2012, is the FDA Adverse Event Reporting System (FAERS), which "supports the FDA's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products. It contains adverse event reports FDA has received from manufacturers as required by regulation along with reports received directly from consumers and healthcare professionals."[15]

FDA has multiple sources for data. "FDA receives voluntary reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others)."[16] Such reports can be filed electronically. In 2018, health care professionals

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[12] *Federal Register*, Volume 63, Issue 205, October 23, 1998, p. 56,802, https://www.govinfo.gov/content/pkg/FR-1998-10-23/pdf/98-28519.pdf

[13] Leslie Kux, Docket No. FDA-1977-N-0018-2404, May 2, 2014, https://www.regulations.gov/document?D=FDA-1977-N-0018-0101

[14] "Determination of Approved and Accepted Off-label Drug Indications," Noridian Healthcare Solutions, June 5, 2018, https://med.noridianmedicare.com/web/jeb/topics/drugs-biologicals-injections/determination-of-approved-and-accepted-off-label-drug-indications; CMS Manual System, Medicare Benefit Policy, Publication 100-02, Transmittal 96, Change Request 6191, October 24, 2008, https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R96BP.pdf

[15] "FDA Adverse Event Reporting System (FAERS)," fda.gov, U.S. Food and Drug Administration, accessed March 28, 2019, https://www.fda.gov/drugs/informationondrugs/ucm135151.htm

[16] "Questions and Answers on FDA's Adverse Event Reporting System (FAERS)," fda.gov, U.S. Food and Drug Administration, accessed March 28, 2019, https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.htm

and consumers filed 2,156,854 reports. From 1968 through 2018, 16,996,785 reports were registered.[17] FDA's Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research review the reports and then issue updated periodic labeling and use information, safety warnings, and, if needed, product recalls.

FDA classifies certain cutting-edge drugs with particular molecular arrangements as new molecular entities.[18] From 2002 to 2014, FDA approved 278 such drugs. During that period, 703 label updates were made to drugs in that treatment group, for issues such as adverse reactions and interactions with other drugs.

Important data collected apart from clinical trials that complement FAERS can be accessed by FDA and the public through its Sentinel Initiative, which was created in 2008.[19] "Through Sentinel, the FDA can rapidly and securely access information from large amounts of electronic healthcare data, such as electronic health records (EHR), insurance claims data and registries, from a diverse group of data partners."[20] One of FDA's goals for the years ahead is to "leverage the Sentinel System to accelerate access to and broader use of Real-World Data … for Real-World Evidence … generation."[21]

FDA's Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research review the reports and then issue updated periodic labeling and use information, safety warnings, and, if needed, product recalls.

While the public has officially had access to FAERS data for a decade, retrieving information has been a complex task. In 2014, to make the FAERS system more easily accessible to the public, FDA created an application programming interface (API) through its "openFDA" initiative.[22] This system was supposed to allow the public to more easily search for drug information, instead of being required to wade through immense amounts of raw data. However, one study identified problems with the updated system that have likely introduced inaccuracies. For example, "the number of adverse events reports retrieved by the API for

[17] "FDA Adverse Event Reporting System (FAERS) Public Dashboard," fda.gov, U.S. Food and Drug Administration, accessed March 25, 2019, https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

[18] "Novel Drug Approvals for 2018," fda.gov, U.S. Food and Drug Administration, accessed March 25, 2019, https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm

[19] "Background," Sentinel Initiative, accessed March 28, 2019, https://www.sentinelinitiative.org/background

[20] "FDA's Sentinel Initiative," fda.gov, U.S. Food and Drug Administration, accessed March 28, 2019, https://www.fda.gov/safety/fdassentinelinitiative/ucm2007250.htm

[21] Sentinel Initiative, *supra* note 19.

[22] "About the openFDA API," fda.gov, U.S. Food and Drug Administration, accessed March 28, 2019, https://open.fda.gov/apis

a particular drug can differ from the FAERS data files due to the open FDA harmonization process and the existence of multiple entries and variations for any given drug name in the FAERS data files."[23]

While FAERS and openFDA are important for researchers and patients alike who are looking for real-world data, one problem is that they both originated in FDA. Government agencies, even with the most well-meaning staff and professionals, are trained to follow bureaucratic rules and procedures rather than what might be the most efficient and entrepreneurial path that would benefit patients. As will be shown below, the attempt to track after-market use of medical devices seems to be on a sounder path because it involves a public-private partnership, rather than relying principally on government. It could also be the case that because the FDA system for tracking after-market use of drugs has evolved over time, with FDA "innovating on the run," the system is on the right path but still needs refining. Developing accurate ways to log and curate data remains an important ongoing challenge.

5. The Real-World Data and Evidence Revolution

While the FAERS initiative works to refine its tracking system for post-market products using real-world data, patients have developed and refined their own real-world data sharing operations for years. In the 1980s, when AIDS/HIV killed tens of thousands of individuals per year, information as well as promising medications were exchanged among those suffering from the ailment, as depicted in the Hollywood film *Dallas Buyers Club*.[24] Today, patientslikeme.com, which began as a social network for people with ALS, now allows sufferers of other serious illnesses to exchange personal data—including their use of prescription drugs, side effects, and information about what seems to help (or doesn't help) to improve their health.[25]

Indeed, the real-world data and evidence revolution in medical testing is growing at a rapid pace. A recent article, which focuses primarily on cancer treatments, published in *Clinical Pharmacology & Therapeutics* put it well:

> The role of real-world evidence (RWE) in regulatory, drug development, and healthcare decision-making is rapidly expanding. Recent advances have increased the complexity of cancer care and widened the gap between randomized clinical trial (RCT) results and the evidence needed for real-world clinical decisions. Instead of remaining invisible, data from the >95% of cancer patients treated outside of clinical trials can help fill this void.[26]

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[23] Jennifer Shin, "Investigating the accuracy of the openFDA API using the FDA Adverse Event Reporting System (FAERS)," 2014 IEEE International Conference on Big Data, October 2014, https://ieeexplore.ieee.org/abstract/document/7004412

[24] Edward Hudgins, *supra* note 7.

[25] "Welcome to PatientsLikeMe," Patientslikeme.com, accessed April 17, 2019, http://www.PatientsLikeMe.com

[26] Rebecca A. Miksad and Amy P. Abernethy, "Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality," *Clinical Pharmacology & Therapeutics*, Volume 103,

While still maintaining that "[for] new oncology therapeutics, conventional [randomized clinical trials] remain the gold standard," the authors of the *Clinical Pharmacology & Therapeutics* article further acknowledged that such clinical trials "produce efficacy and safety results for narrow patient populations, circumscribed clinical settings, and limited drug combinations." They conclude, "By expanding data sources, regulatory-grade RWE can provide critical information needed by clinicians, patients, and regulatory bodies to make informed decisions."[27]

The authors devote much attention to the technicalities of converting real-world data into real-world evidence—curating, harmonizing, and summarizing data to make them useful for researchers, regulators, physicians, and patients. This is a vital task. The real-world evidence created from data should be high-quality, complete, transparent, generalizable, timely, and scalable.[28] Meeting these criteria is a major challenge for FDA's FAERS system.

The study's authors also offer that rigorous real-world evidence "may generate unique hypotheses for future basic science, drug development, health outcomes, and clinical research."[29] This is a crucial point about the potential benefits that would be provided by a full-blown, efficient TEDD system. Such real-world evidence wouldn't only help FDA keep labeling information up to date, it would help researchers in their quest to develop and identify more-effective medications. Indeed, concerning the development of treatments, the authors wrote that "a new oncology therapeutic faces multiple go/no-go decision points. Scientific and safety standards always have primacy. However, limited resources mean some good drugs are never fully explored. By clarifying real-world unmet needs, RWE may help optimize decisions during predevelopment and guide clinical development strategies."[30]

This is a validation of a central tenet of TEDD. Real-world data producing real-world evidence can help researchers move more quickly and create ways to explore and develop new treatments and cures. Further, "During clinical development, RWE may also inform clinical trial design and conduct. RWE about specific populations (e.g., renal cell carcinoma patients with asymptomatic brain metastases) may help avoid unnecessarily restrictive exclusion criteria."[31]

Put more simply, some of the shortcomings of clinical trials would be minimized by expanding the use of real-world evidence.

6. Medical Device Information Consortium and NESTcc Database

The potential of real-world data and real-world evidence is perhaps best displayed by the Med-

Number 2, February 2018, p. 202, https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.946

[27] *Ibid.*, p. 203.

[28] *Ibid.*, p. 204.

[29] *Ibid.*, p. 203.

[30] *Ibid.*

[31] *Ibid.*

ical Device Innovation Consortium (MDIC).[32] The MDIC seeks to track the experiences of patients using already FDA-certified medical devices, both to inform patients which devices might work best for them and to help device developers to improve their products in the future.

The safety and efficacy of medical devices is certified by FDA's Centers for Devices and Radiological Health. Devices include everything from heart valves to knee replacements. Although the specific criteria required for FDA device certification differ somewhat from the criteria that must be met to certify drugs, the general requirements—demonstrating safety as well as efficacy—are similar.

THE SAFETY AND EFFICACY OF MEDICAL DEVICES IS CERTIFIED BY FDA'S CENTERS FOR DEVICES AND RADIOLOGICAL HEALTH.

But as with certifying drugs, certifying medical devices through preferred FDA trials has serious shortcomings. A March 2019 article explained, "Characteristics of medical devices have made the implementation of randomized controlled trials challenging. These include iterative and rapid changes in device design, the need to account for the role of operator expertise in clinical outcomes, and challenges in implementing blinding and using placebos."[33]

This was part of the impetus for the creation of MDIC, which is "the first-ever public-private partnership created with the sole objective of advancing medical device regulatory science for patient benefit. Formed in late 2012, MDIC brings together representatives of the FDA, [National Institutes of Health], [Centers for Medicare and Medicaid Services], industry, non-profits, and patient organizations to improve the processes for development, assessment, and review of new medical technologies."[34]

MDIC activities fall into four categories. The first, "Clinical Science" initiatives, attempts "to address the biggest barriers to collecting adequate clinical evidence in the support of new medical technology by creating blueprints for innovative clinical trials techniques, developing standards and metrics for effective clinical trial designs and encouraging the collection of adequate and appropriate clinical and patient preference data."[35]

The second, "Health Economics and Patient Access" initiatives, "aim to create predictability and transparency of evidentiary requirements for coverage and improve pathways for coverage, coding and payment to speed patient

[32] "Mission & Purpose," Medical Device Innovation Consortium, accessed March 28, 2019, https://mdic.org/about/mission-purpose

[33] Rachael L. Fleurence and Jeffrey Shuren, "Advances in the Use of Real-World Evidence for Medical Devices: An Update From the National Evaluation System for Health Technology," *Clinical Pharmacology & Therapeutics*, March 19, 2019, https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1380

[34] Medical Device Innovation Consortium, *supra* note 32.

[35] "Clinical Science," Medical Device Innovation Consortium, accessed March 28, 2019, https://mdic.org/initiative/clinical-science

access and amplify the patient voice in selection of treatment options."[36]

The third category, "Data Science and Technology" initiatives, "aim to fulfill the promise of advances in data analysis by creating tools and methods to use advanced data analysis techniques and new technology to accelerate the collection of clinical data, remove barriers to patient access and monitor product safety, quality and effectiveness."[37]

Especially important in this category is the "external evidence methods" initiative, which attempts to establish the best ways to use methods "such as new, innovative (Frequentist/Bayesian) methods and the cataloging of existing methods for evidence fusion from data external to a clinical trial. External trial data includes, but is not limited to, real-world data (RWD), real-world evidence (RWE), engineering modeling and simulation, similar device clinical trial data, to support regulatory medical device decisions and other stakeholder decisions."[38] This initiative seeks alternatives that attempt to mitigate or make up for shortcomings of randomized clinical trials.

The fourth category, the National Evaluation System for Health Technology Coordinating Center (NESTcc), might provide the most important information for those considering the proposed TEDD system. The authors of one study aptly explained the need for NESTcc in the following passage: "For many devices … practical limitations related to the device or disease condition require alternative approaches to conducting large, randomized, controlled, double-blind studies and increased flexibility in trial design and statistical analysis. For example, it may be infeasible to conduct a blinded trial of an implantable device because it is impractical or unethical to use a sham control for the target patient population owing to the risk of the implantation or procedure itself."[39]

NESTcc seeks to establish a well-functioning system of real-world data and evidence to track after-market device use. This information is meant to help patients make educated choices and to assist researchers with their ongoing efforts to develop products.[40] About 195 hospitals and 3,942 outpatient clinics are partners in this effort.[41] Patient groups are involved as well. Marc Boutin, CEO of the National

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[36] "Health Economics and Patient Access," Medical Device Innovation Consortium, accessed March 28, 2019, https://mdic.org/program/health-economics-patient-access

[37] "Data Science & Technology," Medical Device Innovation Consortium, accessed March 28, 2019, https://mdic.org/initiative/data-science-and-technology

[38] "External Evidence Methods," Medical Device Innovation Consortium, accessed March 28, 2019, https://mdic.org/program/external-evidence-methods

[39] Owen Faris and Jeffrey Shuren, "An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials," *The New England Journal of Medicine*, Volume 376, Issue 14, April 6, 2017, p. 1,351, https://www.mfprac.com/web2018/07literature/literature/Cardiology/HxPacemakers_Faris.pdf

[40] NEST Coordinating Center, nestcc.org, NEST Coordinating Center, accessed March 28, 2019, https://nestcc.org

[41] "NESTcc Network Collaborators," nestcc.org, NEST Coordinating Center, accessed March 28, 2019, https://nestcc.org/about/network-collaborators

Health Council and a strong patient advocate, is on NESTcc's governing committee.[42]

The NESTcc data-monitoring system is still in development, and its leaders are trying to solve some of the problems that developed within the FAERS system. Partner institutions "have made large financial and human resource investments into the collection, curation, and organization of their data to assure it is research grade with financial support from federal, private, and nongovernmental sources."[43]

Further, "In order to demonstrate proof-of-concept for the generation of robust [real-world evidence], NEST is funding several rounds of test cases."[44] NESTcc launched eight test cases in the fall of 2018. They involve a range of medical devices. Results for these cases are expected in 12–18 months. Other test cases are expected to launch in 2019. NESTcc is also considering a plan to "Expand the Data Network and explore options for using data sources outside the U.S."[45]

NESTcc, FAERS, and the Sentinel Initiative are essentially acknowledgments by FDA and the pharmaceutical industry of the severe limitations of the randomized clinical trial model. These efforts to track safety and efficacy after drugs and devices are certified are commonsense actions that strongly suggest that real world data via TEDD is needed for the initial certification process.

7. The Case for TEDD

The importance of reforming FDA's certification process to facilitate medical innovation based on the use of data and new technology was made manifest in the release by outgoing FDA Commissioner Scott Gottlieb of his "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)."[46] In his solicitation for comments regarding the proposed framework, Gottlieb rightly observed, "Artificial intelligence and machine learning have the potential to fundamentally transform the delivery of health care."

Gottlieb also noted, "The ability of artificial intelligence and machine learning software to learn from real-world feedback and improve its performance is spurring innovation and leading to the development of novel medical devices."[47] The same observation applies to the development of drugs and medications.

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[42] "Governance," nestcc.org, NEST Coordinating Center, accessed March 28, 2019, https://nestcc.org/about/governance

[43] Rachael L. Fleurence and Jeffrey Shuren, *supra* note 33.

[44] *Ibid.*

[45] "Strategic & Operational Planning: 2017–2022," nestcc.org, NEST Coordinating Center, Version I, January 2019, p. 6., https://nestcc.org/wp-content/uploads/2019/01/NESTcc-Strategic-and-Operational-Plan-2019-v1

[46] "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)," U.S. Food and Drug Administration, April 2019, https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/SoftwareasaMedicalDevice/UCM635052.pdf

47 "Statement from FDA Commissioner Scott Gottlieb, M.D. on steps toward a new, tailored review

The precursors of TEDD have already been developed or are in development, most notably with FAERS, the Sentinel Initiative, and MDIC. But such systems are also seen outside of FDA.

The government-run National Cancer Institute's Genomic Data Commons seeks "to provide the cancer research community with a unified data repository that enables data sharing across cancer genomic studies in support of precision medicine."[48]

IHIE HANDLES MILLIONS OF TRANSACTIONS EVERY DAY, SHOWING IT'S POSSIBLE TO CREATE AND MANAGE A ROBUST TEDD SYSTEM.

The Indiana Health Information Exchange (IHIE) attempts to make it "possible for everyone on your [the patient's] healthcare team … to get the information they need to give you the best possible care."[49] IHIE handles millions of transactions every day, showing it's possible to create and manage a robust TEDD system.

The Observational Health Data Science and Informatics group is "a multi-stakeholder, interdisciplinary collaborative that is striving to bring out the value of observational health data through large-scale analysis. Our research community enables active engagement across multiple disciplines … and spans multiple stakeholder groups (e.g., researchers, patients, providers, payers, product manufacturers, regulators."[50]

Tempus is "a technology company that is making precision medicine a reality by gathering and analyzing clinical and molecular data at scale. Through the power of artificial intelligence, we believe all patients will eventually be on their own personalized therapeutic path, enabling longer and healthier lives."[51,52]

Real-world data collecting and collating systems are now in place that help to provide the information researchers need to develop new cutting-edge medications and cures, which will eventually go to FDA for certification. Additionally, FDA already has such systems in place to monitor the after-market effectiveness of products that have successfully made their way through the long, costly FDA Phase II and Phase III clinical trials processes.

Such a system needs to be in place to collect and collate real-world data to effectively and

framework for artificial intelligence-based medical devices," U.S. Food and Drug Administration, April 2, 2019, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635083.htm

[48] "About the GDC," Genomic Data Commons, National Cancer Institute, accessed April 22, 2019, https://gdc.cancer.gov/about-gdc

[49] Indiana Health Information Exchange, ihie.org, accessed April 15, 2019, https://www.ihie.org

[50] "Who We Are," Observational Health Data Science and Informatics, ohdsi.org, accessed April 15, 2019, https://ohdsi.org/who-we-are

[51] A recent survey by Simon Smith found "127 Startups Using Artificial Intelligence in Drug Discovery." See Simon Smith, "129 Startups Using Artificial Intelligence in Drug Discovery," BenchSci.com, March 3, 2019, https://blog.benchsci.com/startups-using-artificial-intelligence-in-drug-discovery#step13

[52] Tempus.com, Tempus, accessed April 16, 2019, https://www.tempus.com

efficiently test the efficacy of proposed new treatments and cures, to fill the hole between pre-clinical development and post-market use. TEDD, as an integral part of FTCM, is that system.

The TEDD system would, in effect, extend to the pre-certification phases of drug testing the powerful system of real-world data collection being employed now for after-market monitoring of drugs and medical devices. Such monitoring is an extension of earlier phases, so why not extend the innovative system to all phases?

TEDD is a simple, elegant system that would perform many of the functions that are currently scattered among numerous data collection systems. Most importantly, the real-world data provided by TEDD would allow drug developers and manufacturers to discover more quickly which products are the least and most promising. This means developers and manufacturers could succeed sooner by failing faster—that is, by weeding out those less-effective products.

TEDD IS A SIMPLE, ELEGANT SYSTEM THAT WOULD PERFORM MANY OF THE FUNCTIONS THAT ARE CURRENTLY SCATTERED AMONG NUMEROUS DATA COLLECTION SYSTEMS.

This time- and money-saving aspect of TEDD would be especially beneficial because it would encourage and facilitate investment and development in new drugs by smaller, more nimble entrepreneurs and companies that don't have the deep pockets to absorb the nearly $3 billion it currently costs to bring new products from the lab to market. Allowing developers to charge for their new drugs available on the FTCM track is a critically important incentive for developers to put their pharmaceuticals on the FTCM track, eventually leading to a system that would offer for all patients better drugs, sooner, and at lower costs.

Modern medical research relies on collecting and utilizing real-world data, and that reliance will surely grow in the coming years and decades. Breakthrough medications developed by new technologies will no doubt require innovative ways to certify efficacy beyond FDA's standard clinical trials. Establishing TEDD, a core element of the FTCM path, would enable informed choice and deliver the benefits of fast-paced knowledge-building to the entire drug development, testing, and approval processes.

Conclusion

In the wake of the modern technological revolution, Americans have increasingly taken more responsibility for their own health. People seek second opinions when given an evaluation of a serious illness. They spend hours online or on the phone researching possible treatments and cures for themselves or their sick children. They use websites to look up the benefits and adverse side effects of particular medications. They join patient groups and associations that share information that helps pinpoint preferred treatments and possible cures. In modern America, patients regularly take their health care into their own hands.

One of the primary justifications originally given for the creation of FDA's tight control over drug approval was the belief patients did not have ac-

cess to relevant scientific data and generally could not be knowledgeable enough to evaluate such data even if it were available. Today, technology makes medical and health care data available and affordable, and Americans and their doctors are tech savvy and sophisticated enough to evaluate much of the information.

Rather than remaining frozen in the world of 1962, when government bestowed on FDA its current powers to restrict access to drugs, Congress or the executive branch should adopt the FTCM model, a modern system for approving cures of the future, thereby giving patients freedom of choice, including the freedom for early access to promising new drugs and the real-world data they and their doctors need to choose the treatment that is in their best interests.

The Free to Choose Medicine track option would empower them to make those life-enhancing and life-saving choices. Now, more than ever, Americans need—and, indeed, deserve—these important reforms.

Effectively developing and designing new drugs and medical therapies in the twenty-first century and beyond will require optimizing the use of all the information possible about proposed treatments. This means not only garnering information from the restrictive randomized clinical trials preferred by FDA, but also from the real-world data that can only be collected when patients use treatments in real-world situations. The FTCM track option for drugs that have passed FDA's Phase I safety tests and at least one Phase II efficacy trial would allow such data to be collected and utilized through FTCM's TEDD system. Most importantly, it would grant to millions of individuals suffering from serious illnesses the freedom to take their health into their own hands, by giving them the power to try safe and promising medications they judge will best treat their illnesses.

Although clinical trials are important tools for gauging the efficacy of medications, they have always had their shortcomings, especially long waits for patients suffering without access to curative and life-saving medications. Information about the efficacy of medications garnered outside of such trials have been recognized and utilized for years by physicians who prescribe FDA-approved drugs for off-label uses not certified by FDA. Further, the advent of new information systems, large databases, powerful computation speeds, artificial intelligence, and new medical tools such as bio-hacking highlight the need for a system that can harness real-world data and give patients and their doctors the option to quickly access safe and promising cutting-edge medications.

Too many patients suffer and die because of FDA's outmoded certification system. The Tradeoff Evaluation Drug Database would make available the real-world data and evidence patients and doctors need to make treatment decisions, and the Free to Choose Medicine track option would empower them to make those life-enhancing and life-saving choices. Now, more than ever, Americans need—and, indeed, deserve—these important reforms.

About the Author

Edward Hudgins, Ph.D., is the research director of The Heartland Institute.

In conjunction with other department directors, Hudgins sets the organization's research agenda and priorities; works with in-house and outside scholars to produce *Policy Studies*, *Policy Briefs*, and books; contributes his own research; and works with Heartland staff to promote Heartland's work.

Before joining Heartland, Hudgins was the director of advocacy and a senior scholar at The Atlas Society, which promotes the philosophy of reason, freedom, and individualism developed by Ayn Rand in works such as *Atlas Shrugged*. His latest Atlas Society book was *The Republican Party's Civil War: Will Freedom Win?*

While at The Atlas Society, Hudgins developed a "Human Achievement" project to promote the synergy between the values and optimism of entrepreneurial achievers working on exponential technologies and the values of friends of freedom.

Prior to this, Hudgins was the director of regulatory studies and editor of *Regulation* magazine at the Cato Institute and a senior economist at the Joint Economic Committee of the U.S. Congress, specializing in trade and regulatory issues.

Hudgins also worked at The Heritage Foundation as deputy director for domestic policy studies and as the director of the Center for International Economic Growth, where he pioneered the concept of an Index of Economic Freedom.

Hudgins has appeared on numerous major TV networks, including CSPAN, Fox News, MSNBC, The History Channel, and CNN, and his op-eds have been featured in papers like the *Washington Times*, *Wall Street Journal*, *Boston Globe*, and *Philadelphia Inquirer*.

Hudgins earned a bachelor's degree in government from the University of Maryland, a master's degree in political theory from American University, and a Ph.D. in political philosophy and international political economy from the Catholic University of America. He has taught at universities in Germany and the United States.

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Our mission is to discover, develop, and promote free-market solutions to social and economic problems. Three things make Heartland unique among free-market think tanks:

- We communicate with more national and state elected officials, more often, than any other think tank in the United States. We contacted elected officials 812,789 times in 2018.
- We produce four monthly public policy newspapers—*Budget & Tax News*, *Environment & Climate News*, *Health Care News*, and *School Reform News*—which present free-market ideas as news rather than research or opinion.
- We promote the work of other free-market think tanks on our websites, in our newspapers, at our events, and through our extensive government and media relations. No other institution does more to promote the work of other think tanks than we do.

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