A matter of choice

Free to choose medicine in the 21st century

The US Food and Drug Administration's system for medicine approval is lengthy and expensive, and only 1 in 12 drugs in human clinical trials obtain approval. Bartley J Madden of the Madden Center for Value Creation at Florida Atlantic University proposes an alternative free to choose medicine (FTCM) pathway. He suggests that with the advice of their doctors, patients should have the right to access drugs for serious or life-threatening medical conditions that have received provisional approval based on initial demonstrations of safety and efficacy. The Promising Pathway Act, which incorporates principles of FTCM, has been introduced in the US government senate and house with bipartisan support and may well be sent to President Biden to sign in 2024.

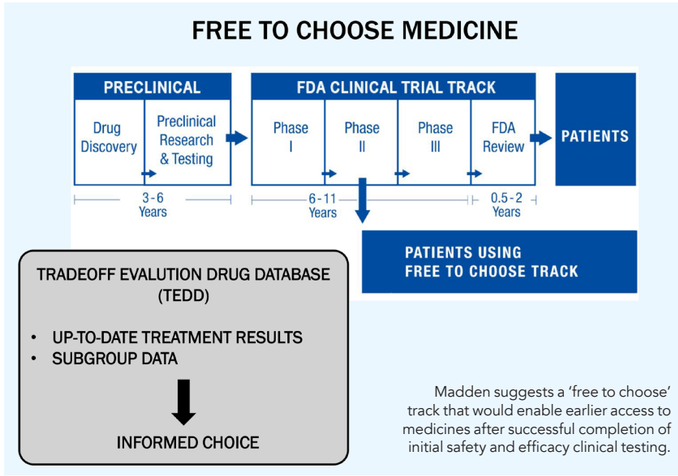
The USA's pharmaceutical watchdog, the Food and Drug Administration (FDA), evaluates safety and efficacy drug data, and approves medicines when the benefits of a drug are shown to outweigh the risks. However, increasingly stringent rules and regulations mean that clinical trials take longer and cost more than ever before. In his published work, Bartley J Madden, Research Fellow at the Madden Center for Value Creation at Florida Atlantic University, USA, highlights the challenges of translating basic science into available drugs. For over two decades, he has called for reform of this process. We take a closer look at his free to choose medicine (FTCM) model that is currently packaged as the Promising Pathway Act under consideration in the USA senate and house.

Madden believes that to avoid negative publicity and blame associated with approving drugs with adverse side effects, the FDA has become very risk adverse and cautious. The result? Patients undergo more tests in longer clinical trials at higher cost. Madden argues that although the FDA is criticised for approving any drugs with negative side effects, they are rarely confronted for denying quicker access to potential life-saving drugs, resulting in what he describes as 'an invisible graveyard'. He calls for an alternative pathway where people are offered the right to choose earlier access to medicines.

THE STATUS QUO

Madden has a background in economics and finance and developed a passion for systems thinking years ago. In a 2020 interview, he emphasised the importance of knowing the purpose of a system and the need to focus on fixing the key constraint degrading performance. He explained, 'better drugs sooner at lower costs should be the purpose of the FDA's regulatory system', and that the extensive time and cost of the drug approval system is the key constraint that needs addressing. Madden believes the FDA's sole focus on safety and efficacy has led to 'the system goal of delivering better drugs to patients, sooner, and at lower cost' not being achieved.

Madden acknowledges the importance of ensuring safety, but the estimated $1.8 billion cost and length of time from drug discovery to FDA approval (10–15 years) causes approved drugs to be excessively expensive and slows innovation. Drug developers may never start highly innovative projects because of an excessively long time to earn a return on their investment. To no surprise, biopharmaceutical startup companies are viewed as extraordinarily high risk by venture capital firms. This means less investment and less innovative new drugs to help patients. However, the opportunity for early success with patients via provisional-approval drugs and early commercialisation would significantly reduce the investment risk and, in particular, lead to a boost in venture capital investments for startup biopharmaceutical companies.



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Randomised clinical trials (RCTs) are the 'gold standard' for assessing drug effectiveness. Madden acknowledges the statistical power of RCTs but makes the point that no drug can be proven 100% safe, and nobody truly knows the right amount of regulation. Critics of FTCM argue that extensive RCTs are needed to ensure safety and test efficacy, but Madden counteracts this by stressing that RCTs are performed in homogeneous populations (those with similar characteristics) in a controlled environment and not always reflective of the diversity in real life. There is also the ethical dilemma in RCTs that usually half or a portion of patients receive the placebo and not the experimental drug. Madden doesn't believe that valuable information about a drug can only be obtained from RCTs. He uses the example of FDA approved drugs being prescribed 'off-label' by doctors to treat diseases other than that for which the drug was approved. The frequent success of this off-label prescribing, Madden argues, illustrates that useful medical knowledge can be gained outside of RCTs.

FREE TO CHOOSE MEDICINE PATH

Madden's belief is that we are all unique with our own health conditions and risk tolerance, and should therefore have the right to choose our treatment. He reasons that some of us will opt for the most stringent safety tests and approval processes as per the FDA's processes; others may wish to access drugs earlier in the process despite risks due to the opportunity for potential life-changing treatments not otherwise available.

BUT HOW WOULD THE FREE TO CHOOSE PATHWAY WORK?

Madden suggests a dual-track system where a 'free to choose' track runs parallel to the existing FDA process. The free to choose track would enable earlier access to medicines after successful completion of initial safety and efficacy clinical testing. Essentially, after a drug has successfully completed phase 1 safety tests in healthy people and one or more phase II safety/efficacy trials (conducted on individuals with the disease), the drug developer could request that the drug move to a free to choose track. This skips out phase 3 efficacy trials where a larger number of patients receive either the drug, placebo, or standard care to demonstrate efficacy. This could occur in parallel with the standard FDA process or could be on the free to choose track only with real-time results guiding future direction.

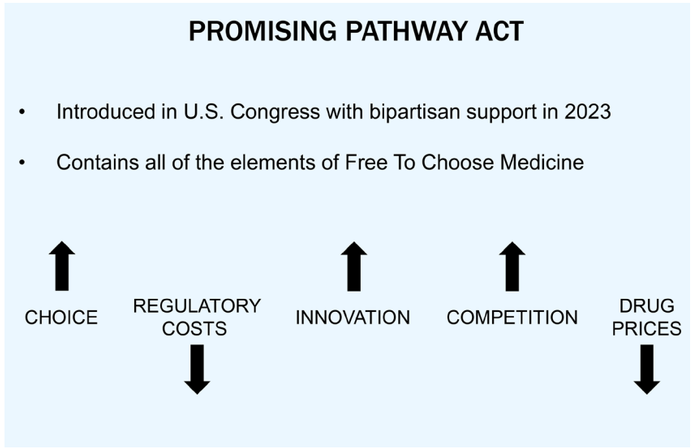
A drug on the FTCM track is given provisional approval dependent upon generating satisfactory safety and efficacy data in actual use. Especially strong real-

MARKET-BASED SOLUTION ... FUNDAMENTALLY BIPARTISAN

"Madden's market-based solution appeals to economists like me who are keenly aware of the critical importance of institutional design for a **system to promote decentralized responses close to the local knowledge that is available to physicians and their patients, but not to the FDA. This book is fundamentally bipartisan and should be read in that spirit.**"

Vernon L. Smith
Chapman University
Nobel Laureate in Economics, 2002

Madden acknowledges the unique risks of individual health conditions and believes that people should have the right to choose their treatment.



The Promising Pathway Act that would implement FTCM principles requires insurance companies to treat provisional-approval drugs the same as conventional-approval drugs.

world data could lead to full approval by the FDA. These real-world results could be housed in a Tradeoff Evaluation Drug Database (TEDD). The TEDD would contain data for provisional approval drugs including anonymised patient characteristics and their treatment results. Keeping track of the drug in real time (an order of magnitude faster than clinical trial data dissemination) can inform both physicians, patients, and drug developers about the drug's safety and efficacy as well as providing data-driven insights leading to better R&D decisions by the biopharmaceutical industry.

The system would be dynamic and self-adjusting so that if a treatment is

According to Madden, TEDD would be managed by a separate authority not linked to the FDA and stipulates that not every drug that passes early testing would be eligible for the free to choose pathway. An advisory committee would assess the suitability of drugs for FTCM and monitor the TEDD for drugs whose risks exceed their benefits.

Discussions between doctors and patients, informed by TEDD treatment results, would address the risk and benefits of a provisional-approval drug from the patient's perspective. There would be legal implications as physicians would need to be given immunity from any malpractice claim as well as

This free to choose track would enable earlier access to medicines after successful completion of initial safety and efficacy clinical testing.

showing safe effective results more people (potentially much higher numbers than in clinical trials) will use it, providing more treatment outcome data. Usage would plummet for provisional-approval drugs that are not effective. In a world of technological innovations and ability to manage big data, TEDD would contain a wealth of genetic and biomarker information that would enable real-time monitoring of drugs and identification of subpopulations who significantly benefit from the drug (or not).

drug developers from design defect accusations or claims that they didn't warn of side effects.

Madden advocates for the economic benefits of this system, suggesting that the free to choose track would enable biopharmaceutical companies, especially smaller companies and startups, to attract more investment. He says FTCM would lower drug prices as a result of heightened competition due to the accelerated opportunity for commercialisation and the need for attracting patients to generate TEDD data. Importantly, the Promising Pathway Act that would implement FTCM principles requires insurance companies to treat provisional-approval drugs the same as conventional-approval drugs and that means insurance reimbursement for clearly effective provisional drugs.

WHAT ABOUT THE CRITICS?

In his 2020 paper, *Science on FDA Liberalization: A Response to the Status Quo Process for Medical Treatments*, Madden gives his rebuttal to scrutiny of FTCM addressing many of the criticisms. From a safety perspective, Madden argues that safety concerns and side effects may well be identified sooner in FTCM drugs because of the real-world data in a heterogeneous population more likely to register side effects as opposed to a tightly controlled homogeneous population like in clinical trials.

Many critics believe patients and doctors do not have the knowledge to make decisions about using provisional-approval drugs. Madden, however, reminds us that the current FDA regulatory system was established with legislation in 1962. Much has changed. Today's internet capabilities, big data analytics, and AI-enabled software constitute a far different environment than the technology in 1962. Current technology is ideally suited for evaluating real-world data in TEDD, identifying subgroups of patients who achieve highly successful (or not) treatment results, and assisting doctors and patients in making informed decisions.

Implementation of FTCM principles is a solution for a long-overdue upgrade to our regulatory process attuned to modern technology. This is reflected in bipartisan momentum supporting the Promising Pathway Act introduced into the USA's senate and house for consideration. Will this FTCM paradigm mark a monumental shift in regulatory mindset, FDA reform, and accelerated access to the most innovative and effective new medicines? Madden believes that patients would certainly benefit.

Behind the Research

Bartley J Madden

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Research Objectives

Bartley J Madden's work on a structural improvement to the FDA's drug approval process has spanned 20 years.

Detail

Bio

Bartley J Madden is a Research Fellow at the Madden Center for Value Creation at Florida Atlantic University. His work is interdisciplinary and connects value creation, knowledge building, and systems thinking. It is summarised in *Value Creation Principles: The Pragmatic Theory of the Firm Begins with Purpose and Ends with Sustainable Capitalism*.

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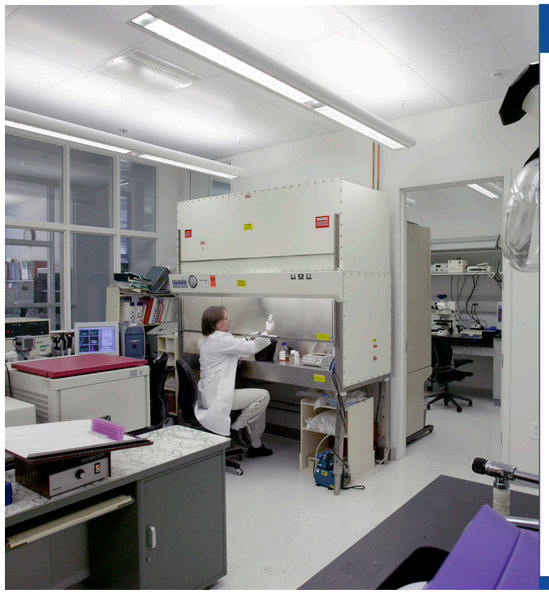

Personal Response

Can you explain for readers unfamiliar with the US legislation what this means now that the Promising Pathway Act has been introduced to the senate and house and what the next steps are?

"The Promising Pathway Act (PPA) in the USA Congress has bipartisan support because the fast pace of medical innovation requires regulatory innovation that ensures patients have the opportunity to quickly access especially promising new drugs that can improve or even save a life. The PPA empowers patients, advised by their doctors, to make informed decisions on the early use of provisional-approval drugs based on up-to-date treatment results. Importantly, these decisions reflect each patient's personal health condition and personal risk preference – information unavailable to the FDA. Those patients comfortable with delayed access but less risk simply continue using conventional FDA-approved drugs. Freedom to choose medical treatments would be a major step in achieving better drugs, sooner, at lower cost. In 2024, PPA supporters will push for committee hearings and a vote."