FREE TO CHOOSE MEDICINE
and
RIGHT TO TRY

Bartley J. Madden

www.FreeToChooseMedicine.com

The most up-to-date version will be posted on SSRN.

Free To Choose Medicine can deliver the power

of informed choice about
life-changing drug treatments

to every American.

“BOTH MY SONS DESERVE TO LIVE”

Jenn McNary, mother of two boys suffering from Duchene muscular dystrophy

This is a muscle-wasting disease that afflicts young boys and invariably leads to death in their early 20s. Eteplirsen—a drug not yet approved by the FDA—has resulted in dramatic improvements for boys in clinical trials. Max was treated with Eteplirsen and now plays on a soccer team. His older brother, Austin, was deemed ineligible for the clinical trial.

While many consider giving a placebo to boys as part of a randomized control trial as simply unethical, nevertheless, the lack of such data has resulted in *endless delays by the FDA in approving this drug.* Free To Choose Medicine solves this problem.

Austin suffered permanent loss of basic bodily functions during the 170 weeks before finally receiving the drug in a new clinical trial likely started due to the news media attention his mother generated.

UNDERSTANDING FDA MOTIVATION

"In the early 1980s, when I headed the team at the FDA that was reviewing the NDA for recombinant human insulin, the first drug made with gene-splicing techniques, we were ready to recommend approval a mere four months after the application was submitted (at a time when the average time for NDA [New Drug Application] review was more than two and a half years). With quintessential bureaucratic reasoning, my supervisor refused to sign off on the approval – even though he agreed that the data provided compelling evidence of the drug's safety and effectiveness. If anything goes wrong, he argued think how bad it will look that we approved the drug so quickly."

Henry I. Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration,* 2000.

UNDERSTANDING FDA MOTIVATION

"In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them… The message to FDA staff could not be clearer."

Former FDA Commissioner Alexander M. Schmidt

Quoted in Sam Kazman, "Drug Approvals and Deadly Delays," *Journal of American Surgeons*, 15(4), 2010.

DEADLY OVER-CAUTION

- FDA gives enormous weight to avoiding negative publicity about unanticipated adverse side effects from approved drugs.

- Relentless demand for ever more extensive clinical trials causes significant delays in our access to the most innovative medicine as well as sky-high prescription drug prices.

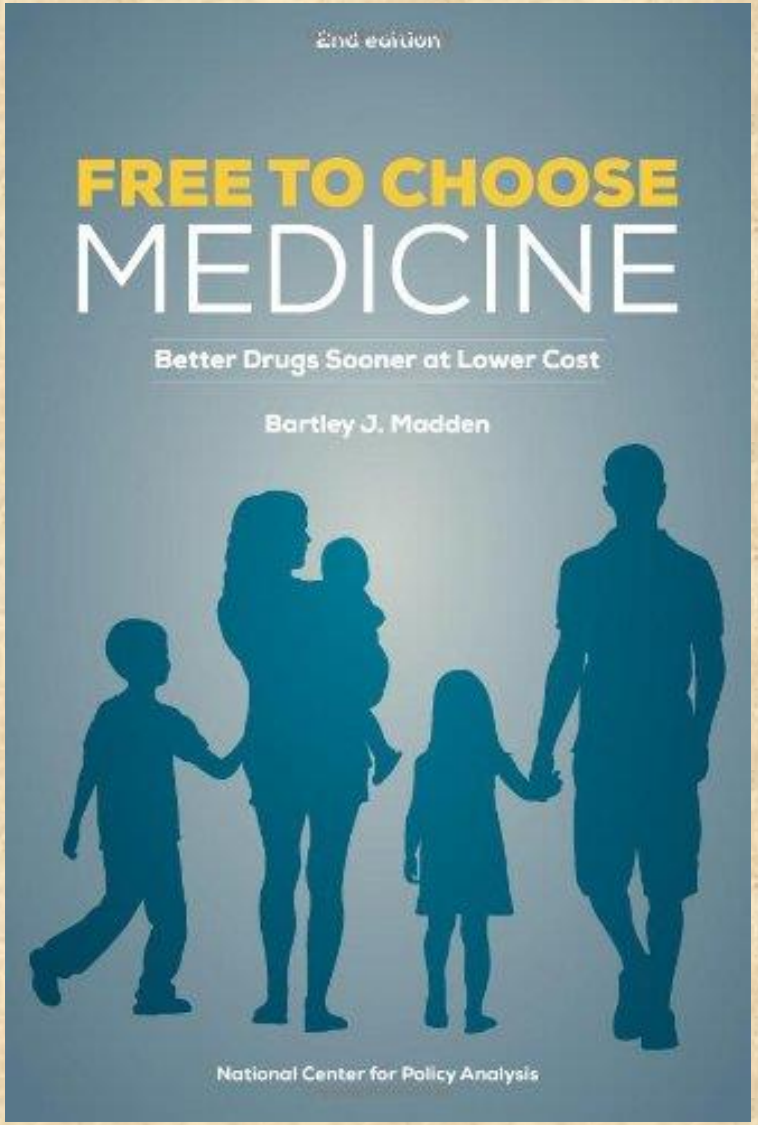
- Blocks consumer choice and competition which work so well in the private sector.

DEADLY OVER-CAUTION

- FDA clinical trial requirements – especially for randomized control trials – greatly slow potential benefits, including the following:
  - accelerating medical innovations
  - big-data analytics
  - patient desire to share data/participate in cures

- Unacceptable suffering and loss of life.

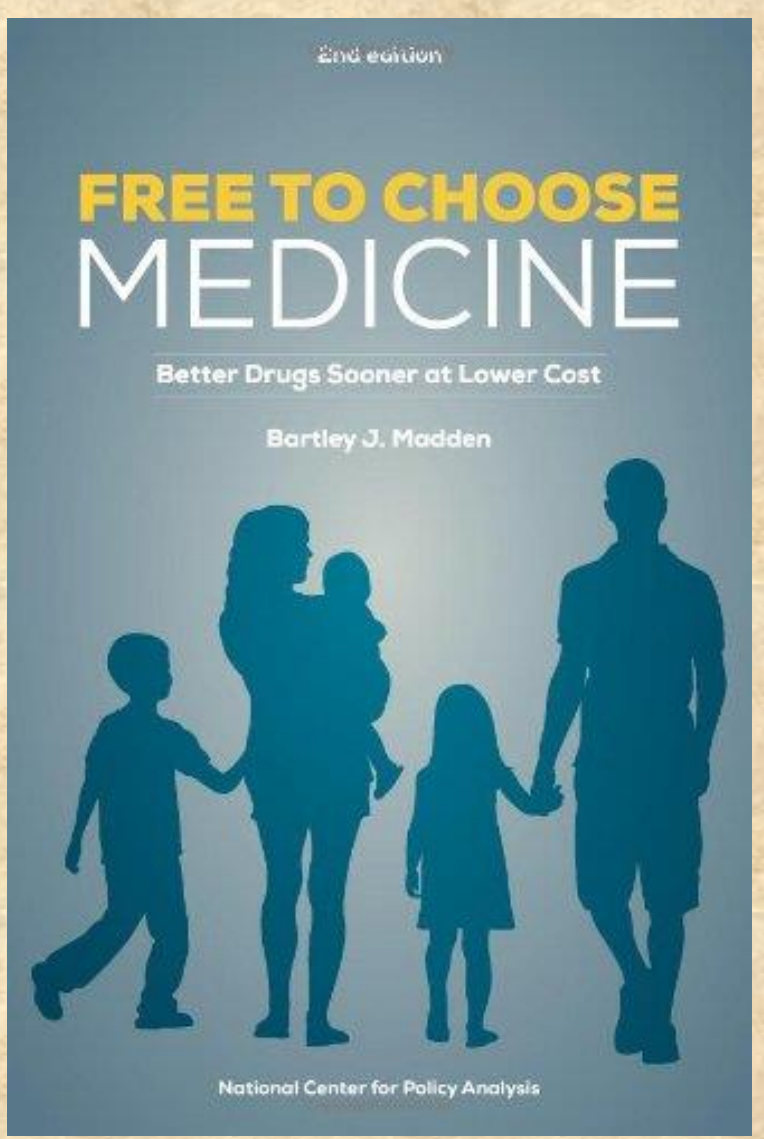
MARKET-BASED SOLUTION … FUNDAMENTALLY BIPARTISAN



"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

FREE TO CHOOSE MEDICINE PROVIDES A MARKET-BASED DISCIPLINE



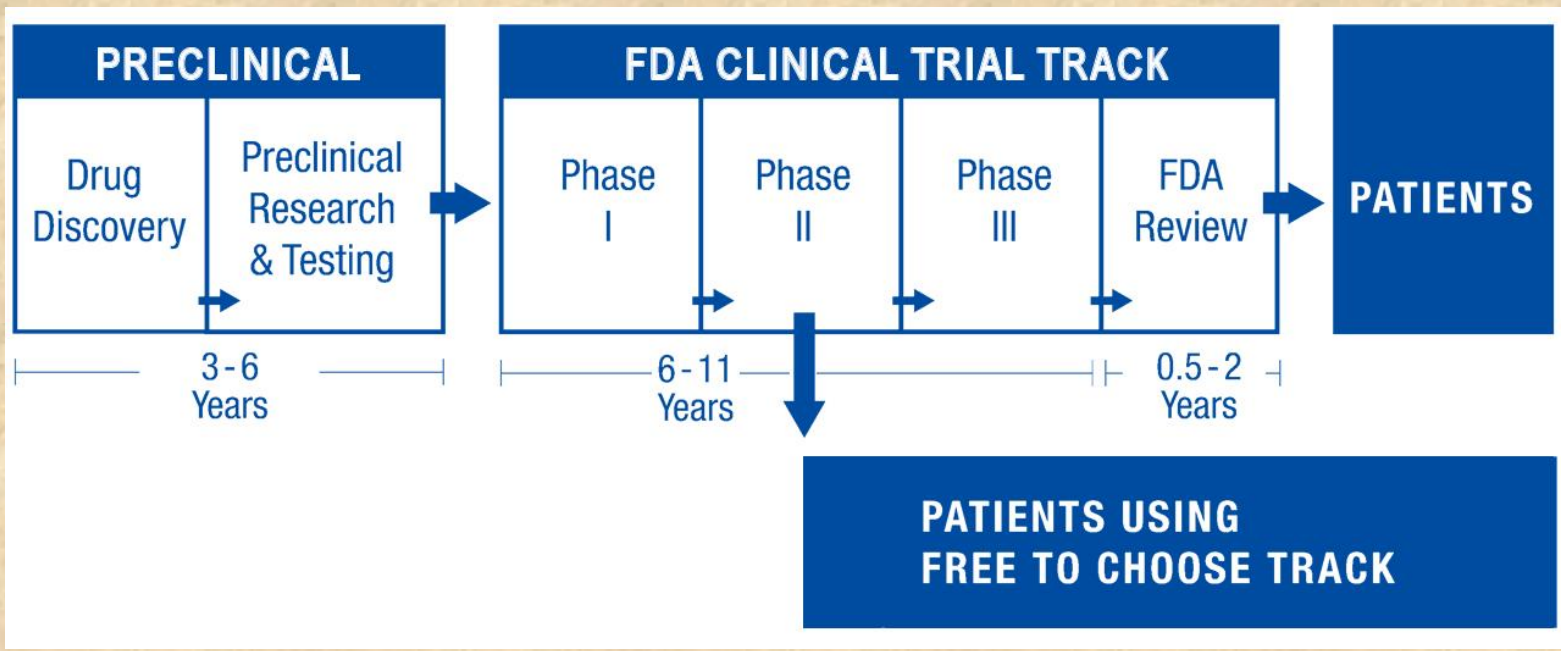
"Nothing is more precious to every American than their health and that of their families, and we know we have a lot to do to achieve the combination of quality, price and access that will support the American Dream.

Through Free To Choose Medicine, we can speed innovation; deliver to consumers (patients) the information they need to live healthier lives; and assume the accountability they want—just like every other high-quality consumer industry. In my experience over the years with cancer patients, I have seen the improved results that come from patients who understand their health situations; have the information they need to select the right options for care; and have access to the most up-to-date innovations. Free To Choose Medicine accelerates this patient-centric discipline that fundamentally improves the process to deliver value-based care.

Free To Choose Medicine, at its very core, creates a path forward to implement a much needed market discipline that can deliver a level of quality, cost, and access that would make Americans proud of their healthcare system."

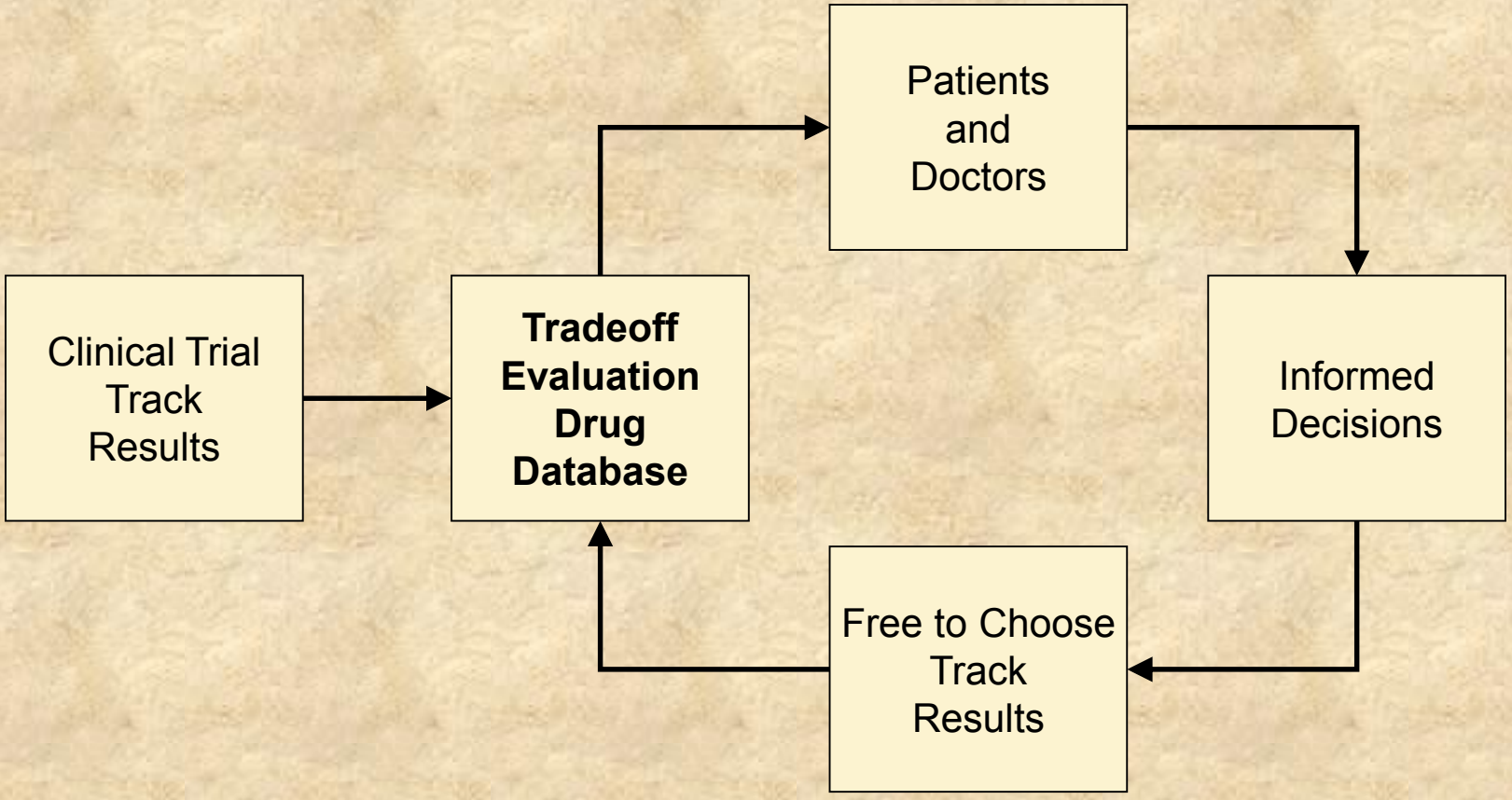
Stephen B. Bonner, Entrepreneur in Residence, Harvard Business School; former CEO of Cancer Treatment Centers of America

THREE PRINCIPLES OF FREE TO CHOOSE MEDICINE
#1 FREE TO CHOOSE TRACK OPERATED INDEPENDENTLY OF THE FDA



FTCM legislation would create a dual track system that preserves the existing FDA clinical trial process while offering patients an alternative. Patients, advised by their doctors, would be able to contract with a drug developer to use not-yet-approved drugs after Phase I safety trials are successfully completed and one or more Phase II trials have demonstrated continued safety and initial efficacy. The resulting early access could make FTCM drugs available up to seven years before conventional FDA approval, which entails Phase III randomized control trials and a lengthy FDA review before the FDA makes an approval decision.

#2 TRADEOFF EVALUATION DRUG DATABASE (TEDD)



TEDD makes available to the public through a government-sponsored web portal the information that patients and doctors need to make informed decisions about a FTCM drug's potential benefits and risks before choosing to use it. TEDD would be a treasure trove of data about patients' genetic makeup, biomarkers, and treatment results. Data from a heterogeneous patient population that mimics real-world use better than tightly controlled clinical trials do. The FTCM track and TEDD constitute a self-adjusting system wherein increased usage of FTCM drugs corresponds to demonstrated effectiveness and vice versa.

SHARE DATA AND LEARN FAST

"Importantly, information on the TEDD regarding Free To Choose track drug use would provide real-time, observational data showing the safety and effectiveness, or lack thereof, for new drugs. Inclusion of a wealth of relevant data on patient characteristics would also help physicians and manufacturers identify sub-populations of patients that do especially well or poorly.

… the TEDD and other Free To Choose track functions would have to be operated by a separate but still competent authority, such as the **National Institutes of Health**. Furthermore, not every drug completing some or all of Phase II trials would be automatically eligible for Free To Choose track status. A Free To Choose Medicine Advisory Committee … would be established within NIH to determine which experimental drugs are sufficiently promising to merit entry on the FTCM track and to monitor the TEDD to determine when drugs should be removed because risks clearly outweigh their benefits.

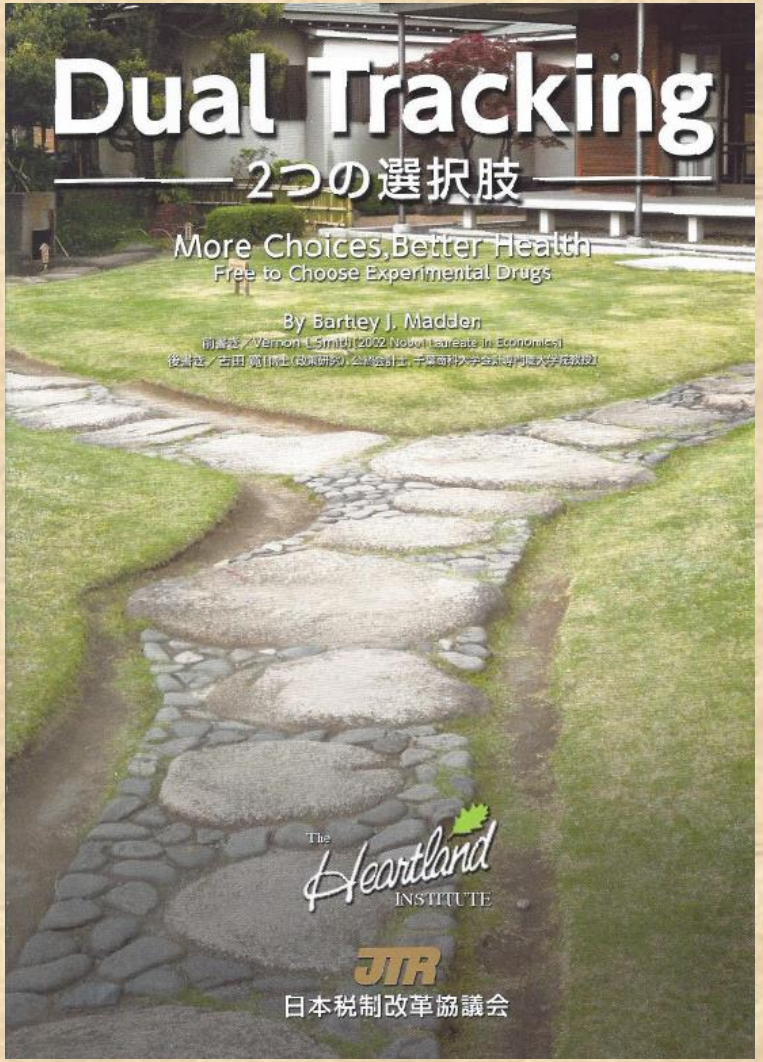
… legislation implementing the FTCM process should grant physicians **immunity** from malpractice claims and grant manufacturers immunity for design defect or negligent failure to warn clients, except in the case of gross negligence or willful misconduct, so long as patients certify they have been informed of the product's experimental nature."

Gregory Conko and Bartley J. Madden, 2013, "Free To Choose Medicine," *Engage – Administrative Law & Regulation*, Vol. 14 (3).

#3 OBSERVATIONAL APPROVAL

- FDA could grant Observational Approval due to compelling **safety and effectiveness demonstrated in use**.
- Based not on randomized control trial data, but on treatment data for **real-world patients**.
- Consistent with recent regulatory advancements in **Japan**.
- Drug developers would be motivated to charge **lower prices** in order to gain increased usage for their FTCM drug.
- TEDD's **up-to-date observational data** would guide patients and doctors, especially when genetic/biomarker tags identify patients who experienced especially favorable treatment outcomes.
- Observational Approval would **expedite insurance reimbursement**.

FREE TO CHOOSE MEDICINE IN JAPAN



This 2007 Japanese translation of an early FTCM booklet was heavily promoted to Japanese politicians by Masaru Uchiyama (Mr. You), President of the Japanese for Tax Reform.

FTCM principles contributed to the passage in 2013 of Japanese legislation permitting early access to regenerative medicine drugs which will be monitored via observational data.

PREFERRED 21ST CENTURY BUSINESS AND REGULATORY MODEL

"Unless fundamental change takes place, biopharmaceutical companies may well have to deal with government price controls which will have a disastrous impact on long-term innovation. A market-based solution—Free To Choose Medicine (FTCM)—has been widely published and implemented in Japan. … With favorable FTCM experience, expect the country to expand freedom of choice to cover a great many diseases. We can look to Japan to see a test of the preferred 21st century business and regulatory model for the biopharmaceutical industry."

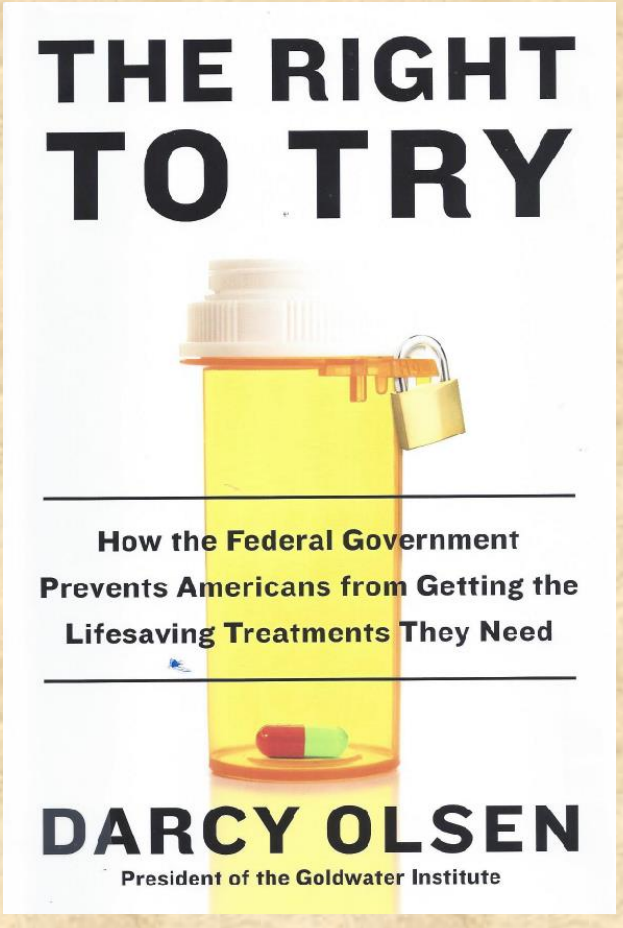
Bartley J. Madden and Vernon L. Smith, 2015, "Give the FDA Some Competition With Free To Choose Medicine," *Forbes Online.*

DON'T-ROCK-THE-BOAT FDA "REFORM" LEGISLATION DEGRADES U.S. BIOPHARMACEUTICAL LEADERSHIP

"How should U.S. politicians respond? The U.S. can continue to pass occasional legislation that does not encounter much political opposition and makes small incremental improvements. If so, we can get ready for worldwide leadership in biopharmaceutical research to begin shifting to Japan. Also, in the future U.S. citizens who can afford to travel to Japan for treatment for regenerative diseases will do so instead of waiting years for FDA testing and approval of innovative new drugs which are already being sold legally in Japan. Alternatively, there is a huge public support for many recent state-level initiatives in the form of Right To Try legislation which conceptually gives patients with life threatening diseases the right to overrule the FDA's monopoly power over access to not-yet-approved drugs. Every American should have the right to make their own informed decisions that can improve and save lives."

Bartley J. Madden and Vernon L. Smith, 2015, "Give the FDA Some Competition With Free To Choose Medicine," *Forbes Online.*

31 states have passed Right To Try legislation showing the public's overwhelming support for freedom of choice



- Patient has exhausted conventional treatments and has a terminal illness
- Patient's doctor supports the use of a not-yet-approved drug that has completed Phase I safety trials
- Informed consent
- Drug developer is willing to supply the drug

" … 40 percent of cancer patients try to get into trials and only 3 percent succeed, that means most fail to get access to emerging treatments through clinical trials. Since there will be about 1,658,370 new cancer diagnoses in 2015, that means there are hundreds of thousands of cancer patients who want experimental medicines but cannot get them. And that is not counting all the hundreds of thousands of other Americans who will be diagnosed with other terminal illnesses this year. And yet the FDA considers twelve hundred compassionate use requests each year a system that 'seems to work quite well'? When so many Americans are fighting terminal illnesses and fewer than 1 percent are getting access to investigational drugs, the system isn't working at all. It is broken."

BUT, PROBLEMS WITH RIGHT TO TRY

- Drug developers face a two-part **disincentive** to participate: (1) likely be pressured to provide the drug for free to help dying patients and drug could be in very limited supply and/or expensive to produce, and (2) an especially big concern is that adverse side effects, including deaths, from treating very sick patients might well become part of the FDA's decision-making regarding drug approval.

- Right To Try is **restricted** to "terminal illnesses" whereas FTCM has no such restriction. Patients with severe rheumatoid arthritis, multiple sclerosis, and other debilitating, but not terminal illnesses, could not participate.

- Most importantly, Right To Try does not address the **infrastructure** (FTCM three components) needed for successful implementation.

THREE FUTURE SCENARIOS AND A BIG OPPORTUNITY

(1) Assuming federal Right To Try legislation is not passed, the FDA and the Department of Justice could take forceful steps to stop Right-To-Try access.

(2) FDA does not explicitly oppose. But, with rare exception, drug developers decline to participate aware that the unspoken word is that state level participation may hinder obtaining FDA approvals.

(3) In order to avoid (1) and (2) and not be seen as blocking freedom of choice, Congress passes one of two categories of federal legislation:

- Don't-rock-the-boat FDA reform bill that keeps the FDA in the driver's seat for orchestrating changes in accelerated approval/compassionate access
- **Paradigm change using the three key principles of FTCM**

CONCLUSIONS

- The hugely successful Right To Try campaign shows genuine public demand for changes that actually help patients gain early access.

- With the FTCM paradigm, everyone learns at a rapid pace. FTCM is a dynamic, self-adjusting system where we learn about results and subpopulations of patients who do extremely well or poorly and we are able to make informed decisions.

- Past FDA reform legislation focused on incremental improvements and invariably assumed that the FDA must play the central role. **Who has ever seen a government agency willingly reduce its own power? The FTCM track and the TEDD must operate independently of the FDA** to bring private-sector innovation and efficiency to the slow-moving bureaucratic FDA process.

CONCLUSIONS

- **FDA Observational Approval could solve a serious dilemma** that the FDA faces with its allegiance to the "gold standard" of randomized control trials. On one hand, there is a growing consensus that oftentimes this creates an ethical problem of huge proportions. Steven Walker of the Abigail Alliance summarizes as follows:

  "Enrolling in a randomized placebo control trial is far more dangerous to a patient with a terminal disease than it would be to simply be given the drug. Because getting the placebo, under blinded conditions, is for many, many people a death sentence. It's a gamble. The company is betting that fewer people will die in the arm that gets the drug than in the placebo arm. This pile of bodies is smaller than the placebo pile, that's what they want to see. And that's literally what they are measuring. That is our clinical research system for cancer."
  "Fight To Live," 2010 film documentary.

- On the other hand, the FDA wants to employ the highest scientific testing standards in order to defend its approval decisions. The solution is to empower big data analytics for analyzing TEDD observational data, which involves a much larger heterogeneous sample of patients versus a smaller homogeneous sample in randomized control trials. Simply treat FDA Observational Approval as distinctly different from FDA Standard Approval. Perhaps the FDA could **outsource this entire process** and keep its preferred approval process under its control.

CONCLUSIONS

- FTCM would bring **competition** to the FDA by enabling the public to evaluate how patients fare with freedom of choice.
- Expect **lower drug prices** because streamlined clinical testing and review translates into greatly reduced costs. This enables drug developers to charge much less while maintaining their profitability. Keep in mind that drug developers would face heightened competition due to the rapid introduction of new, FTCM drugs.
- FTCM puts a **premium on scientific skill** in developing breakthrough medical treatments and efficiency in commercializing new innovations.
- Every American should have the **right** to make their own informed decisions that can improve and save lives.