Seamless Cancer Drug Development: Patient Protections & Ethical Considerations

The Drug Development Paradigm in Oncology
National Cancer Policy Forum
Washington, DC

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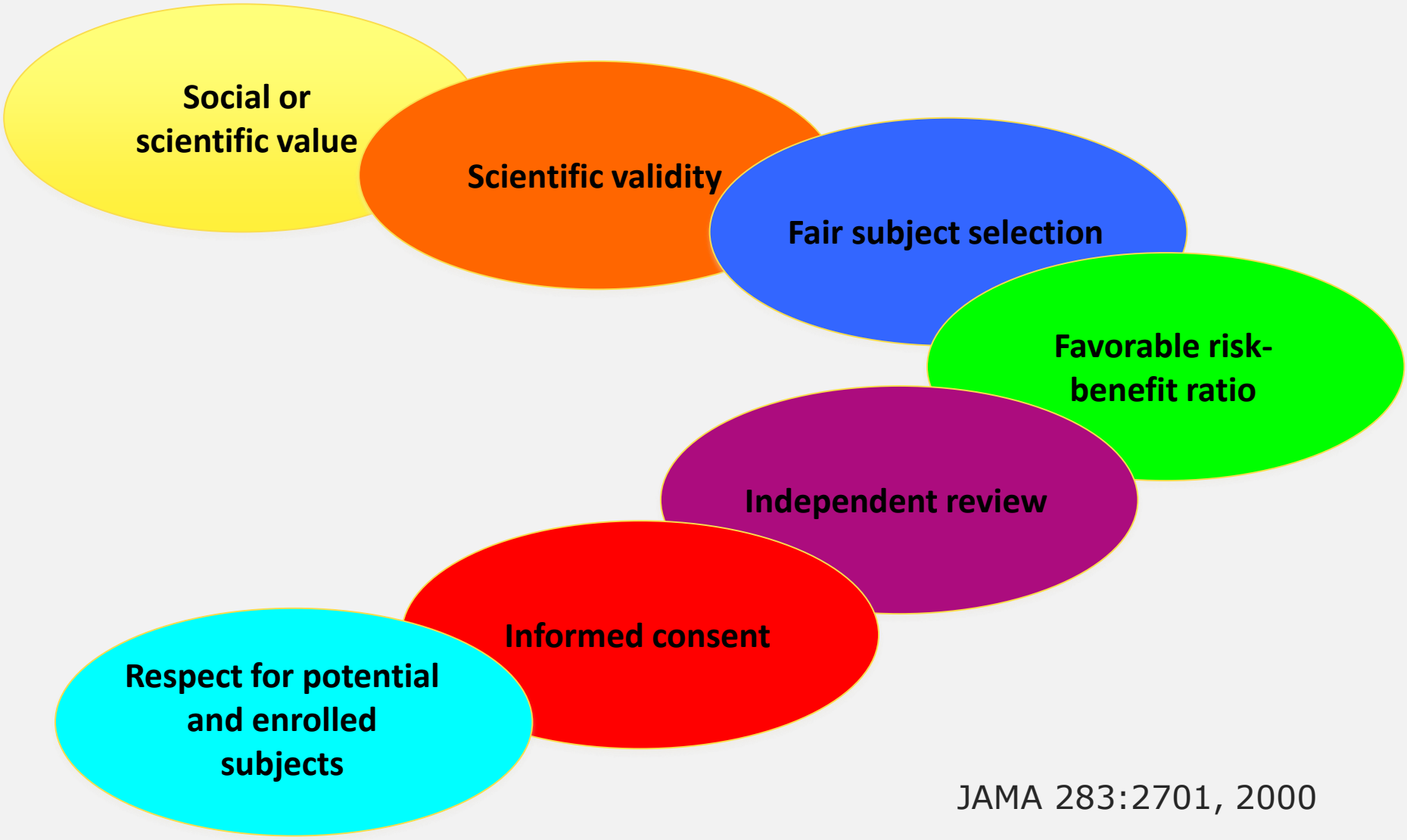
Key points (hypotheses)

- Seamless designs pose real but manageable risks to study participants
- Seamless designs pose greater risks to patients whose treatment they influence
- Minimizing these risks, and maximizing their benefits, requires attention to both methodological and operational challenges

Ethical research must meet 7 requirements



JAMA 283:2701, 2000

Patient protection: three relevant principles, two classes of patients

Principle
Social value
Scientific validity
Favorable risk-benefit balance

Patient protection: three relevant principles, two classes of patients

Principle	Future beneficiaries
Social value	X
Scientific validity	X
Favorable risk-benefit balance	X

Patient protection: three relevant principles, two classes of patients

Principle	Future beneficiaries	Trial participants
Social value	X	
Scientific validity	X	
Favorable risk-benefit balance	X	X

Overarching goal of drug development process

- Provide evidence of safety & efficacy so that physicians and patients can make good decisions

Four options to speed drug development & approval

- Approve based on surrogate markers
- Skip controlled trials
- Accept lower levels of statistical precision
- Most radically: require only evidence of safety, not efficacy
  - Incoherent, IMHO

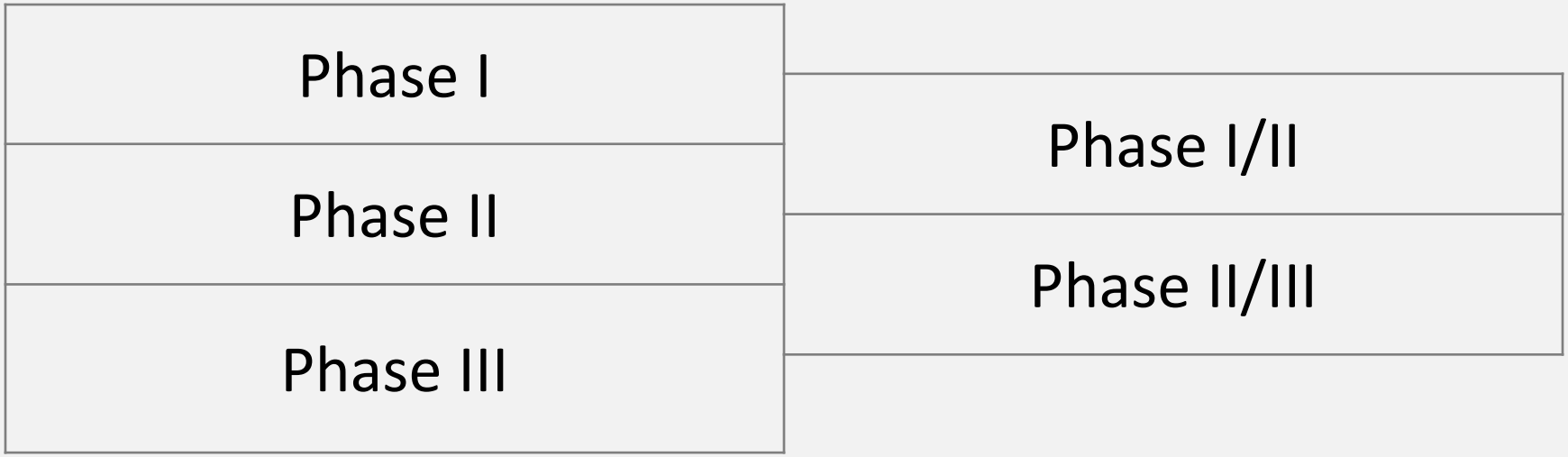
Rationale for speeding drug development process

- Version 1: some requirements of traditional process add little (or no) value in terms of evidence about safety and/or efficacy
- Version 2: We can accept lower levels of evidence about safety &/or efficacy when approving drugs
  - Acknowledges tradeoff between speed & evidence

Seamless designs have precedent…

Phase I
Phase II
Phase III

Seamless designs have precedent…



…but raise novel go/no-go challenges

- Traditional phase I/II and II/III designs have explicit, prespecified criteria for phase transitions
  - Involve statistical justification
  - Subject to independent prior approval for both validity & benefit/risk considerations
- Seamless designs, in contrast, may involve ad hoc decisions about cohort expansion
  - Statistical justification & prior approval are more challenging

Seamless designs have upsides & downsides

- Potential upside:
  - Avoid *unnecessary* delays in demonstrating the safety and efficacy of novel agents
- Potential downsides:
  - Increase risk to *trial participants* due to more rapid evaluation of safety
  - Increased risk to *future patients* (and the public's purse) due to approval of unsafe or ineffective agents

Speeding the drug development process has risks for participants

Risks and Benefits Associated With Novel Phase 1 Oncology Trial Designs

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BACKGROUND. Although aggressive dose escalation strategies were designed to improve the risk-benefit profile of phase 1 oncology trials, they have not been adequately studied. The prevalence of several novel trial designs and their association with a variety of clinical endpoints was evaluated.

METHODS. A review of the literature was performed to identify phase 1 oncology studies of cytotoxic agents published from 2002 through 2004.

RESULTS. Of 955 phase 1 oncology articles initially identified, 149 studies, comprising 4532 patients, were analyzed. Only 34% of studies utilized aggressive dose

Cancer 110:1115, 2007

Speeding the drug development process has risks for participants

RESULTS. Of 955 phase 1 oncology articles initially identified, 149 studies, comprising 4532 patients, were analyzed. Only 34% of studies utilized aggressive dose escalation schemes, 22% permitted intrapatient dose escalation, and only 28% enrolled fewer than 3 patients to any dose level. Studies that allowed intrapatient dose escalation or used fewer than 3 patients per dose were not associated with different rates of response or toxicity, nor did they increase the number of patients who received the recommended phase 2 dose. However, aggressive dose escalations were associated with increased rates of both hematologic (17% vs 10%) and nonhematologic (17% vs 13%) toxicity with similar response rates. Only studies that used conservative dose escalation designs and those that studied U.S. Food and Drug Administration (FDA)-approved agents required fewer patients to complete a trial. Trials of FDA-approved agents were also associated with higher response rates than trials of non-FDA-approved agents (10% vs 2%), without an increased risk of toxicity.

Cancer 110:1115, 2007

Rapid drug development carries risks

www.nytimes.com/2016/12/03/health/immunotherapy-cancer.html

The New York Times

One Weight-Loss Approach Fits All? No, Not Even Close

Rise in Infant Drug Dependence in U.S. Is Felt Most in Rural Areas

When Bathroom Runs Rule the Day (and Night)

One in 6 American Adults Say They Have Taken Psychiatric Drugs, Report Says

HEALTH

Immune System, Unleashed by Cancer Therapies, Can Attack Organs

By MATT RICHTEL DEC. 3, 2016

Chuck Peal, 61, at home in Southbury, Conn. He developed acute-onset diabetes, as did other patients who received immunotherapy at Yale. Angel Franco/The New York Times

As Chuck Peal lay in a Waterbury, Conn., emergency room one Sunday in early September, doctors furiously tried to make sense of his symptoms. Mr. Peal, 61, appeared to be dying, and they were not sure why.

Seamless designs will challenge IRBs' oversight function

- To approve a trial, IRBs must find that "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result."
  - Rapid protocol modifications in seamless designs will challenge this function
  - DSMB equivalent might perform this role, but ?regulatory compliance
  - Specialized (central) IRBs may be needed

21 CFR 56.111(a)(2)

Speeding the drug development process also carries risks for the patient-beneficiaries

Context: intense public, political & industry pressure for speed & access

https://www.statnews.com/pharmalot/2016/09/19/sarepta-wins-dmd-drug-approval/

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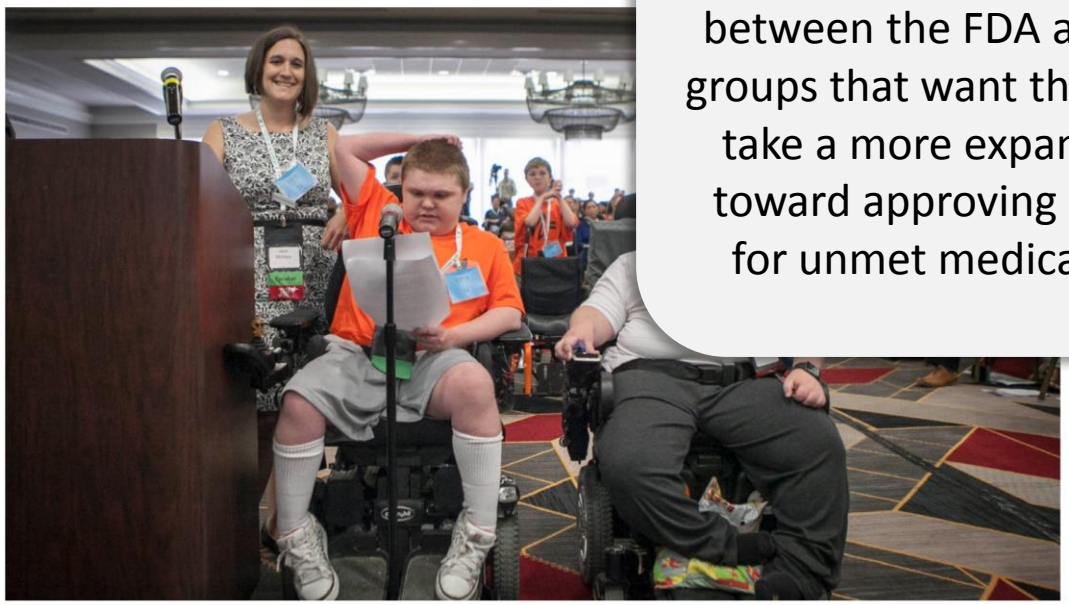
PHARMALOT

FDA approves Sarepta's controversial drug for Duchenne muscular dystrophy

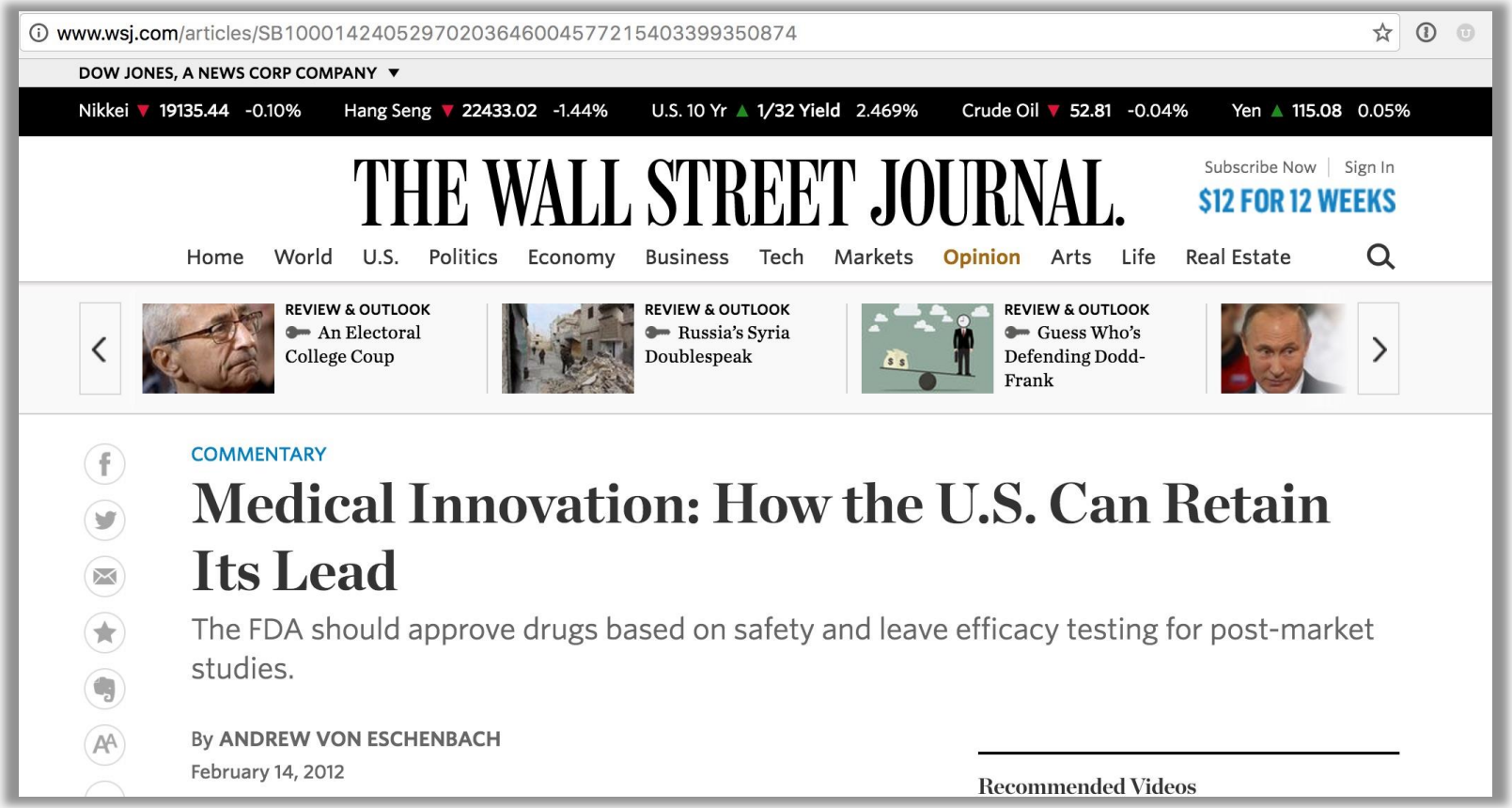


JOHN BOAL / BOSTON GLOBE

Two boys with Duchenne muscular dystrophy spoke earlier this year during hearings over conflicting interpretations of findings from Sarepta's clinical trial of an experimental drug.

"The fate of [Sarepta] has been closely watched as a litmus test for an intensifying struggle between the FDA and patient groups that want the agency to take a more expansive view toward approving medicines for unmet medical needs."

Context: intense public, political & industry pressure for speed & access



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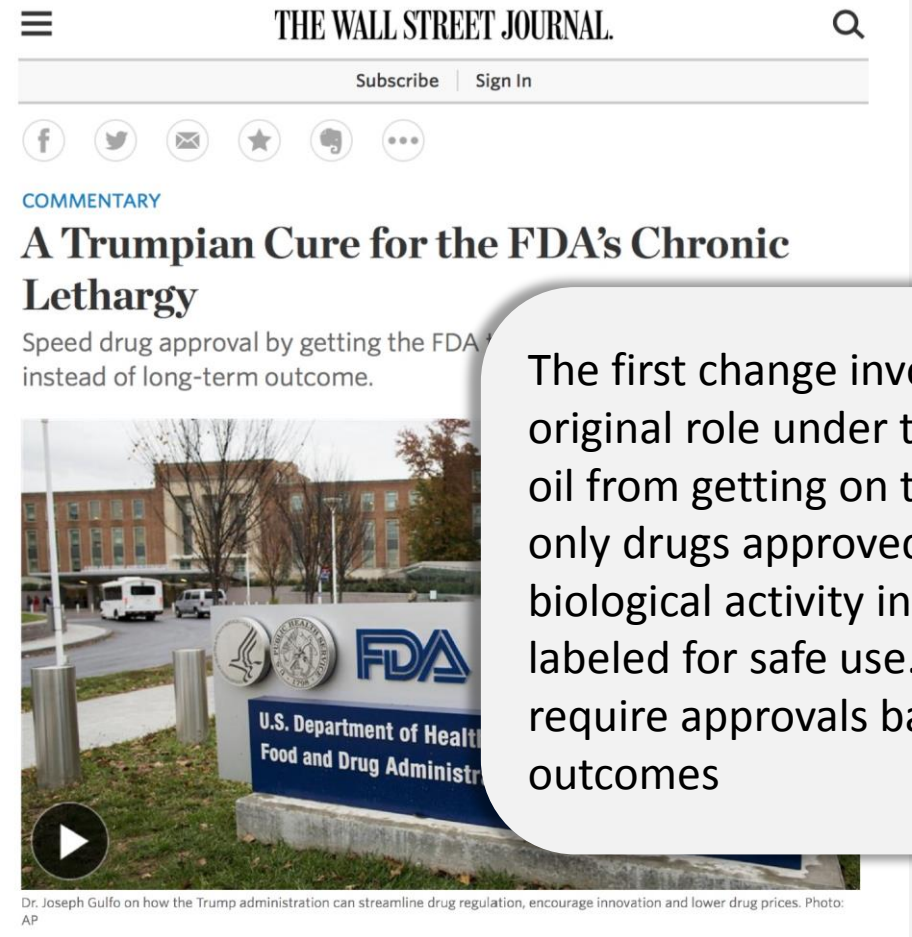

The first change involves returning the FDA to its original role under the law. That is to prevent snake oil from getting on the market by ensuring that the only drugs approved for sale have demonstrated biological activity in fighting a disease and can be labeled for safe use. The FDA would no longer require approvals based on long-term health outcomes

http://www.wsj.com/articles/a-trumpian-cure-for-the-fdas-chronic-lethargy-1479773883

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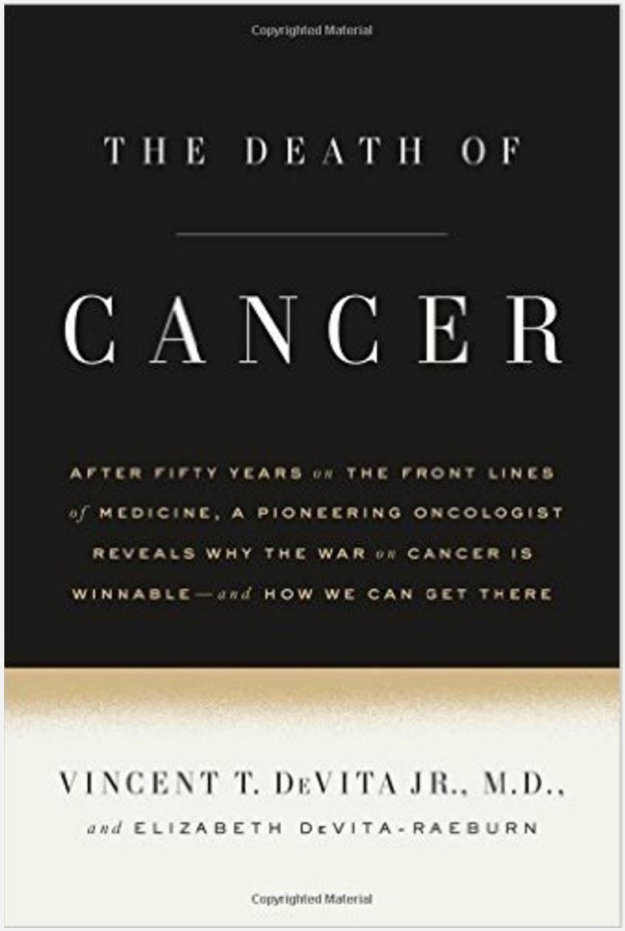
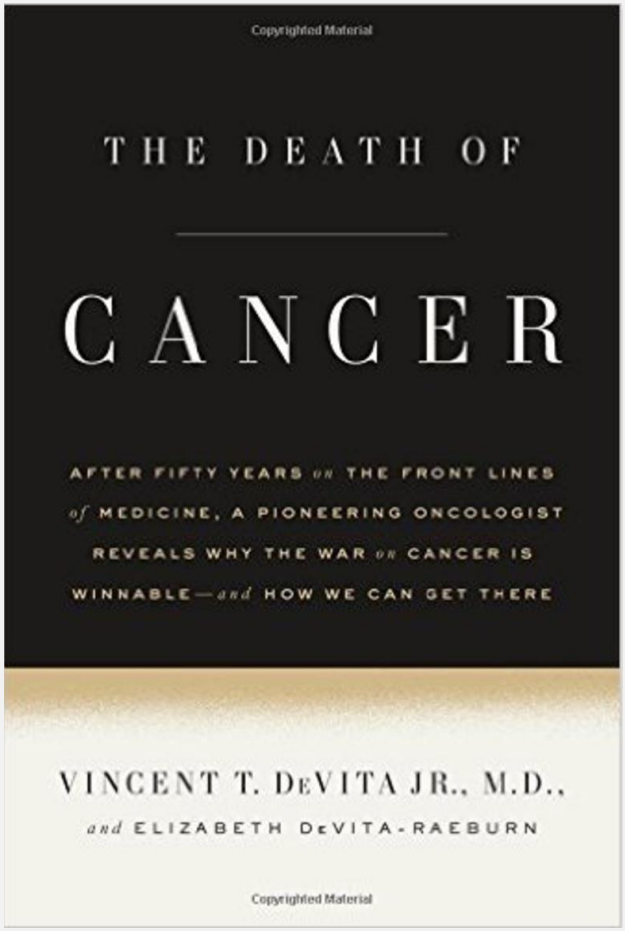


"When it comes to cancer, the FDA has reached far beyond its central responsibility—assuring the safety of new drugs."

Context: intense public, political & industry pressure for speed & access



"A legion of 'Dr. No's' has been created, and they're particularly prone to saying no to cancer drugs. That's very bad news for cancer patients."

Context: intense public, political & industry pressure for speed & access

https://www.statnews.com/2016/11/30/21st-century-cures-act-house/

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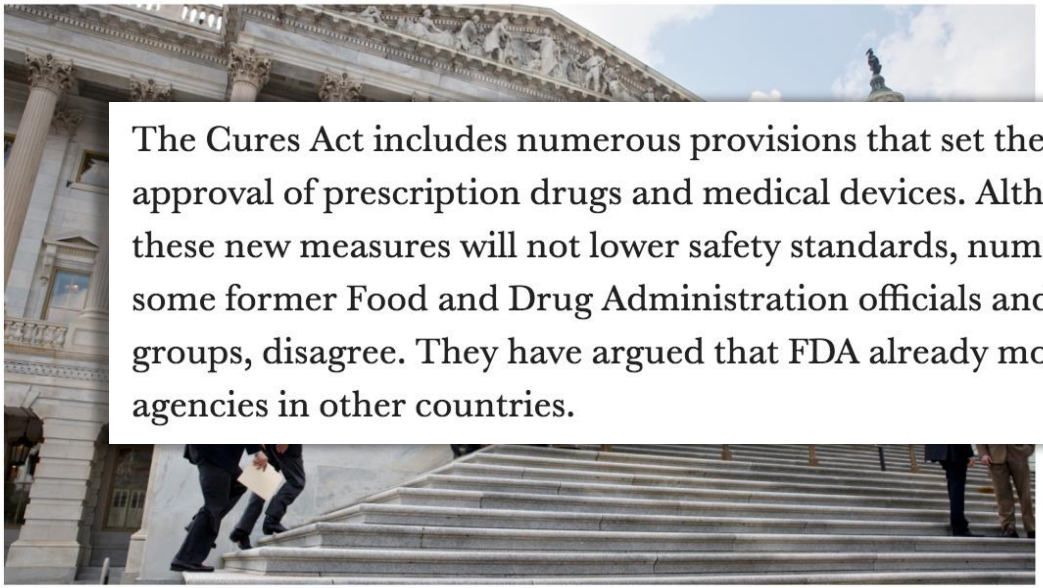
POLITICS

House approves the 21st Century Cures Act, sending landmark bill to Senate



J. SCOTT APPLEWHITE/AP

The Cures Act includes numerous provisions that set the stage for the faster approval of prescription drugs and medical devices. Although proponents claim these new measures will not lower safety standards, numerous critics, including some former Food and Drug Administration officials and national consumer groups, disagree. They have argued that FDA already moves faster than similar agencies in other countries.

It is possible to design trials with contingent, prespecified modifications

PLOS | MEDICINE

RESEARCH ARTICLE

Evaluating Clinical Trial Designs for Investigational Treatments of Ebola Virus Disease

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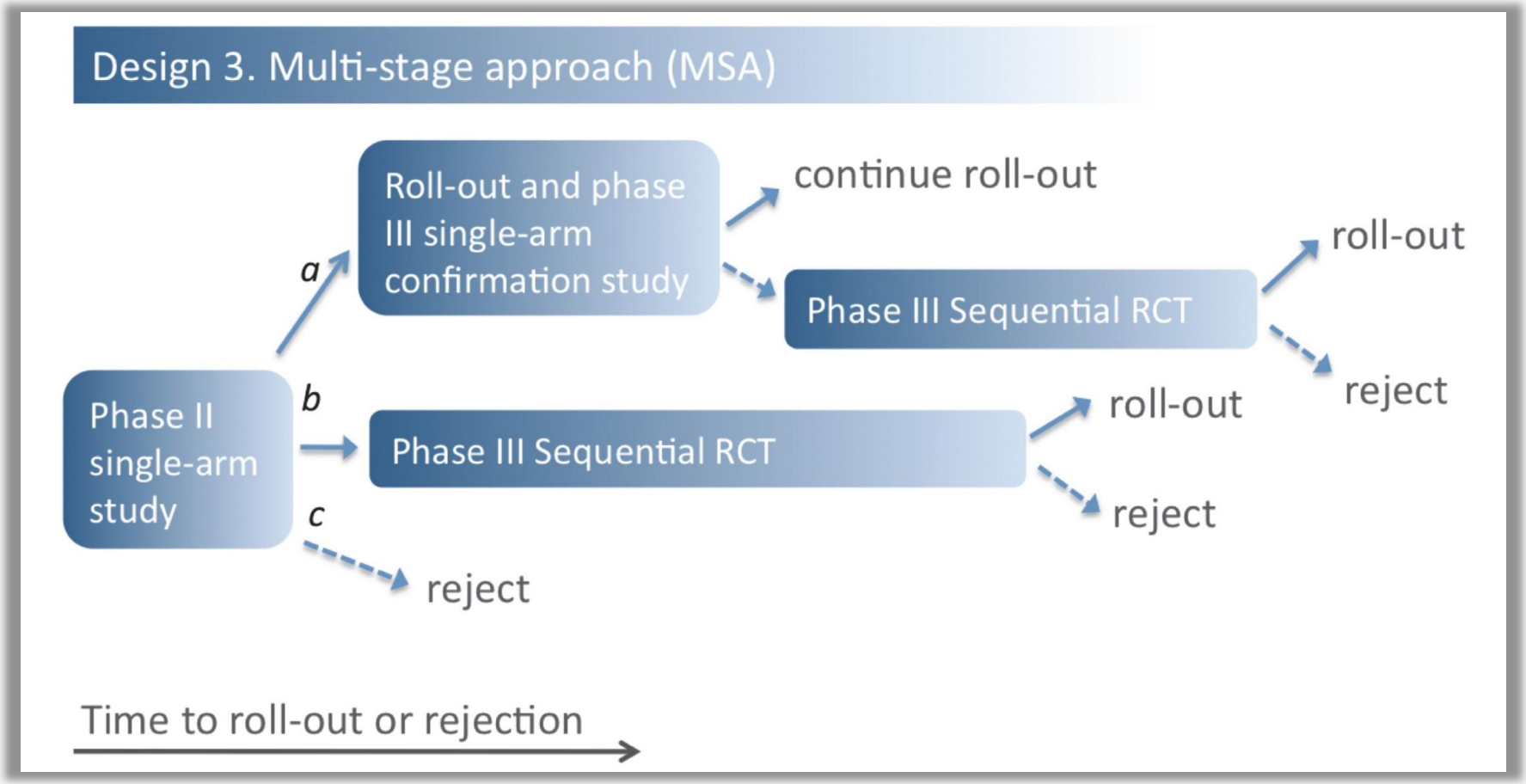
PLOS Medicine | DOI:10.1371/journal.pmed.1001815

It is possible to design trials with contingent, prespecified modifications



PLOS Medicine | DOI:10.1371/journal.pmed.1001815

The importance of effect size

- Large effect sizes → unlikely to wrongly approve
- Small to moderate effect sizes → high risk of mistaken approval
- Designs & decisions must be contingent on observed effect size

Recommendations to protect trial participants & future patients

- Model properties & performance of various designs
- Establish registry to allow tracking of real-world performance, learning from experience
- Assign review to central IRBs with methodological expertise & ability to review & respond rapidly
- Ensure close coordination between IRBs and DSMBs
- Randomize! (unless very large effect size)