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

- Social or scientific value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

JAMA 283:2701, 2000
Patient protection: three relevant principles, two classes of patients

<table>
<thead>
<tr>
<th>Principle</th>
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Patient protection: three relevant principles, two classes of patients

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Patient protection: three relevant principles, two classes of patients

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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...

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...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
Risks and Benefits Associated With Novel Phase 1 Oncology Trial Designs

Shlomo A. Koyfman, MD
Manish Agrawal, MD
Elizabeth Garrett-Mayer, PhD
Benjamin Krohmal, BA
Elizabeth Wolf, BA
Ezekiel J. Emanuel, MD, PhD
Cary P. Gross, MD

**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
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.
Rapid drug development carries risks
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.
“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.”
Medical Innovation: How the U.S. Can Retain Its Lead

The FDA should approve drugs based on safety and leave efficacy testing for post-market studies.

By ANDREW VON ESCHENBACH
February 14, 2012
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.
Context: intense public, political & industry pressure for speed & access

“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.”
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.
It is possible to design trials with contingent, prespecified modifications.
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)