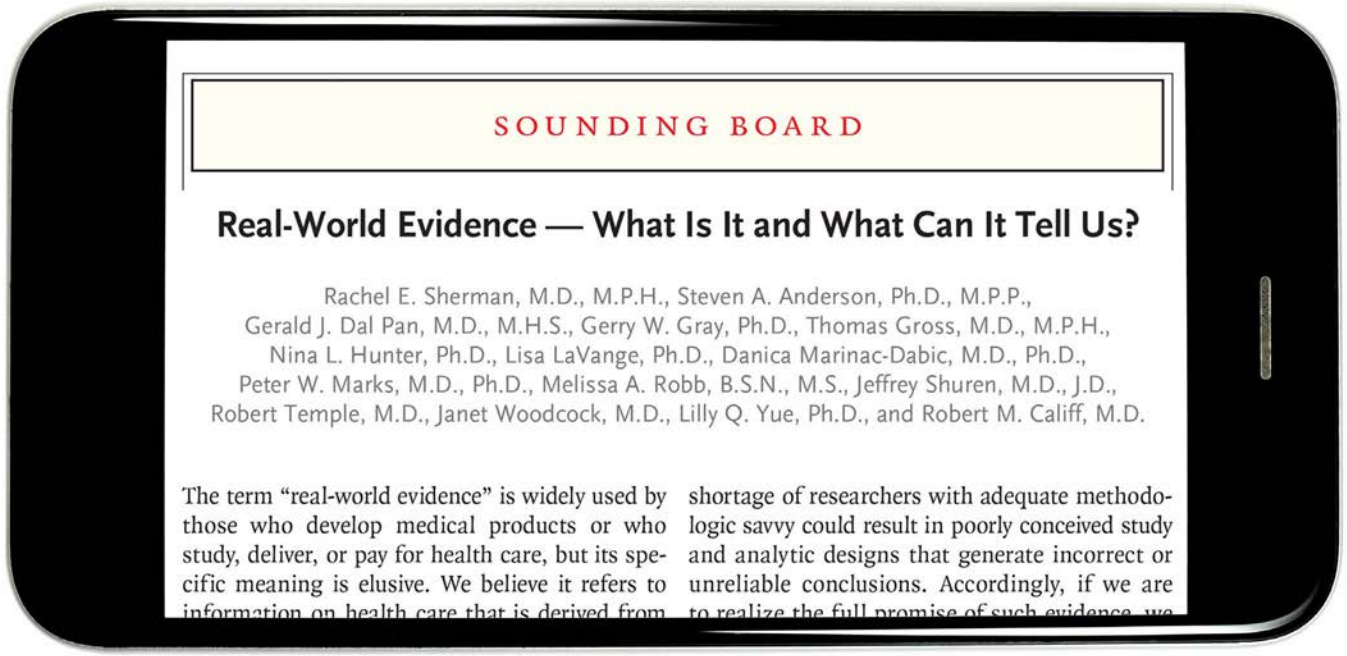
Complex Innovative Designs

Advancing the Use of Complex Innovative Trial Designs (CID)

Introduction

U.S. FOOD & DRUG ADMINISTRATION

The Changing Landscape of Drug Development



SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

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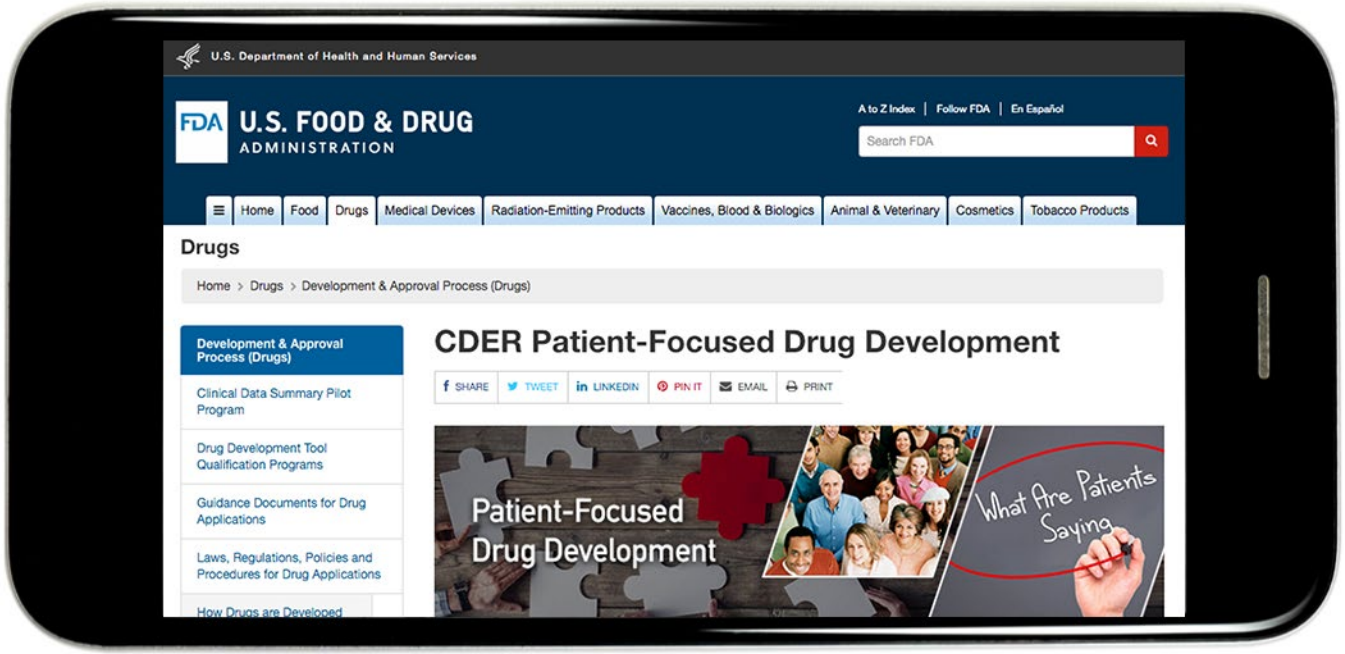
The term "real-world evidence" is widely used by those who develop medical products or who study, deliver, or pay for health care, but its specific meaning is elusive. We believe it refers to information on health care that is derived from

shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions. Accordingly, if we are to realize the full promise of such evidence, we

The Changing Landscape of Drug Development



The Changing Landscape of Drug Development

PDUFA VI

- Enhancing regulatory decision tools to support drug development and review
  - Complex Innovative Trial Designs
    - Includes designs involving complex adaptations, Bayesian methods, or other features requiring simulations to determine statistical properties (e.g., type I error)

PDUFA VI Provisions: Complex Innovative Trial Designs (CID)

- Objective: To facilitate the advancement and use of CIDs
  - Develop staff capacity
  - Conduct a pilot meeting program
  - Develop or revise relevant Manuals of Policies and Procedures (MAPPs), Standard Operating Policy and Procedures (SOPPs), and/or review templates
  - Publish draft guidance
  - Convene a public workshop

CID Leadership

The CID efforts are jointly led by statisticians in FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), with participating staff representing relevant disciplines.

The Need for CIDs

- FDA's public health mission includes ensuring safe and effective therapeutic options for patients.
- The optimal study design for the population of interest benefits drug development.
- CIDs can provide a path forward for challenging drug development problems that benefit from innovative thinking.

The Use of CIDs

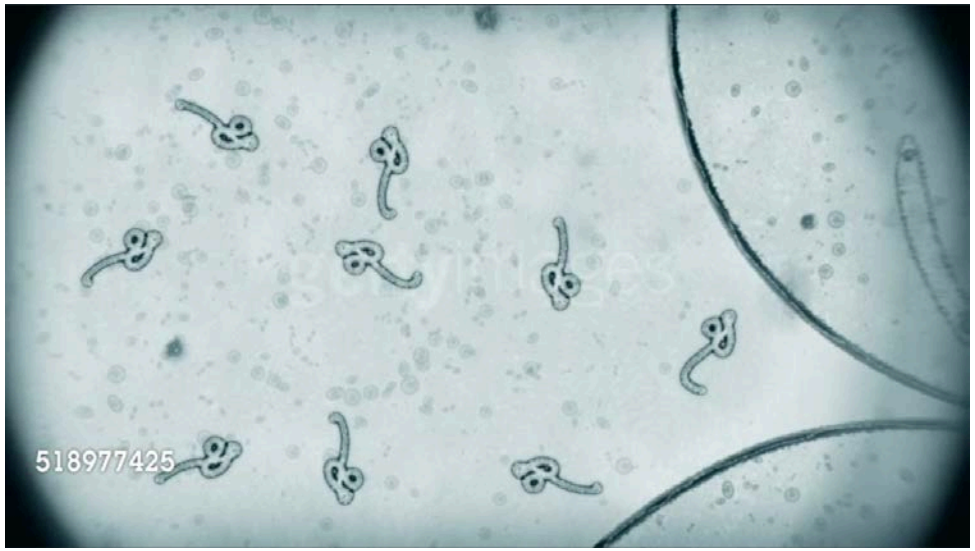
- Leverage data
  - Rare diseases
  - Multiple body sites in anti-infective drug development
- Assess multiple interventions, diseases, and/or subgroups under a master protocol
  - PREVAIL II
  - Lung-MAP

Possible CID Features

- Use of external controls
- Incorporation of adaptations to multiple design features
- Formal incorporation of prior knowledge

Revisit the 2014–2016 Ebola Outbreak

- Urgent need to identify safe and effective therapies
- Limited or intermittent drug supply for several potential therapeutic agents
- Need to maximize information from limited data
- Flexible design and analysis needed



Ebola Response: A Master Protocol

- "… a need to answer more questions more efficiently and in less time."*
- PREVAIL II**
- Shared control arm
- Ability to simultaneously evaluate multiple therapies
- Add or remove treatment arms
- Bayesian decision rules

*Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017; 377:62-70.

**The PREVAIL II Writing Group. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med 2016; 375:1448-1456.

PDUFA VI CID Provisions

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CID Public Workshop

- March 20, 2018
- Purposes:
  - Facilitate discussion and information sharing about the use of CID in drug development and regulatory decision-making
  - Obtain input from stakeholders about the CID Pilot Meeting Program

PDUFA VI CID Provisions

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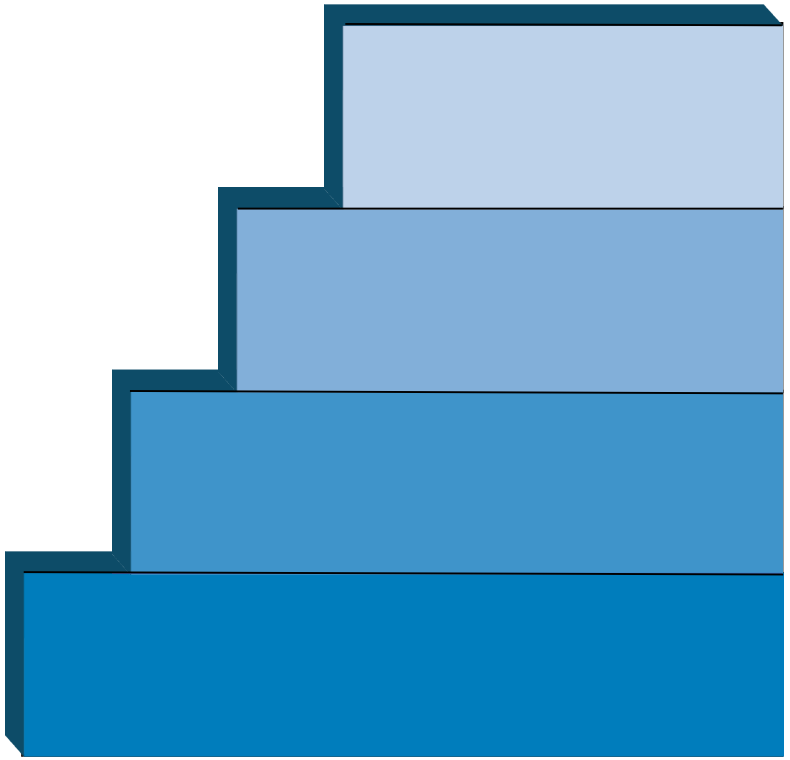
CID Pilot Meeting Program

- Designed for highly innovative trial designs for which analytically derived properties may not be feasible and simulations are needed to determine statistical properties
- Sponsors
  - Submit meeting requests to discuss proposed CIDs (up to two requests selected per quarter).
  - Have the opportunity to engage with FDA regulatory staff on designs via two meetings.

CID Pilot Meeting Program (continued)

- FDA will grant two meetings.
  - Initial and follow-up meetings on the same CID
  - Meetings occur within a span of approximately 120 days
  - May present trial designs as case studies for continuing education and information sharing

Summary



Benefit to Patients

Advancement of CID

Opportunity for Collaboration

Innovative Medical Product Development

Thank you!

For more information, visit https://www.fda.gov/CIDpilot

For questions, please email CID@fda.hhs.gov