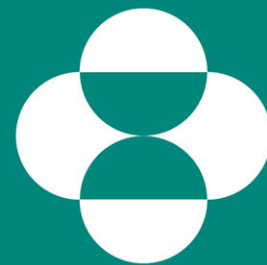


# THE EXPANDING UNIVERSE OF PATIENT ADHERENCE SOLUTIONS: LONG-ACTING IMPLANTABLES, MICRO-CHIP, SMART PACKAGING, APPS, AND SOCIAL ROBOTICS



**MERCK**

**INVENTING FOR LIFE**

Stephanie E. Barrett, Ph.D.

April 2019

# Patient Adherence in Disease Management

“The extent to which a person’s behavior - taking medications, following diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider.”

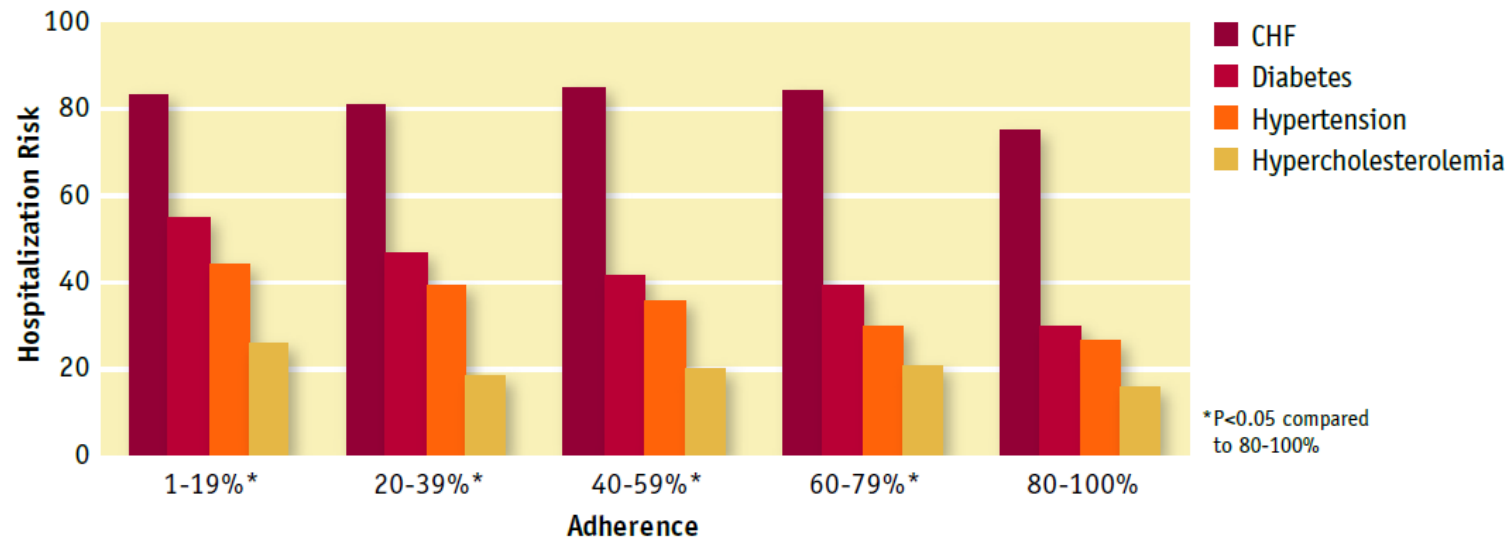
- 1/5 take meds nearly perfectly
- 1/5 take nearly all doses, but irregularly
- 1/5 miss an occasional single day’s dose and have irregular timing
- 1/5 take "drug holidays" monthly or more often with frequent omissions
- 1/5 take few or no doses



*Adherence to Long-term Therapies: Evidence for Action.* World Health Organization Press; 2003.  
Urquhart J. Br J Clin Pharmacol 2002;54:212-20.

# Non-Adherence: A \$300 Billion Problem

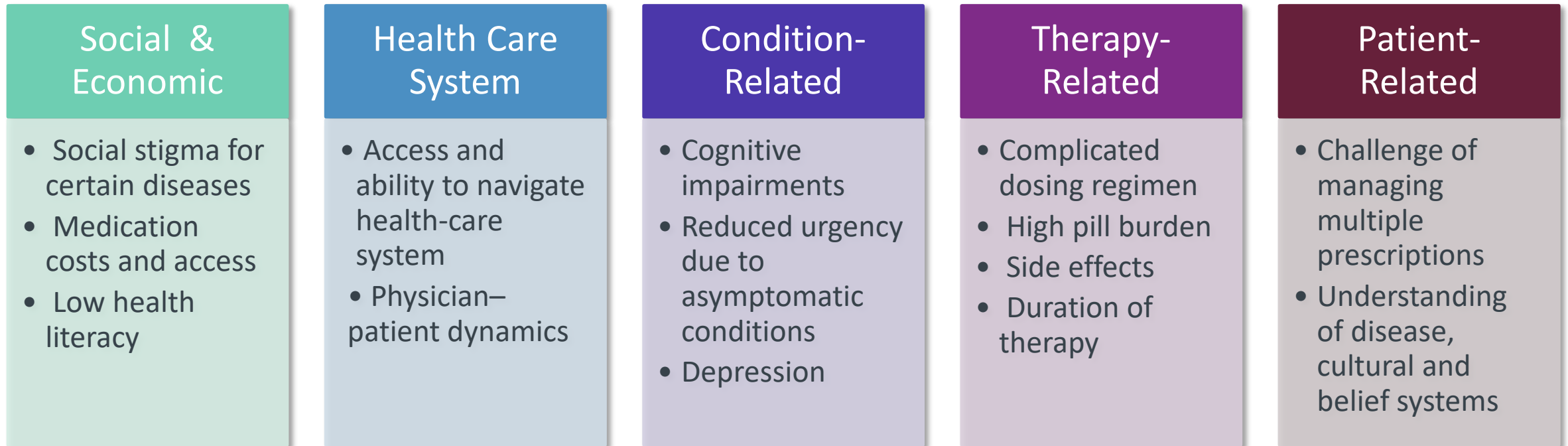
- Poorer health outcomes
- Higher mortality: > 125,000 deaths annually in US
- Increased hospitalization: non-adherence has been shown to result in approx. \$100 billion due to excess hospitalizations each year in the US
- Yearly expenditures for the consequences of non-adherence are estimated to be in the hundreds of billions of US dollars



*Adapted from Sokol et al., 2005.*

NEHI Research Brief,  
“Thinking Outside the  
Pillbox: A System-wide  
approach to Improving  
Patient Medication  
Adherence for Chronic  
Disease.” NEHI, 2009.

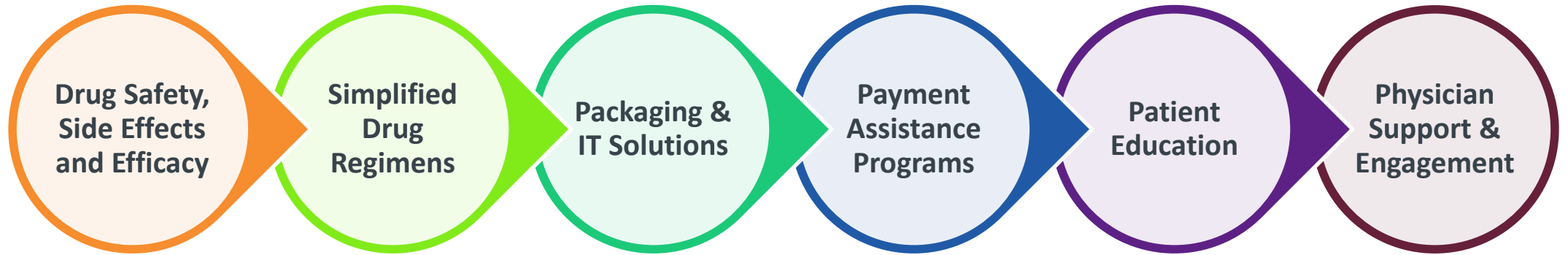
# Factors Affecting Medication Adherence



Source: World Health Organization, 2003

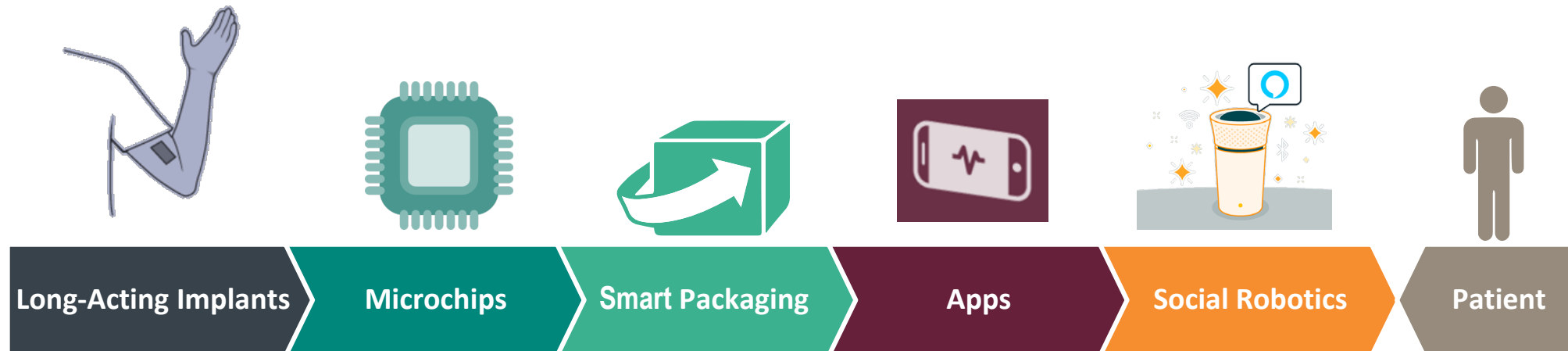
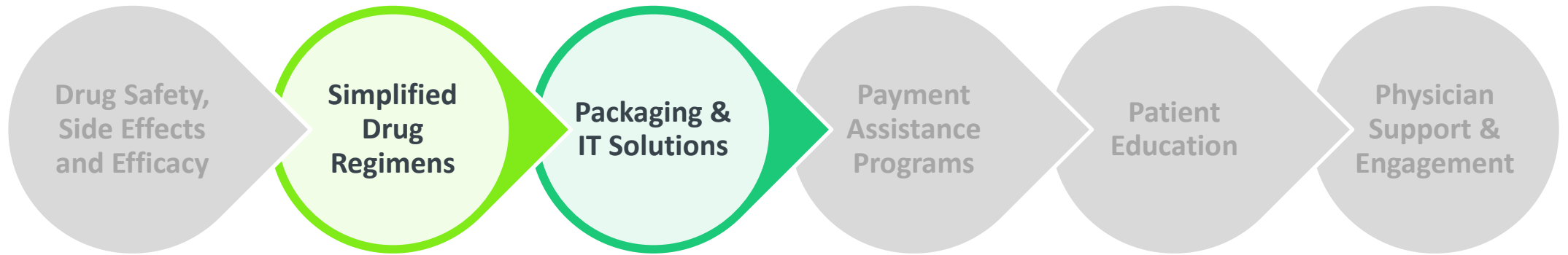
# Opportunities to Improve Patient Adherence

No single intervention strategy can improve the adherence of all patients



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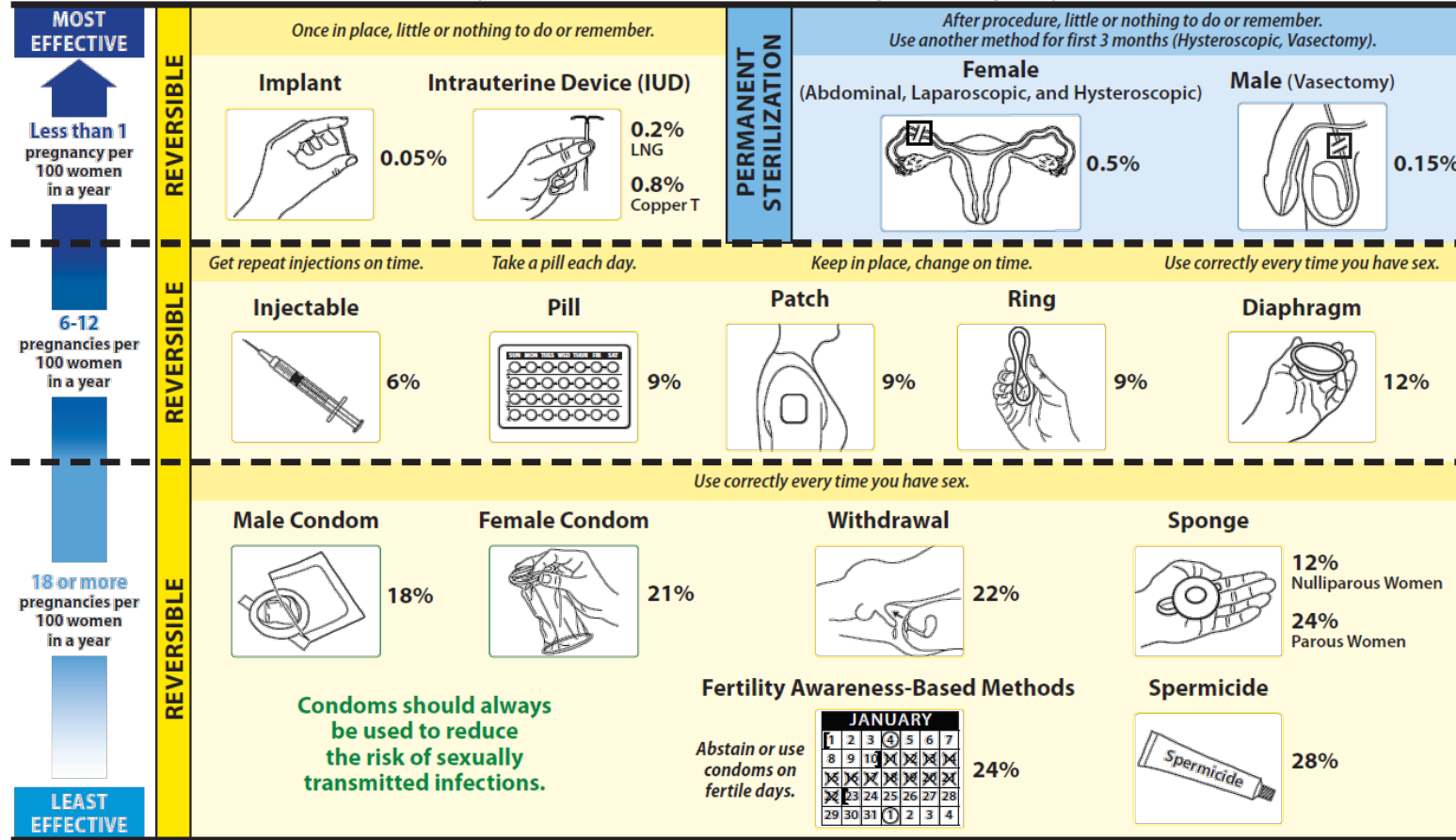


# The Impact on Adherence in Contraception through the use of Long-Acting Implants

Simplified Drug Regimens

## EFFECTIVENESS OF FAMILY PLANNING METHODS\*

\*The percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method.



Other Methods of Contraception: (1) Lactational Amenorrhea Method (LAM): is a highly effective, temporary method of contraception; and (2) Emergency Contraception: emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy. Adapted from World Health Organization (WHO) Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health's Center for Communication Programs (CCP). Knowledge for health project. Family planning: a global handbook for providers (2011 update). Baltimore, MD; Geneva, Switzerland: CCP and WHO; 2011; and Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397-404.



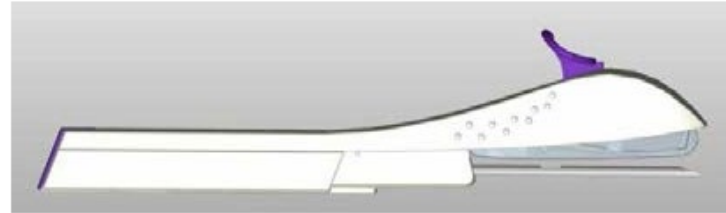
# Case Study: The Impact on Adherence in Contraception

## NEXPLANON®

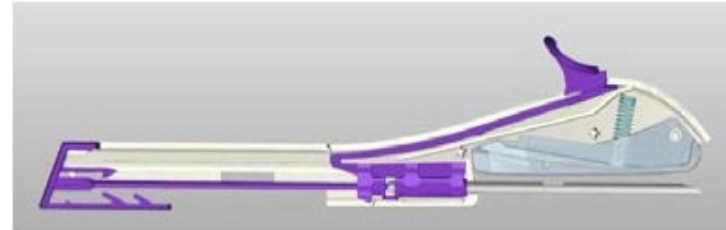
Simplified  
Drug  
Regimens



1998



2011



- Nexplanon® is a sterile implantable rod pre-loaded into a disposable applicator
- More than 99% effective
- Implantation was performed in 27.9 sec ( $\pm$  29.3 SD) as part of a clinical trial<sup>1</sup>
- Access in Family Planning 2020 countries is made possible by collaboration between Merck, Bill and Melinda Gates Foundation, and other partners<sup>2,3</sup>

1. *Monsour et al., Contraception 82(3) pp 243-249 (2010)*

2. *Making Markets Work for the Poor, "Guaranteed Impact" by David Bank, Summer 2016*

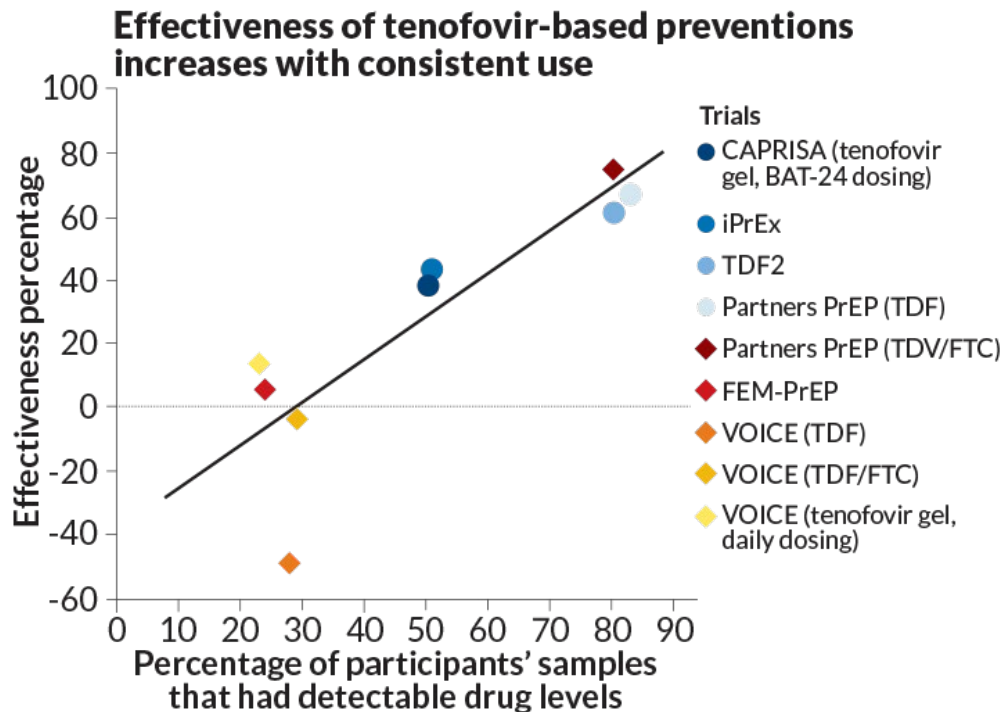
3. *M Kohn, Merck's Commitment to Reproductive Health, Presentation to Johns Hopkins, 2016*



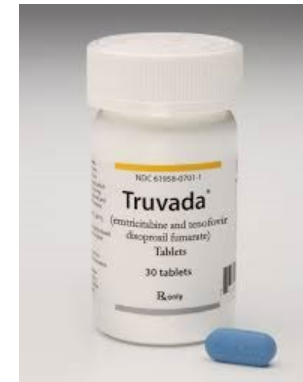
# Pre-Exposure Prophylaxis for Prevention of HIV Infection

Simplified  
Drug  
Regimens

- Pivotal evidence from clinical trials show that pre-exposure prophylaxis (PrEP), using oral tenofovir disoproxil fumarate in combination with emtricitabine, was effective and safe for prevention of HIV infection
- Adherence challenges limit virologic efficacy to only 60% of patients at 82 weeks (Carr, 40,000 Pt Meta-Analysis, IAS 2013)

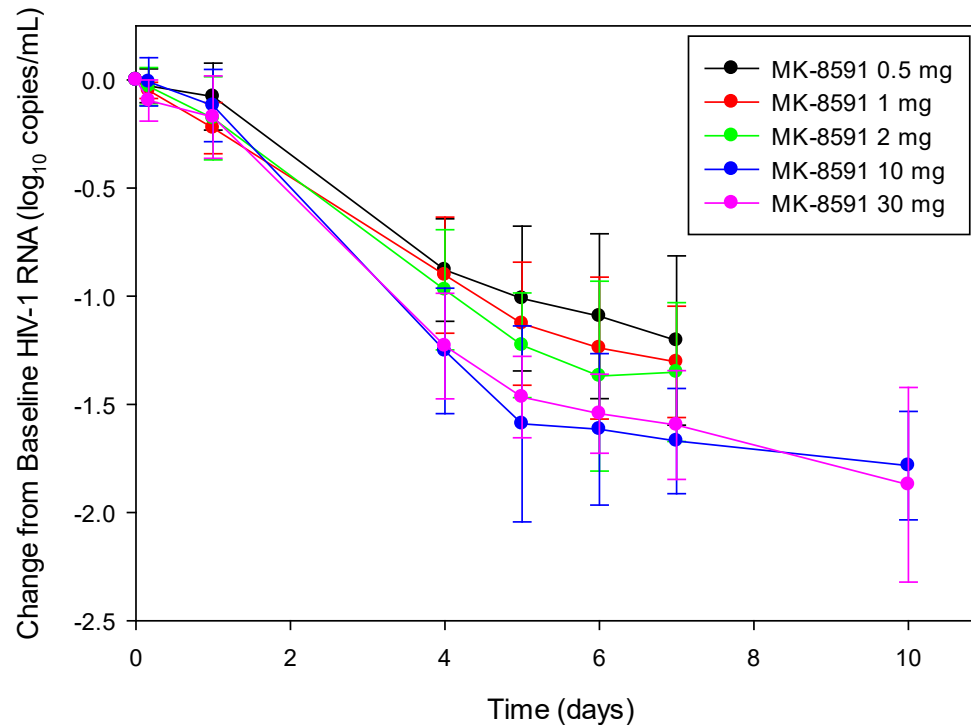


Source: Salim S. Abdool Karim/CAPRISA, AVAC Report 2013



# Single Doses of MK-8591 as Low as 0.5 mg Lead to HIV-1 Suppression in Treatment-Naïve Subjects

Simplified Drug Regimens



MK-8591-P003 All Panels	
Dose (mg)	Posterior mean of placebo-corrected VL change from baseline
30	-1.57
10	-1.64
2	-1.32
1	-1.28
0.5	-1.18

Mutant screening in post-treatment samples negative in all subjects with sufficient VL for testing (17).

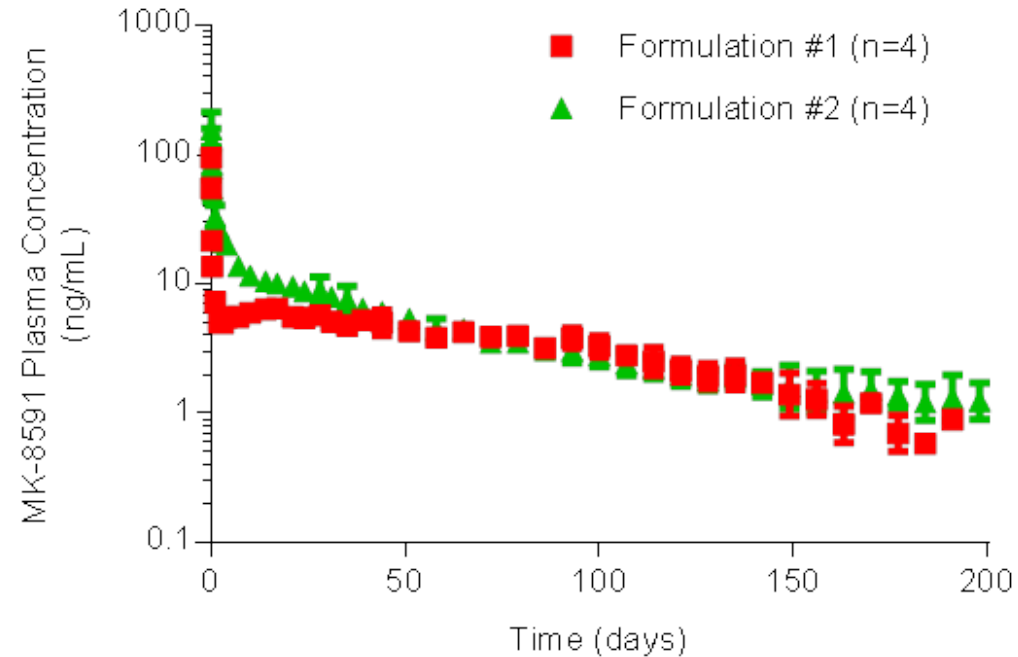
Single doses as low as 0.5 mg of the novel NRTTI MK-8591 suppress HIV for at least seven days; IAS, July 2017

R. P. Matthews, D. Schürmann, D. J. Rudd, V. Levine, S. Fox-Bosetti, S. Zhang, M. Robberechts, I. De Lepeleire, A.s Hüser, D. J. Hazuda, M. Iwamoto, and J. A. Grobler<sup>1</sup> on behalf of the HIV Early Development Team (Merck & Co., West Point, PA)



# MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days

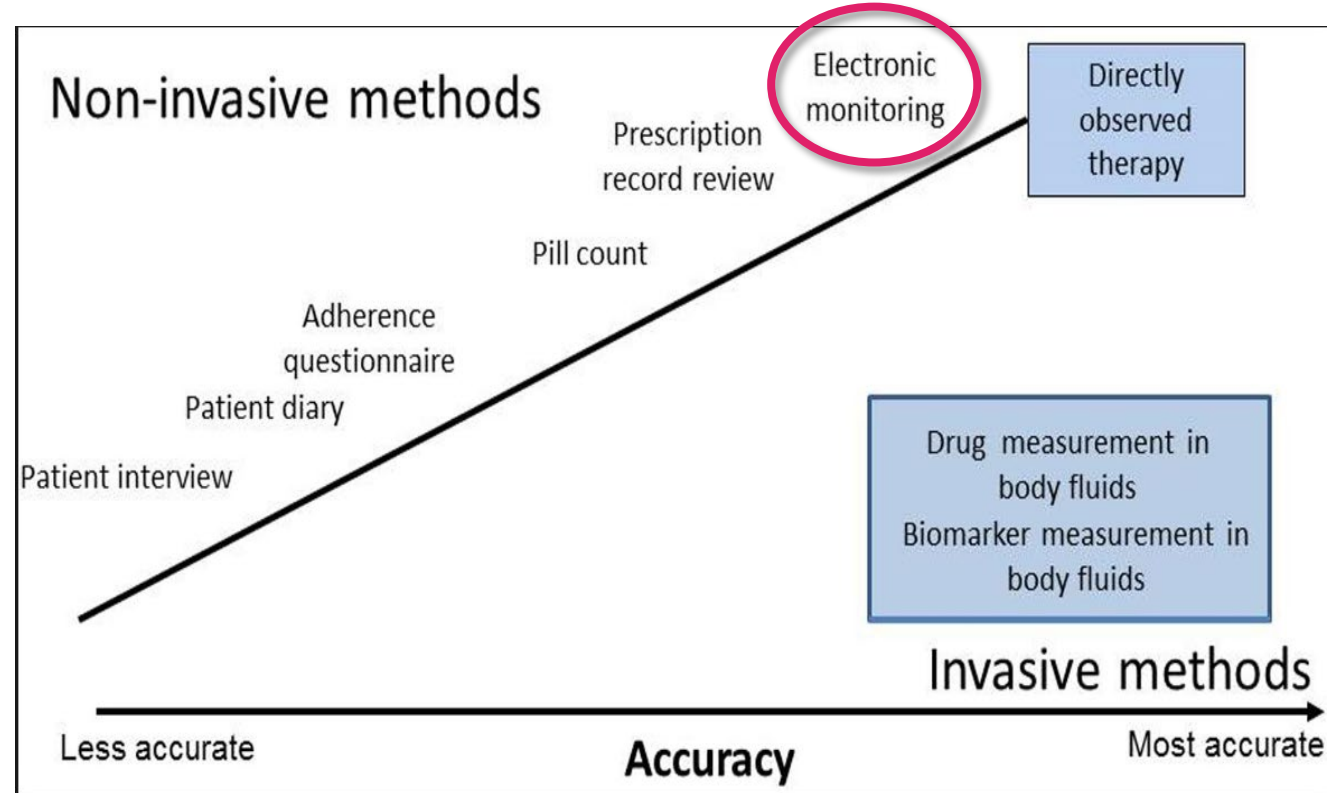
Simplified  
Drug  
Regimens



- Low dose amenable to extended-duration parenteral formulation
- >180-day extended release from solid state formulations after a single injection in rat
- Data suggest the potential to provide coverage for durations up to 1 year

Long-Acting Oral and Parenteral Dosing of MK-8591 for HIV Treatment or Prophylaxis; CROI, Feb 2016; J. Grobler, M. Lai, S. Barrett, M. Gindy, K. Fillgrove, W. Ankrom, S. Wood, E. Friedman, M. Iwamoto, D. Hazuda on behalf of the MK-8591 Early Development Team (West Point, PA)

# Options for Understanding Adherence



The FDA recognizes the need for better adherence data:

- “Decreasing heterogeneity in clinical trials by...automating tracking of compliance has now become standard”<sup>4</sup>
- “Adherence based on patient self-reported compliance and pill count is unreliable....reliability of this data should be improved”<sup>5</sup>

Image: Current Situation of Medication Adherence in Hypertension. *Frontiers in Pharmacology* March 2017 | Volume 8 | Article 100

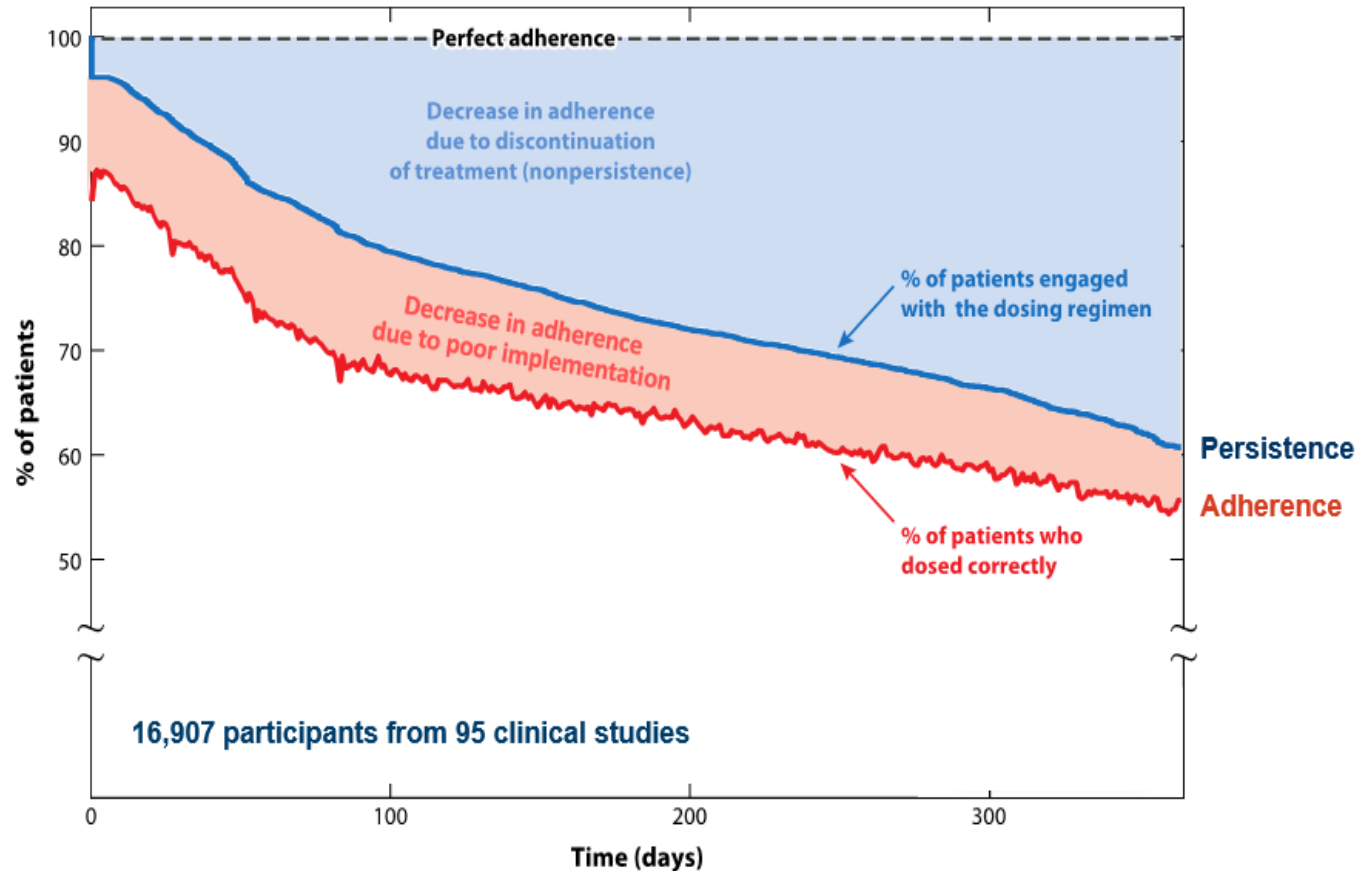
<sup>4</sup>FDA draft guidance: “Enrichment strategies for clinical trials to support approval of human drugs and biological products”, Dec 2012

<sup>5</sup>FDA advisory committee memo, April 2012



# What is Adherence? And Why Does it Matter?

Packaging &  
IT Solutions



## Patients in clinical trials<sup>1</sup>:

- ~4% never initiate therapy
- 20% stopped meds within 100 days
- 40% stopped meds within 1 year

## Substantial evidence in literature that pill counts don't accurately estimate adherence

## In a migraine prophylaxis study<sup>2</sup>, adherence rate of patients:

- Per pill count: 91%
- Per package: 66%
- **25%** of data was non-informative

10

<sup>1</sup>Blaschke TF et. al. Annual Rev Pharmacol Toxicol, 2012

<sup>2</sup>Mulleners et al, Cephalgia 1998

# Smart Dosing: Four categories of adherence technologies

Packaging & IT Solutions

## Diary (electronic/paper)

## Smart packaging

## Photographic documentation

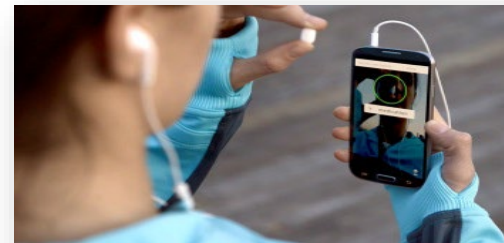
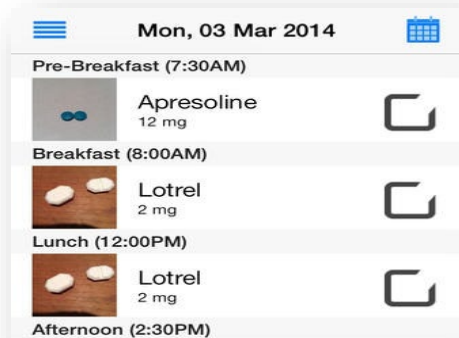
## Ingestible sensor

Self-assessment of drug intake by patient

Micro-circuitry allowing for date and time stamp of entry into packaging, dispensing or actuation

Facial and medication identification and ingestion confirmation

Microcircuit integrated into medication, activated internally, and able to transmit to an external source



# Electronic Adherence Monitoring Options

Packaging &  
IT Solutions

## Why Choose Smart Packaging?

- If passive monitoring is the goal
  - Can still facilitate intervention when patient returns to the site
- If patient population might be challenged by technology use (e.g. smartphone operation)
- If using non-standard dosage forms that require 2 hands
  - Inhaler, injector, etc.

## Why Choose Photographic Documentation?

- If “cheating” is of high concern
- If there are adjunctive therapies we want to track adherence for
- If product stability is a concern
- If we want to go “beyond the package” to engage with patients outside of site visits
- If repeat enrollers (professional patients) are a concern
- If we want the site to intervene in near-real-time

**Regardless of monitoring option, engagement with patients is key**



**MEMS cap<sup>®</sup>**



**Electronic Dosepak<sup>®</sup>**



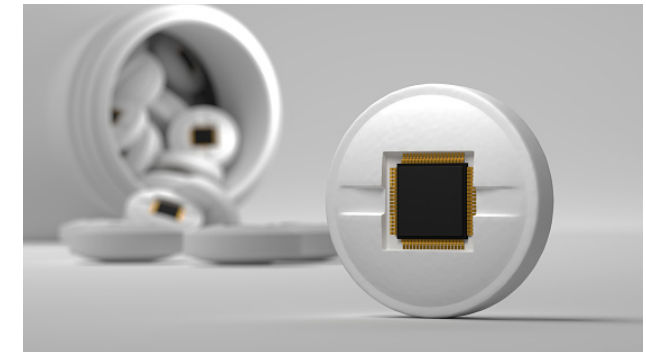
**Cerepak<sup>®</sup>**



**CMT CleverCap<sup>®</sup>**



**AdhereTech Bottle<sup>®</sup>**



**Proteus<sup>®</sup> Pill**



Disclaimer: for example purposes only. Not an endorsement of any product





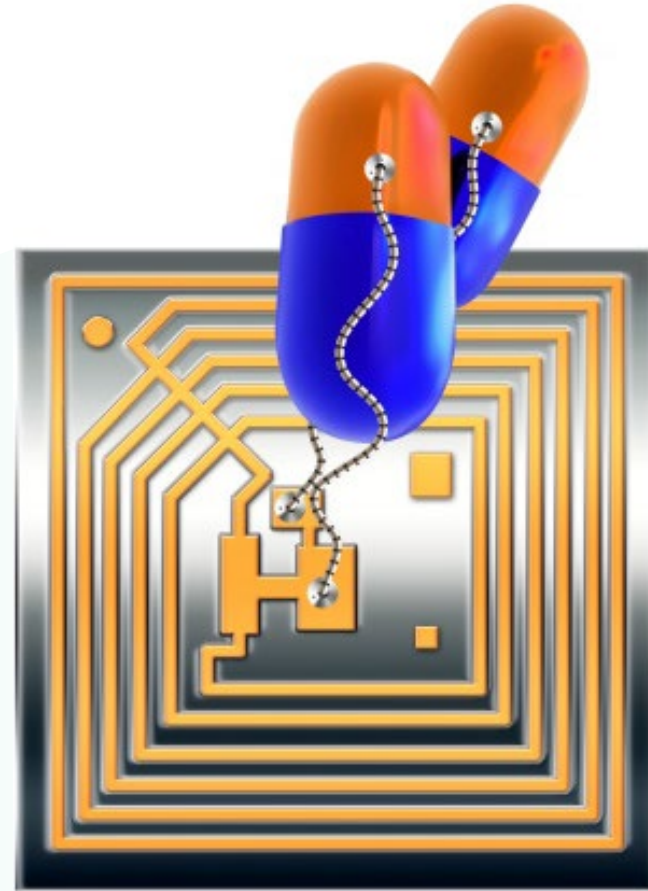
 **NBC NEWS**

**FDA Approves Pill That Tracks Whether You Took Your Meds**

**Nov.14.2017**

**The Food and Drug Administration approved a new pill Tuesday that can track whether people have taken their medications — and report back to the patient or the doctor.**

The idea is to help people remember to take their pills



# What's Next? Social Robotics & Telemedicine

Packaging &  
IT Solutions



Disclaimer: for example  
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It is not a matter of *if*, but *when* we start using the technology

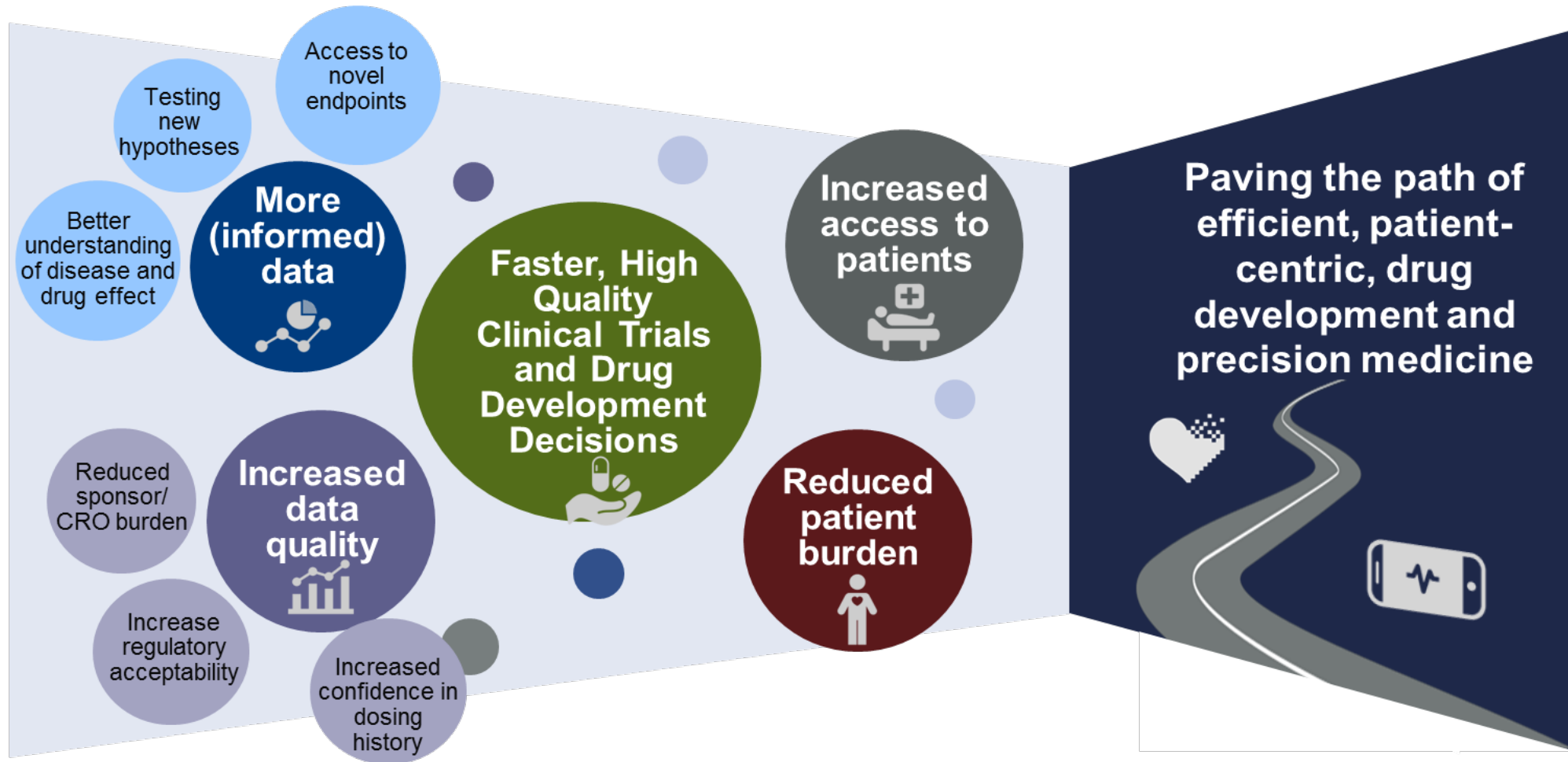


Image: <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1100>

# Summary



- Poor medication adherence represents a significant health care challenge
  - Factors leading to non-adherence are complex and include a spectrum of patient-, social-, economical-, and therapy-related influences
- Impact of non-adherence is significant
- Patient engagement is at the core of adherence improvement
- Simplified dosing regimens, including extended duration dosage forms, offer a valuable opportunity to improve adherence
- Smart dosing technologies offer substantial opportunity to:
  - Create an independent passive (or active) monitor for adherence
  - Engage the patient at their convenience
- Advances in digital health technologies provide additional opportunities

THANK YOU

MERCK

