



# Insights From Monitoring Adherence in Clinical Trials and in Clinical Care: Understanding the Key Question of Drug Forgiveness

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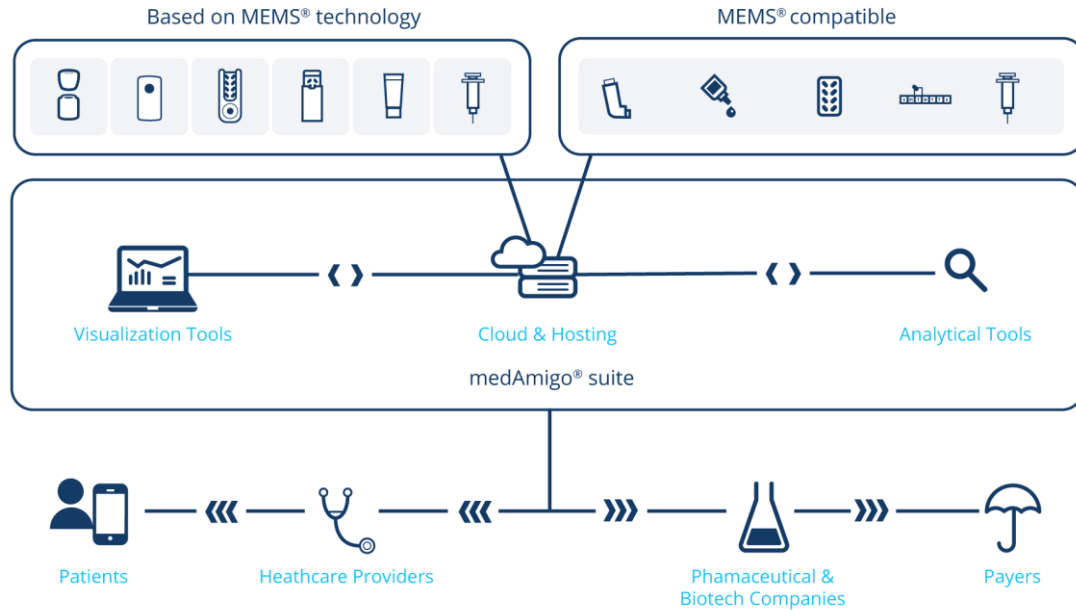
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# Disclosure: CEO of AARDEX Group Advanced Analytical Research on Drug EXposure



Medication  
Event  
Monitoring  
System



### MEMS Bibiometry

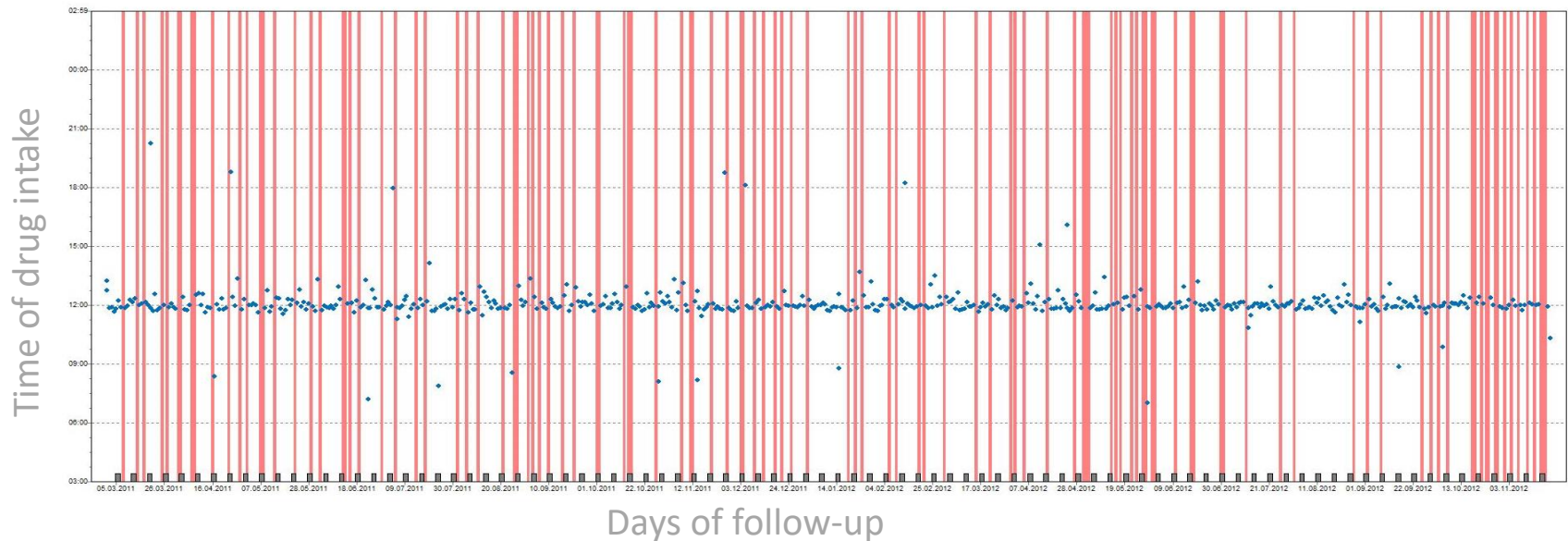
802	70k	138
peer-reviewed publications	journal citations	h-index

March 2019, Google Scholar.

# Case Study



## Dosing History Data over 2 years (2011-2012)



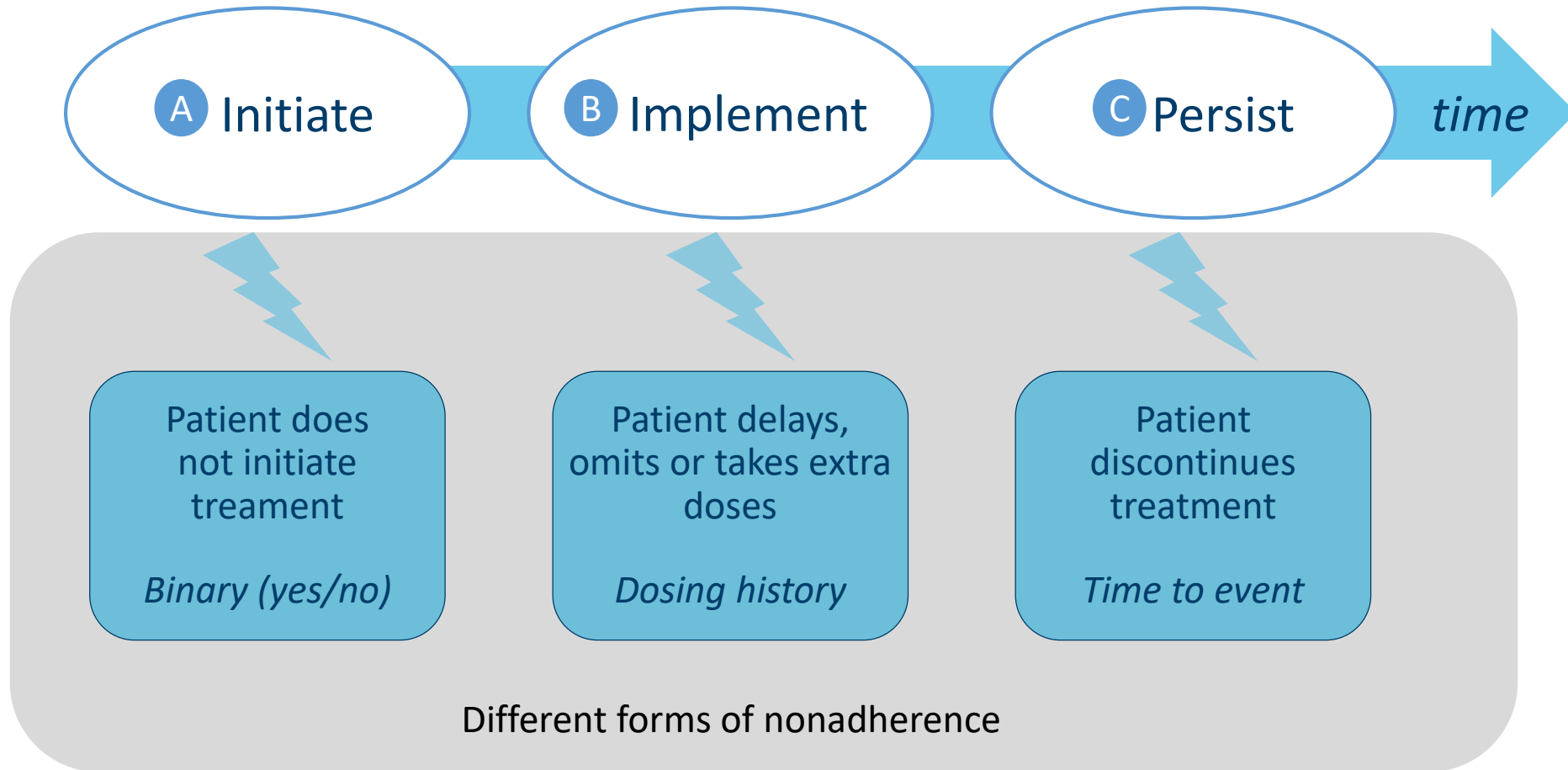
Follow-up: 632 days – 14 days (2%) with double dose & 115 days (18%) no doses

➔ 84% of prescribed doses taken

How much implementation is enough? DRUG'S FORGIVENESS

# ABC Taxonomy & EMERGE guideline

Medication Adherence is the process by which patients take their medications as prescribed



# 20 to 30% of patients do not initiate a new prescription

A Initiate

195,930 e-prescriptions for >75,000 patients

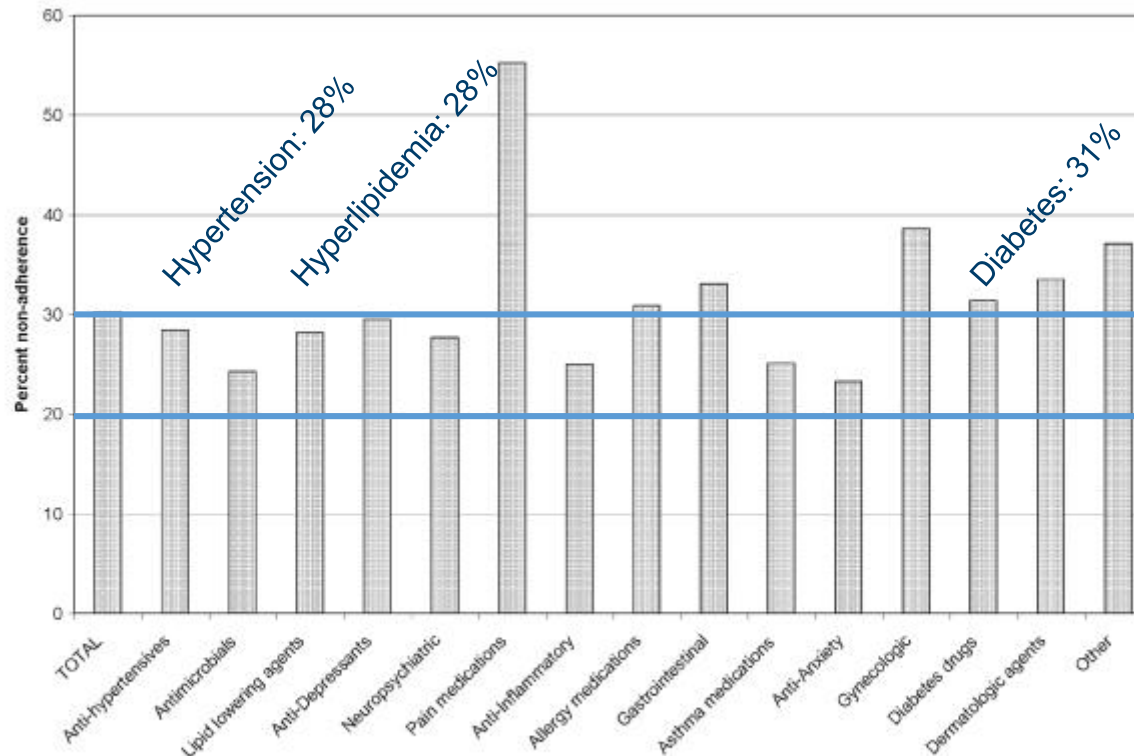


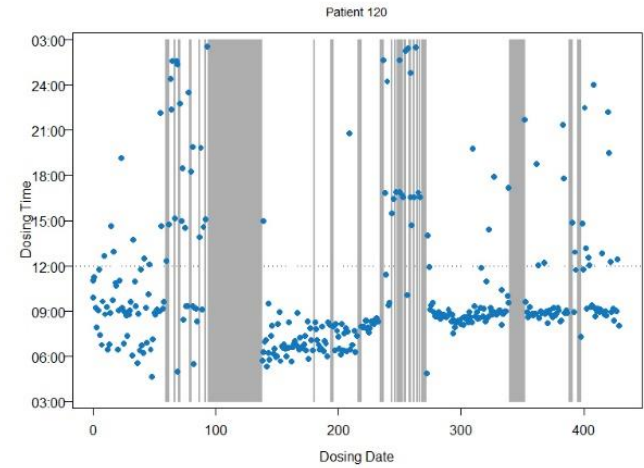
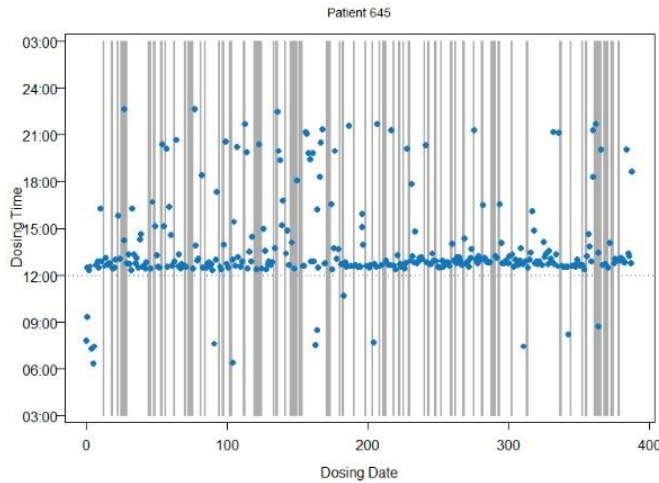
Figure 1. Primary non-adherence to newly prescribed medications. Patients aged 19 and over.

# The Unfortunate 80% rule!

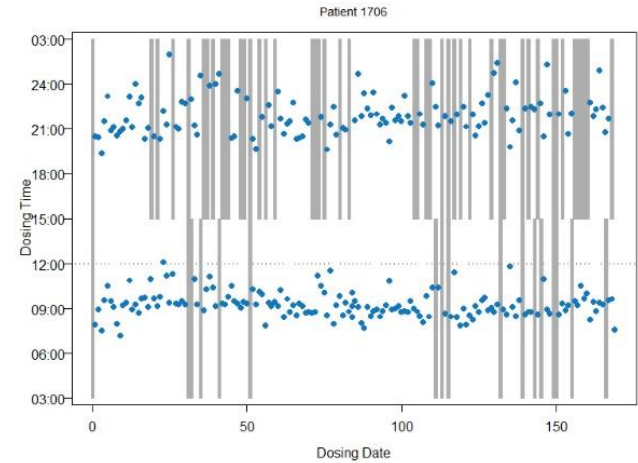
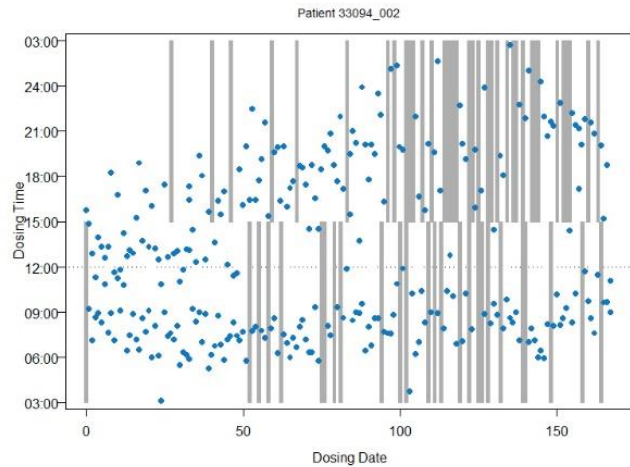


Each of these 6 patients took the same percentage (81%) of prescribed doses

Once daily dosing



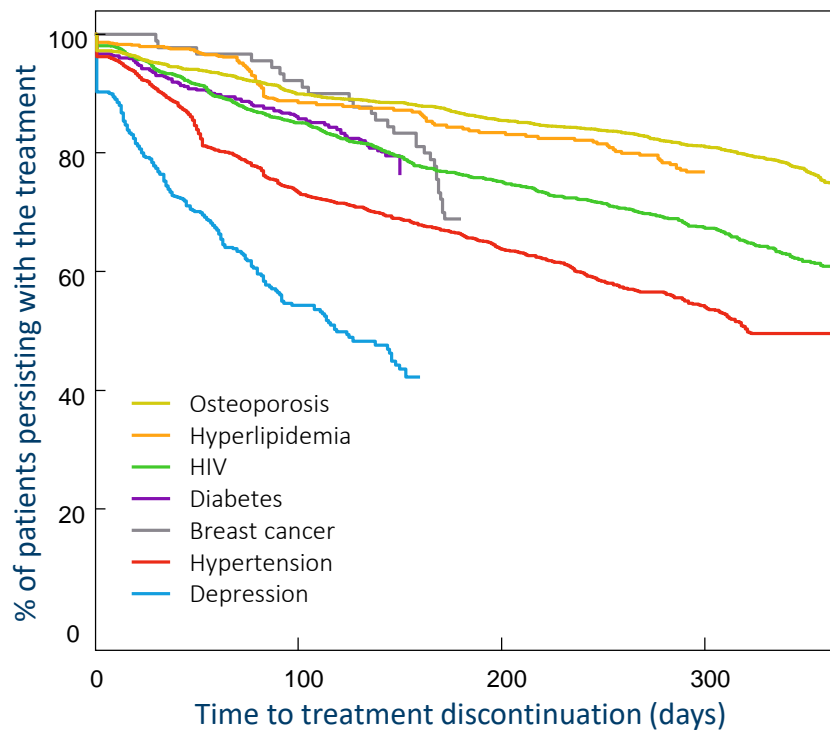
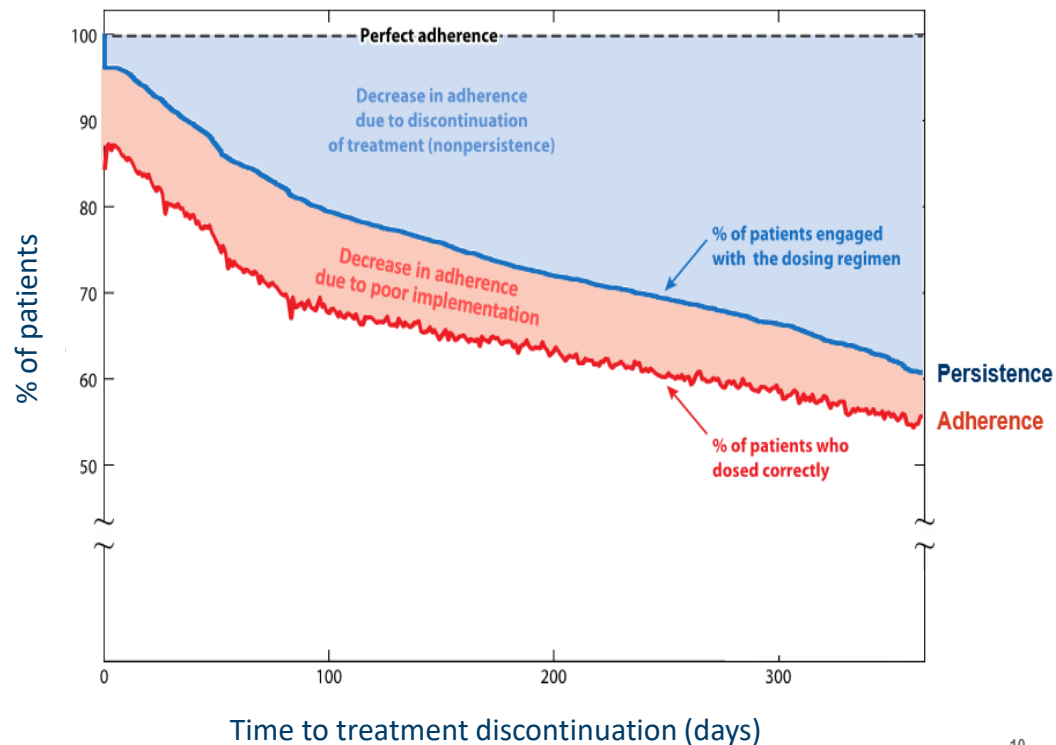
Twice daily dosing



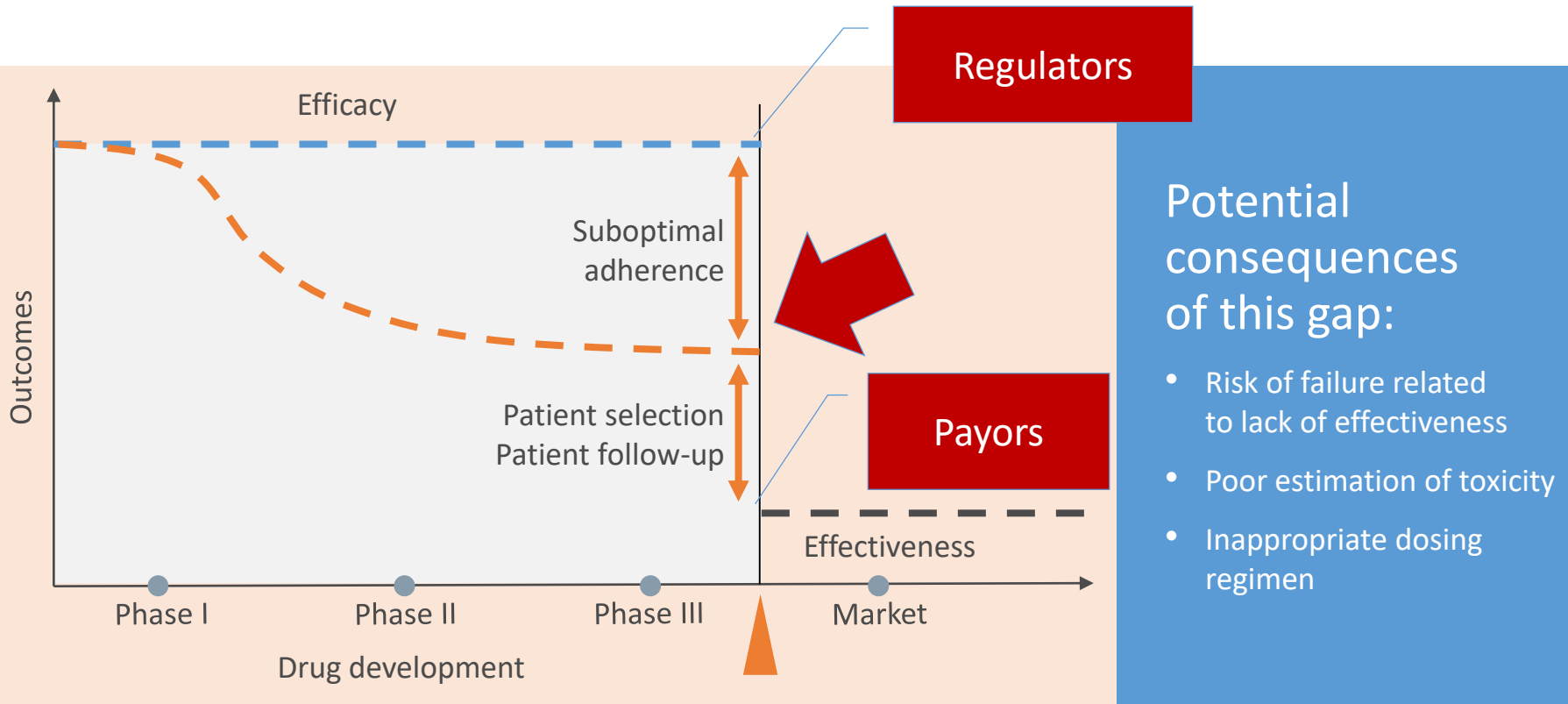
# Overall, 40% of patients will have discontinued treatment by the 12<sup>th</sup> month



N=16,907 participants from 95 clinical studies



# The Adherence Gap



## Adherence is Becoming a Regulatory Priority

Draft guidance from the US FDA explicitly addresses adherence strategies

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. Dec 2012

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2017/08/WC500233916.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/08/WC500233916.pdf). Aug 2017



# Seminal example: the contraceptive pill

**TABLE 2. Efficacy of commonly used methods of contraception\* and percentage of couples using the method — United States, 1995**

Contraceptive method	% women experiencing unintended pregnancy in first year of use		% couples using the method
	Perfect use	Typical use	
Implant (Norplant® and Norplant-2®)	0.05%	0.05%	1.3%
Male sterilization	0.10%	0.15%	10.1%
<b>Pill</b>	<b>0.1%</b>	<b>5.0%</b>	<b>24.9%</b>
Injectable (Depo-Provera®)	0.3%	0.3%	2.7%
Female sterilization	0.5%	0.5%	25.6%
Intrauterine device	0.6% <sup>†</sup>	0.8% <sup>†</sup>	0.7%
Condom (male)	3.0%	14.0%	18.9%
Withdrawal	4.0%	19.0%	2.9%
Diaphragm	6.0%	20.0%	1.7%
Spermicides	6.0%	26.0%	1.3%
Periodic abstinence	9.0% <sup>§</sup>	25.0%	2.2%

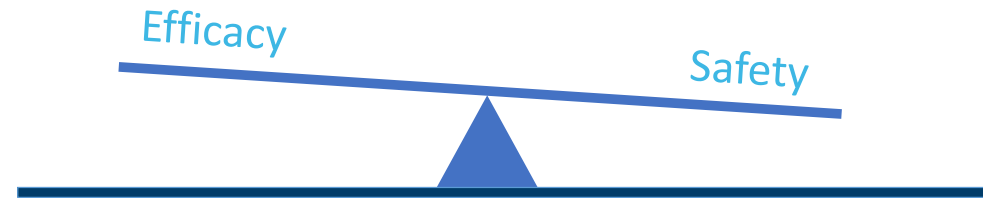


## Key learnings:

1. Today's estrogen dose is one third lower than the first marketed oral contraceptive
2. 50-fold difference in efficacy between perfect use and typical use
3. When possible other delivery systems should be investigated

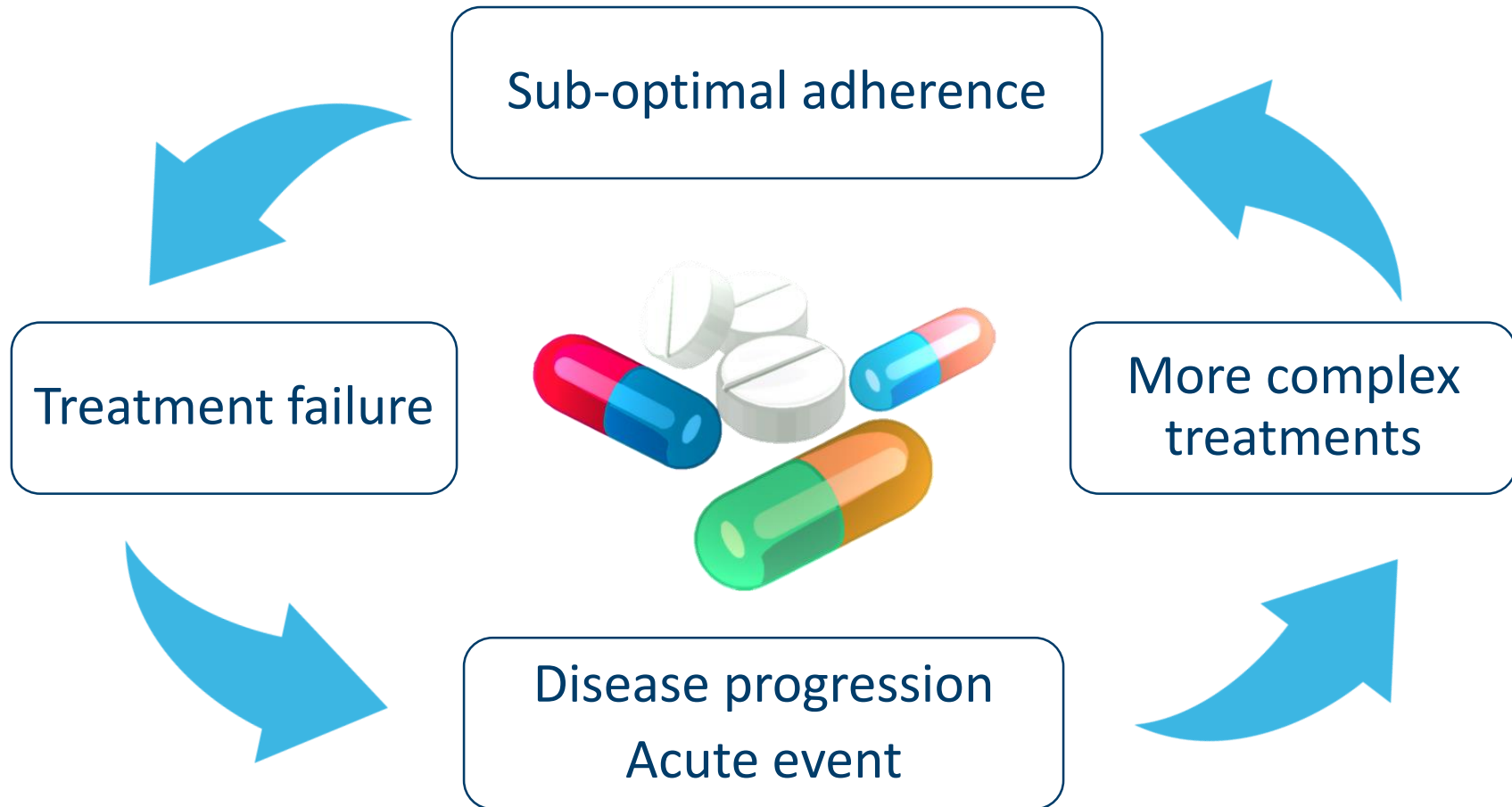
# Adherence un-informed clinical development

« *the quest for the magic dose* »

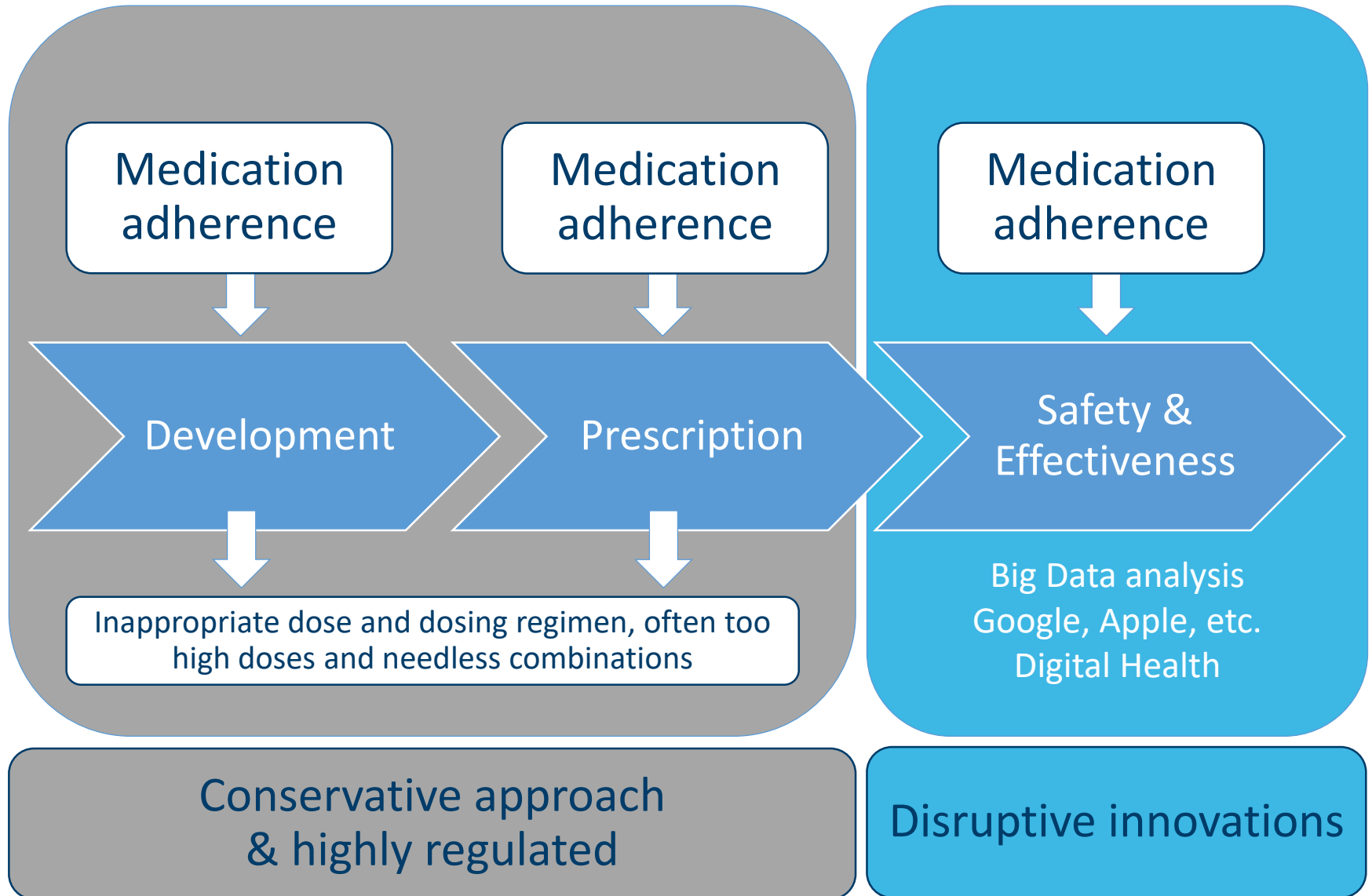


\*based on small, controlled, (adaptive) designs

# Adherence un-informed prescription leads to inappropriate treatment escalation & needless combination therapies



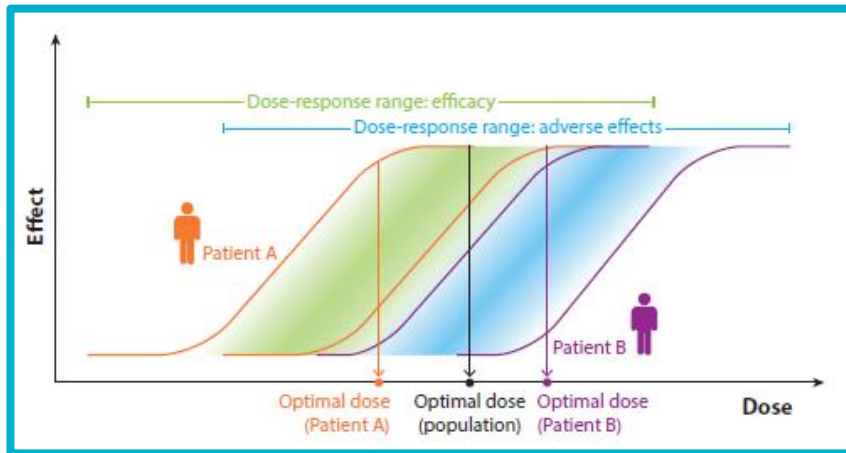
# Adherence-informed development and prescription is urgently needed



# Powerful treatments require a major change in the care model

One dose fits all ?

One dose does not fit all

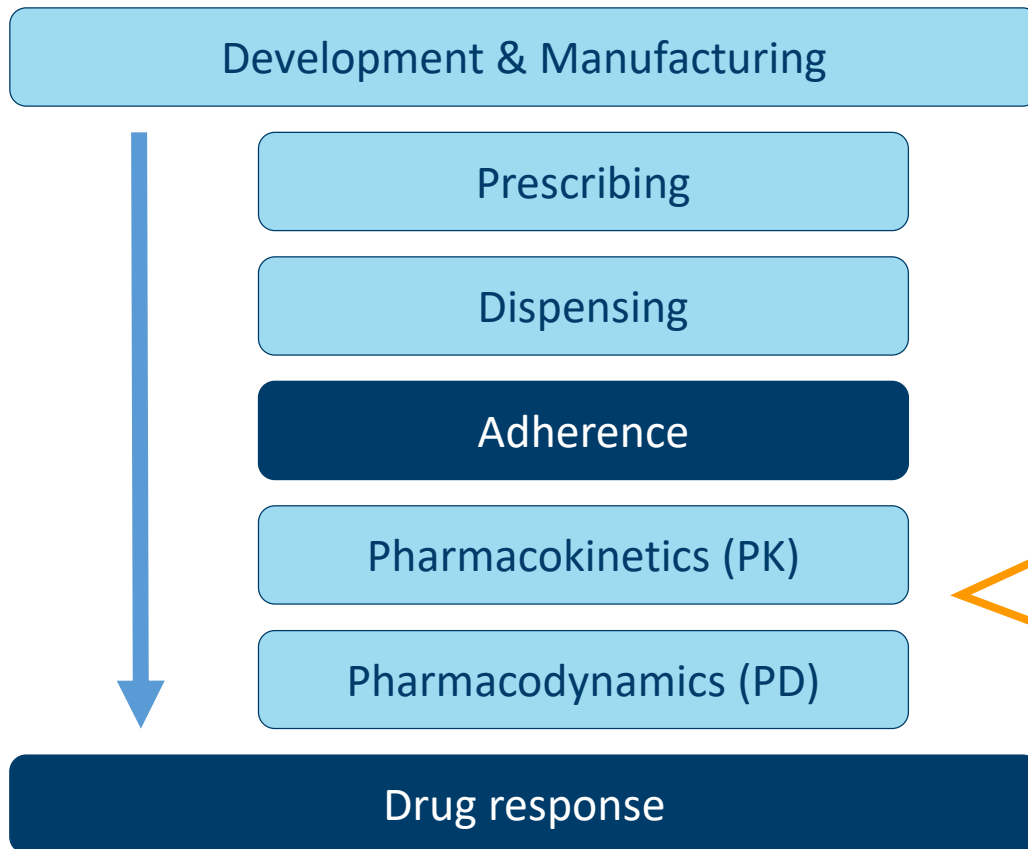


Peck R, Annual Review, 2018

- Need knowledge at point of care
  - Precision medicine
  - Personalized therapy
  - Individualized treatment
  - Patient-centered care
  - m-health / e-health

➔ Medication Adherence is a vital sign to measure and manage

# The solution requires a systematic approach of each process

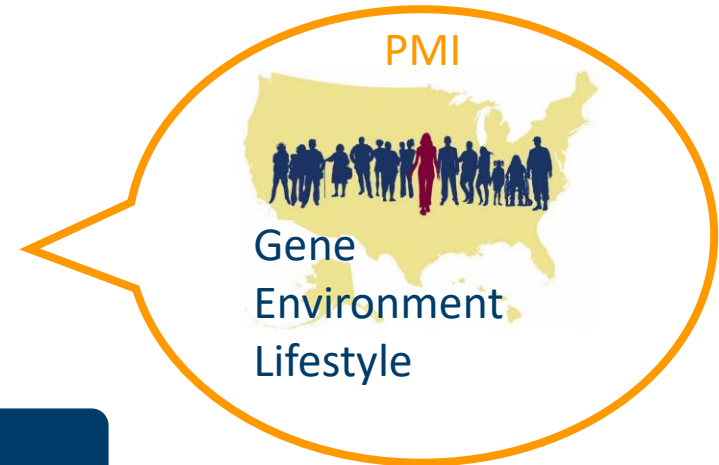


## Poor medication adherence in clinical trials: consequences and solutions

Alasdair Breckenridge<sup>1</sup>, Jeffrey K. Aronson<sup>2</sup>, Terrence F. Blaschke<sup>3</sup>, Dan Hartman<sup>4</sup>, Carl C. Peck<sup>5</sup> and Bernard Vrijens<sup>6</sup>

Poor adherence to medicines in clinical trials can undermine the value of the trials; for example, by compromising estimates of the benefits and risks of a medicine. In this article, we highlight such consequences and also discuss approaches to tackle this problem.

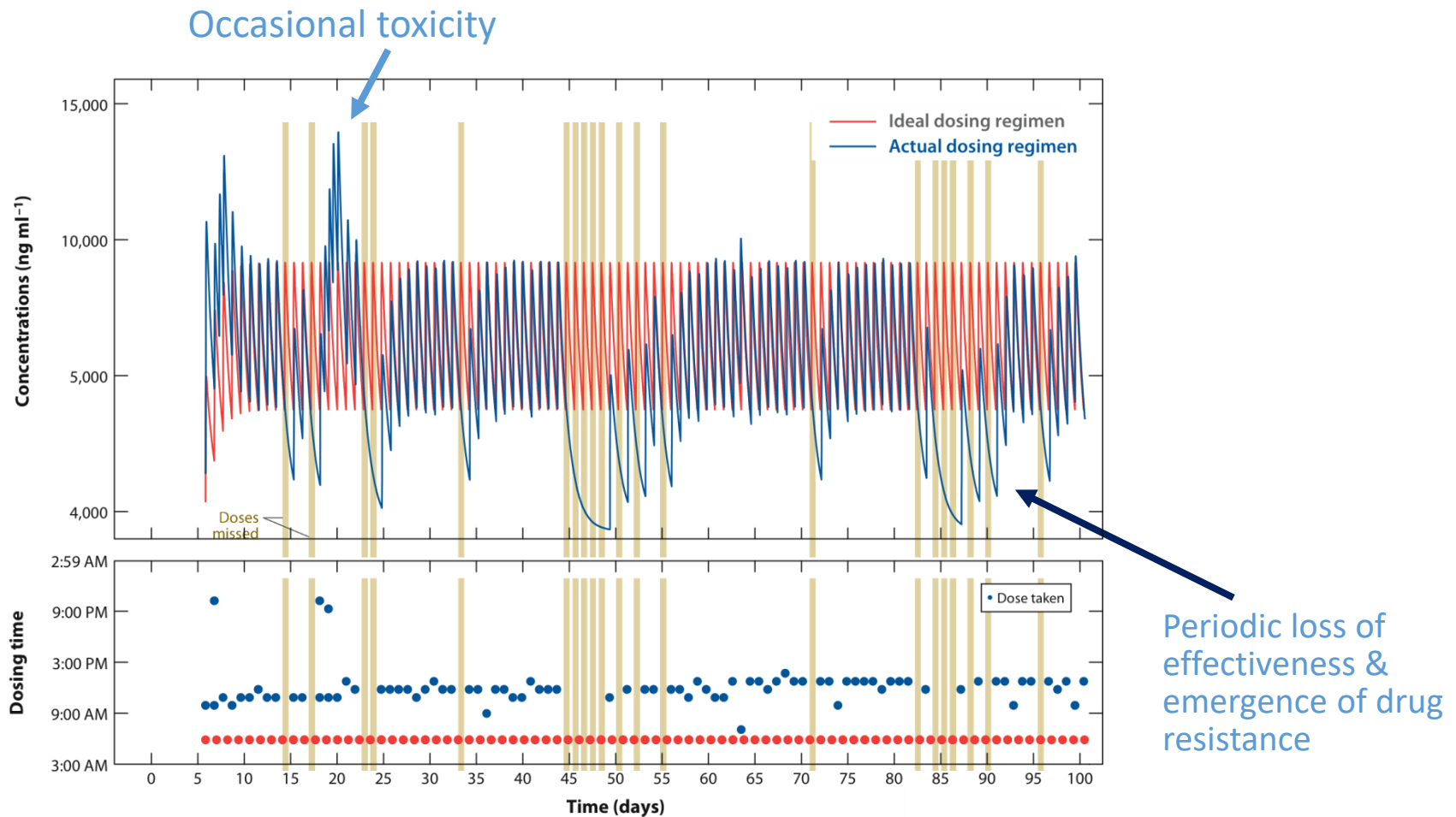
NATURE REVIEWS | DRUG DISCOVERY  
Feb 2017



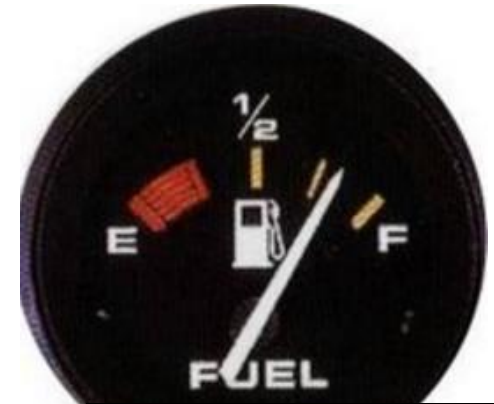
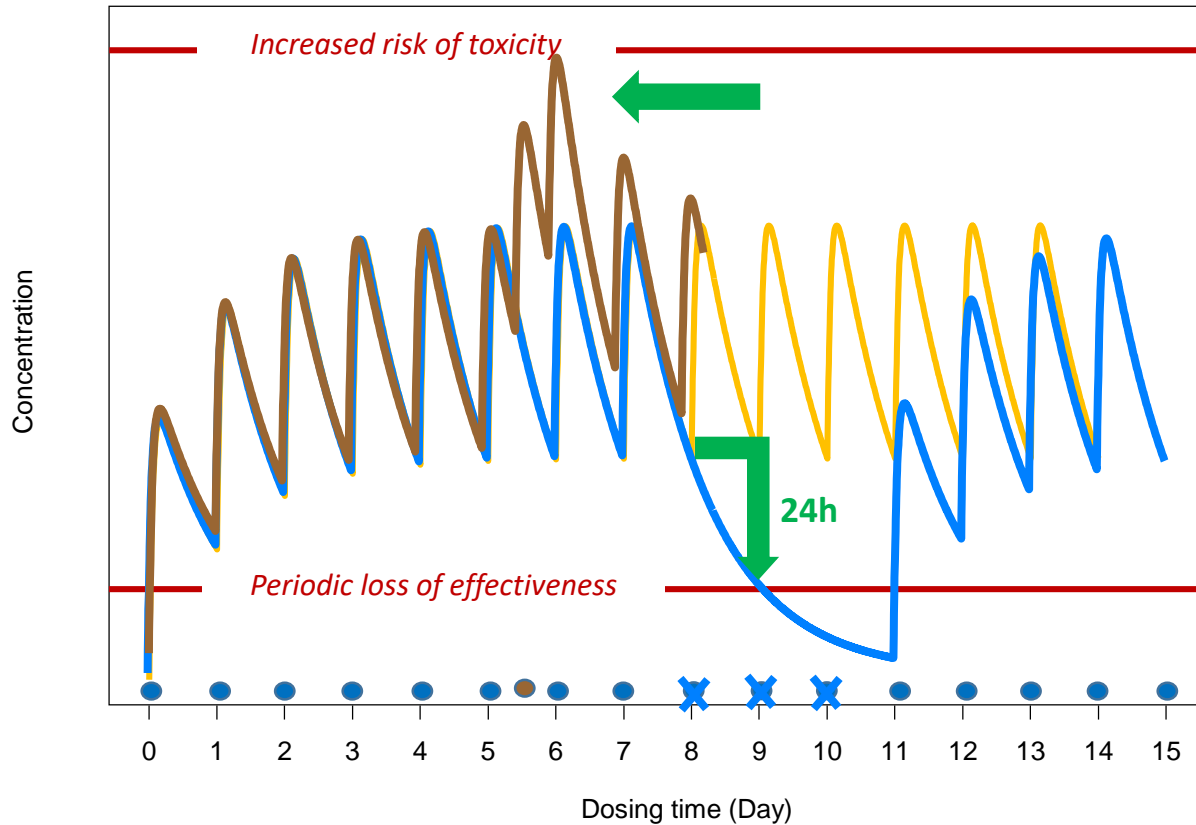
[www.nih.gov/precision-medicine-initiative-cohort-program](http://www.nih.gov/precision-medicine-initiative-cohort-program)

Variable adherence is a major source of variance in drug response

# Variable adherence creates drug-specific issues of efficacy, safety, & drug resistance



# The Concept of Drug Forgiveness Or How Much Implementation is Enough?



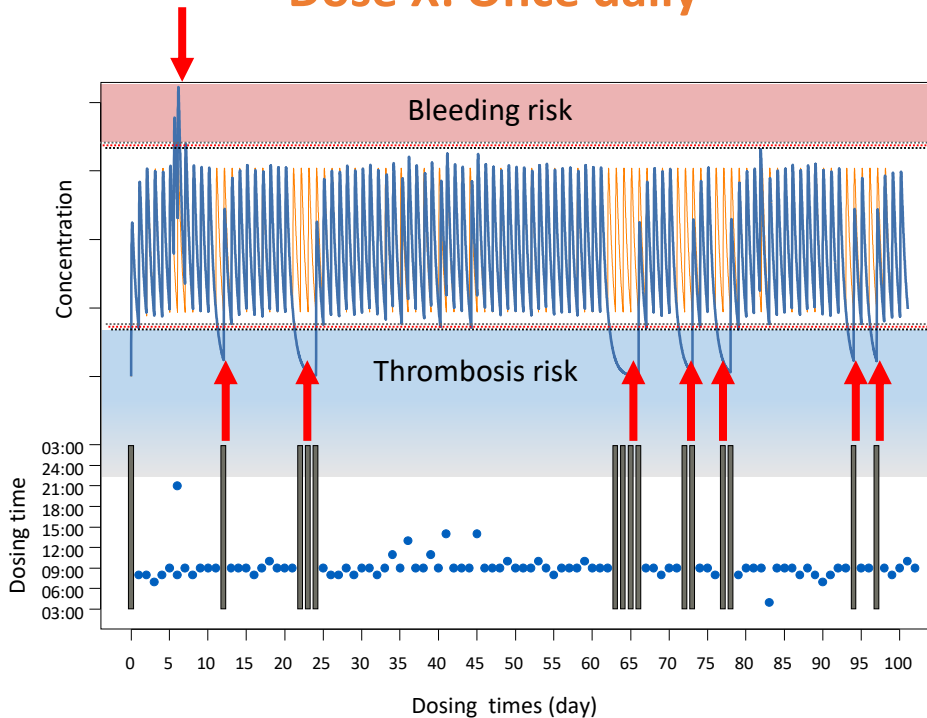


# Beyond adherence, think drug forgiveness

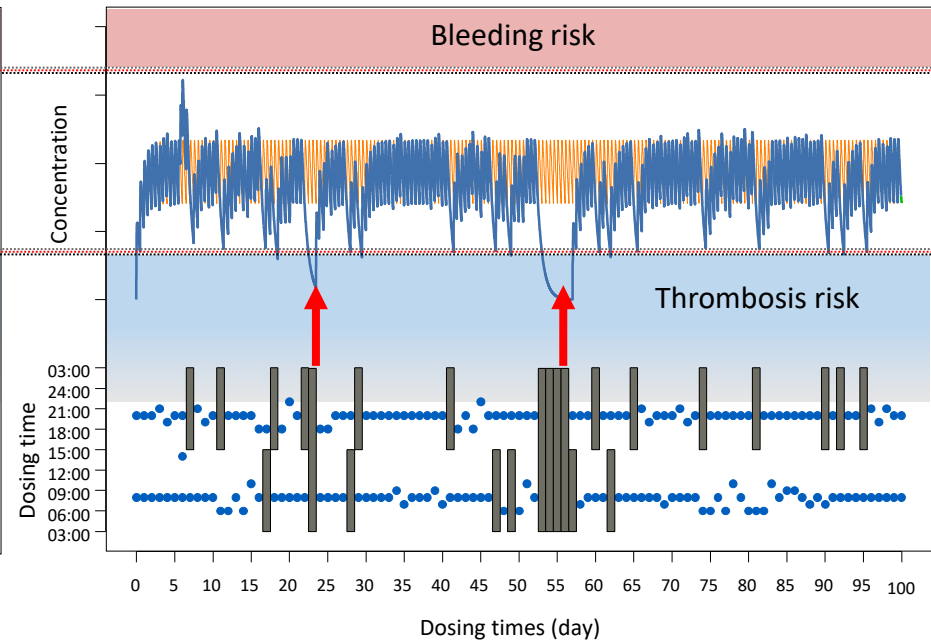
The NOACs example:

Drug exposure simulations assuming  $T_{1/2}=12\text{h}$ ;  $T_{\max}=3\text{h}$

Dose X: Once daily

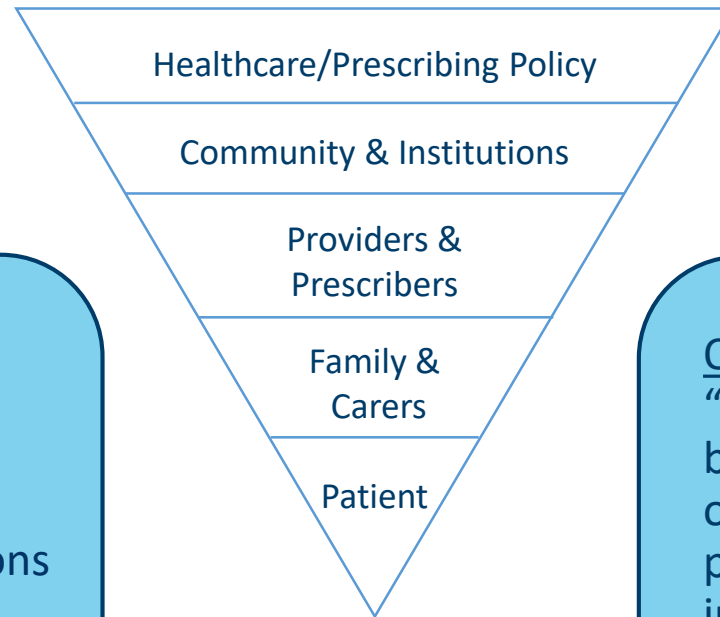


Dose X/2: Twice daily



- 15% missed doses
- 15 once-daily missed doses vs. 30 twice-daily missed doses over 100 days

# Management of adherence: A systems approach



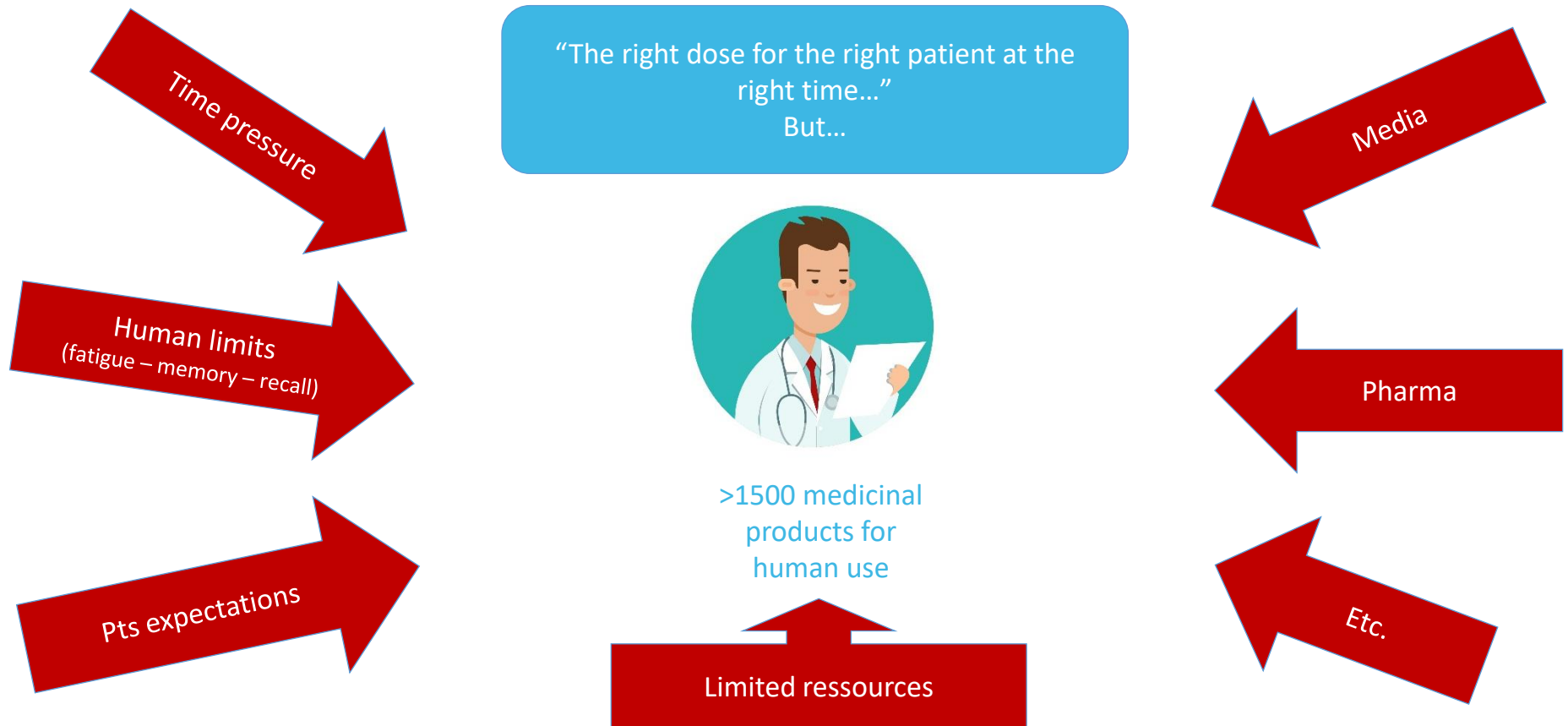
## Definition

“the process of monitoring and supporting patients’ adherence to medications by healthcare systems, providers, patients and their social networks”

## Objective

“to achieve the best use, by patients, of appropriately prescribed medicines in order to maximize the potential for benefit and minimize the risk of harm”

# The Challenge: Integration into care models



# Digitally-Enabled Integrated Person-Centered Care

## A Multi-Disciplinary Approach



# The Age of Patient-Empowerment

## Adherence-Informed Clinical Trials

- Greater efficacy and lower variability (increased power/decreased sample size)
- Better informed benefit/risk and developmental decisions
- Supports strategic trials (adaptive trials, bayesian)
- Faster proof of efficacy
- Validation in broader populations
- Less trial failures



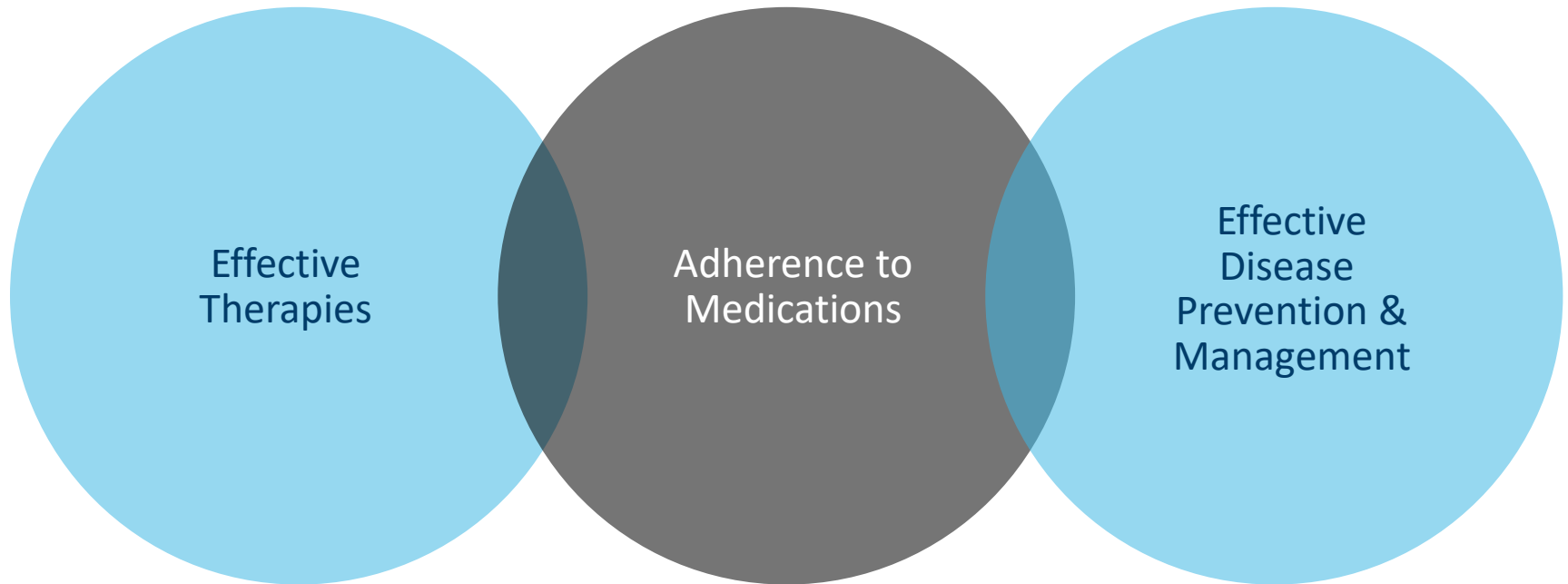
Low Complexity

## Adherence-Informed Digital Health

- More informative safety
- More effective dosing regimens
- Enable individualization / personalization of therapies
- Facilitate a multidisciplinary approach



# Adherence is Key to Therapeutic Success



**“Drugs don’t work in patients  
who don’t take them.”**

– C. Everett Koop, former US Surgeon General