

NIH Adherence Network Distinguished Speakers Webinar

February 2016

High-fidelity measurement of patients' medication adherence: A missing link in precision medicine

Bernard Vrijens, PhD

Chief Science Officer, WestRock Healthcare

Associate Professor of Biostatistics

University of Liège, Belgium



@BernardVrijens

One size does not fit all patients



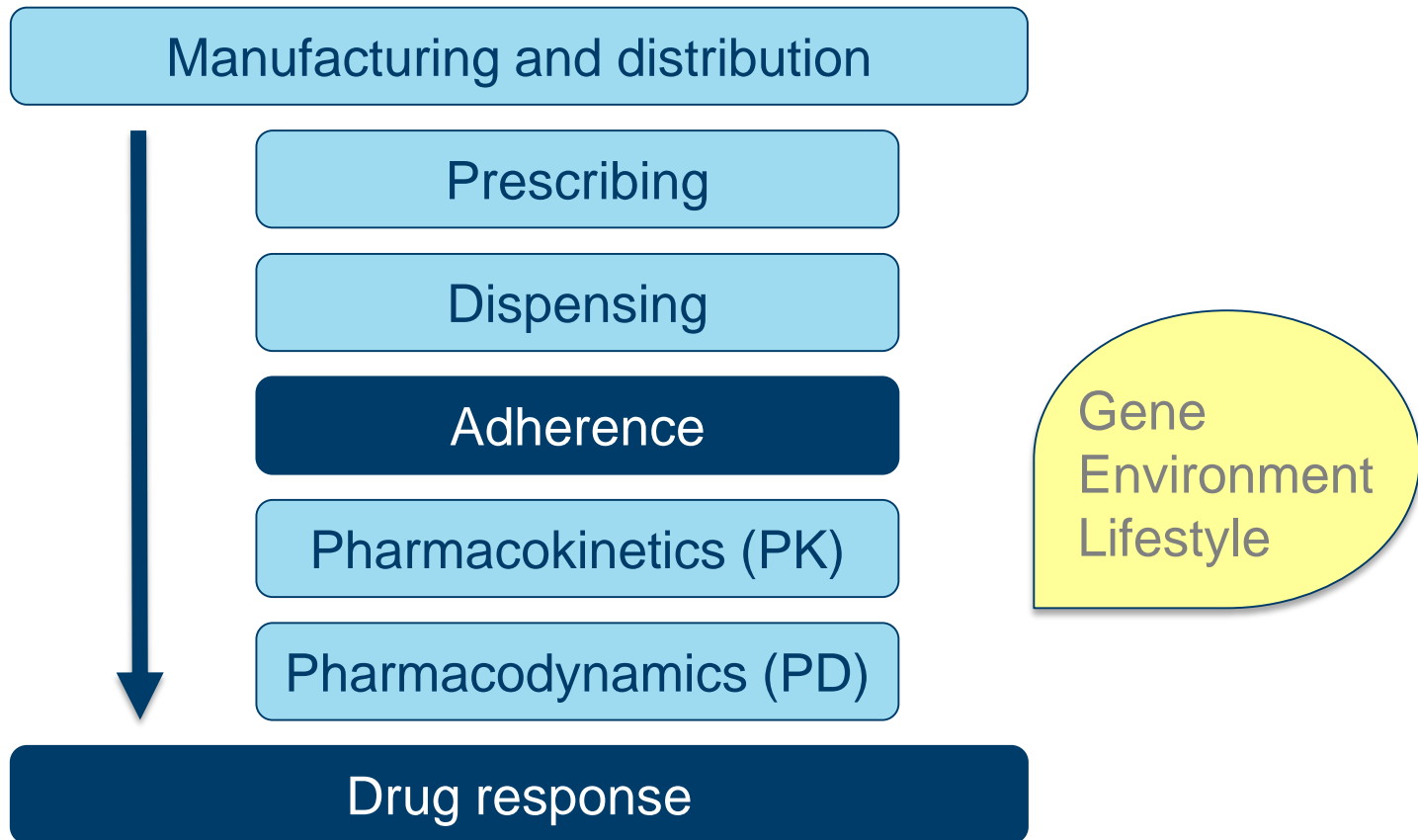
“Individual Variations”

WHAT IS IT?

Precision medicine is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative® will generate the scientific evidence needed to **move the concept of precision medicine into clinical practice.**

Variable adherence is a major source of variance in drug response



Why is high-fidelity measurement of medication adherence a missing link?



NEAR-TERM GOALS

Intensify efforts to apply precision medicine to **cancer**.

Innovative **clinical trials** of targeted drugs for adult, pediatric cancers



Use of **combination therapies**



Knowledge to overcome **drug resistance**



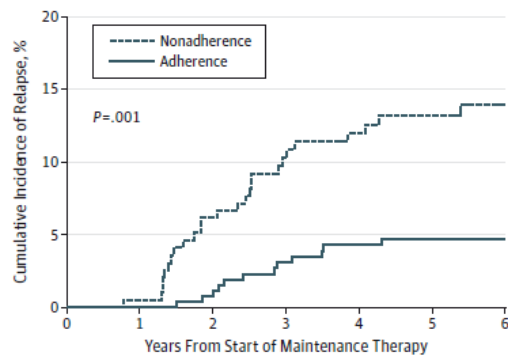
Innovative Clinical Trials for adult, pediatric cancers ... Adherence matters!

Original Investigation

Systemic Exposure to Thiopurines and Risk of Relapse in Children With Acute Lymphoblastic Leukemia A Children's Oncology Group Study

Smita Bhatia, MD, MPH; Wendy Landier, PhD, RN; Lindsey Hageman, MPH; Yanjun Chen, MS; Heeyoung Kim, MPH; Can-Lan Sun, PhD; Nancy Kornegay, MS; William E. Evans, PharmD; Anne L. Angiolillo, MD; Bruce Bostrom, MD; Jacqueline Casillas, MD, MSHS; Glen Lew, MD; Kelly W. Maloney, MD; Leo Mascarenhas, MD, MS; A. Kim Ritchey, MD; Amanda M. Termuhlen, MD; William L. Carroll, MD; F. Lennie Wong, PhD; Mary V. Relling, PharmD

Figure 2. Cumulative Incidence of Relapse Associated With Low vs High Adherence to 6-Mercaptopurine (6MP) Regimens in Children With Acute Lymphoblastic Leukemia



No. at risk at each year	1	2	3	4	5	6
Adherence	272	267	259	244	222	203
Nonadherence	198	195	182	166	146	124

Adherence is defined as a 95% or greater adherence rate; nonadherence is an adherence rate lower than 95%.

EDITORIAL

Thiopurines for the Treatment of Acute Lymphoblastic Leukemia in Children What's Old Is New

Franklin O. Smith, MD; Maureen M. O'Brien, MD, MS

The treatment of children with acute lymphoblastic leukemia (ALL) is one of the greatest success stories in the history of medicine. The 5-year overall survival rate for children with ALL has improved from approximately 10% in the 1960s to greater than 90% with contemporary treatment regimens,^{1,5} with almost all children who remain in remission for more than 4 years after completion of treatment considered "cured."⁶ One of the key reasons for this remarkable achievement has been the enrollment of children with

in response to findings from serial monitoring of the patient's ANC, platelet count, and hepatic transaminases, with the most recent trials incorporating TPMT genotype and intermittent monitoring of erythrocyte TGN levels in select circumstances (eg, Children's Oncology Group [COG] trial AALL0922; clinicaltrials.gov/identifier/NCT0190990). This practice results in dose reductions, dose increases, and interruptions in therapy most commonly in response to ANC or platelet count outside of the target ranges. Titrating the dose of 6MP is clearly complex and requires a high level of monitoring, education, communication, and compliance. As a result, it is well known that

40% of children had <95% adherence leading to a 2.7 fold increase in relapse rate (N=600)

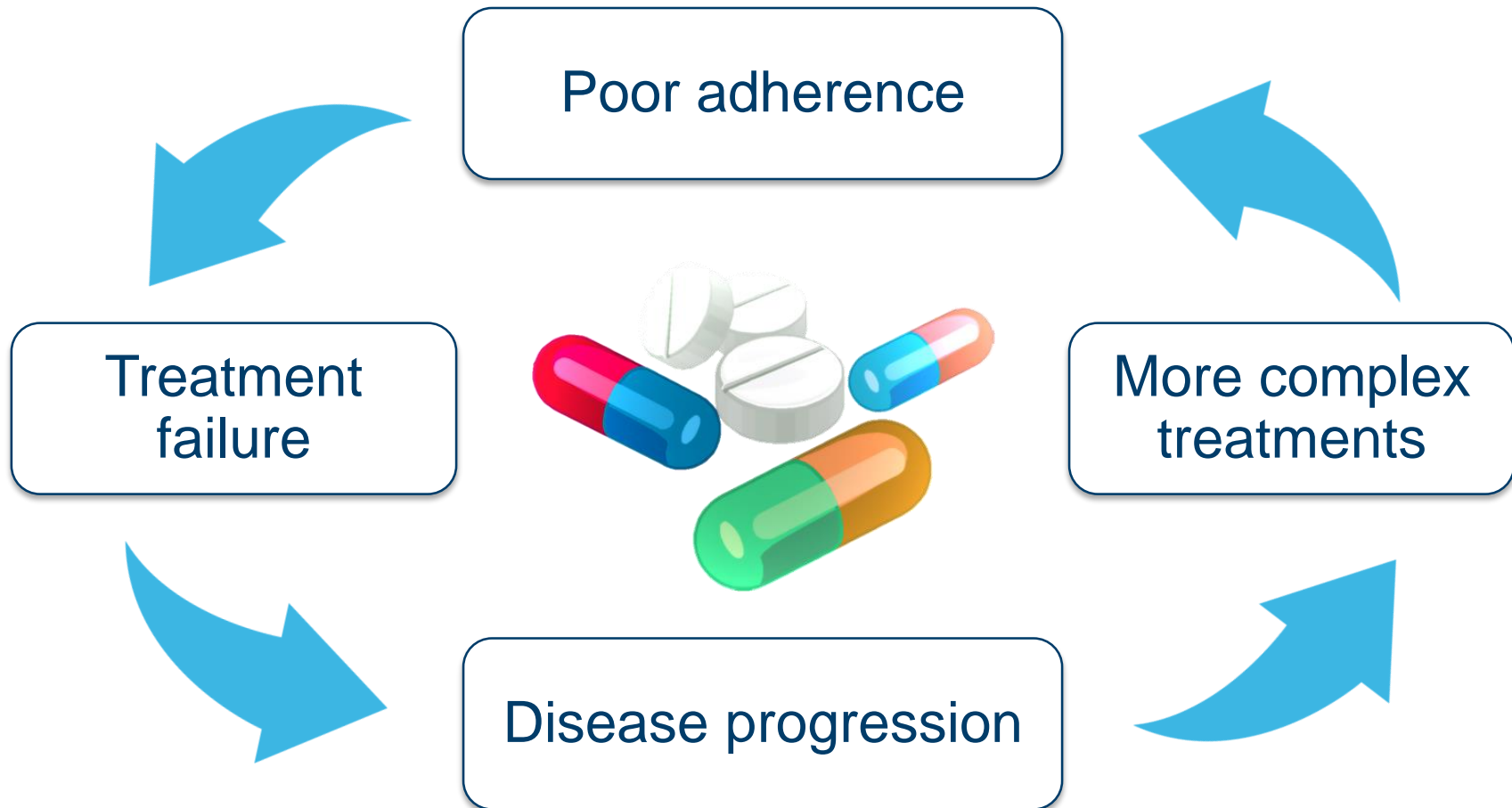
"... we must not lose sight of the fact that precision medicine also applies to optimizing known effective therapy"



thioguanine nucleotide (TGN) metabolite level polymorphisms (eg, thiopurine methyltransferase) and measurement of absolute neutrophil counts (ANC) to guide drug administration according to circadian thiopurine transferase levels, physician compliance, and adherence to prescribed therapy.⁷ As a result of this, the maintenance phase dosing is now based on the

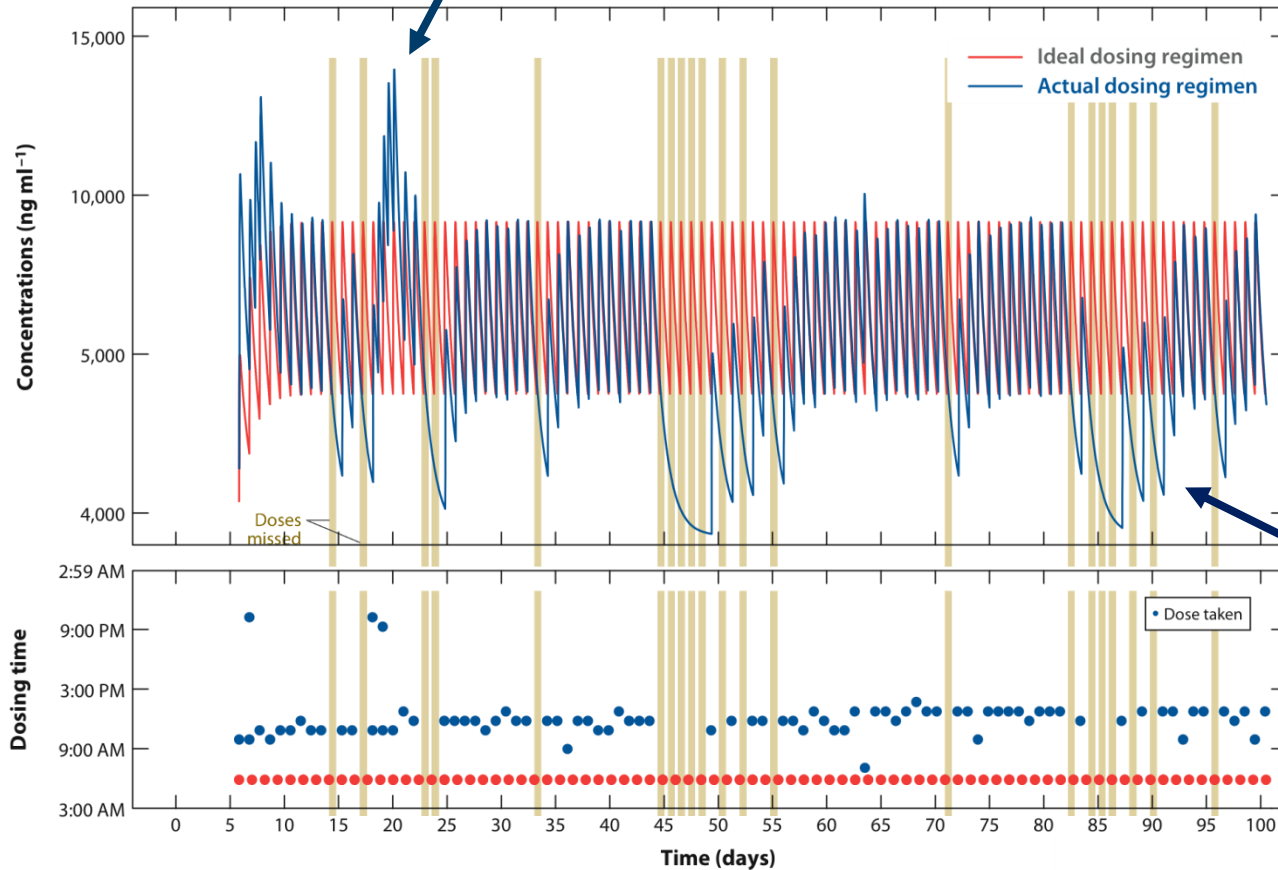
jamaoncology.com

Addressing adherence is key to avoid treatment escalation & needless combination therapies



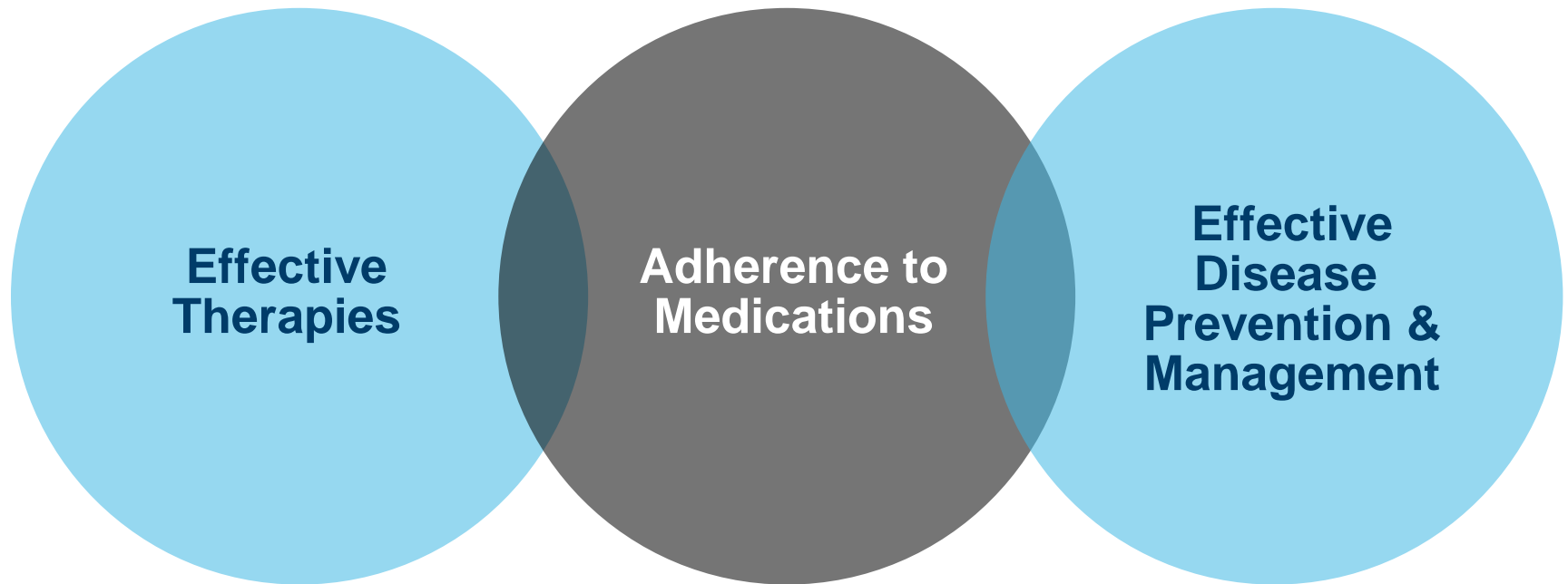
Variable adherence creates drug-specific issues of efficacy, safety, & drug resistance

Occasional toxicity



Periodic loss of effectiveness & emergence of drug resistance

Adherence is Key to Therapeutic Success

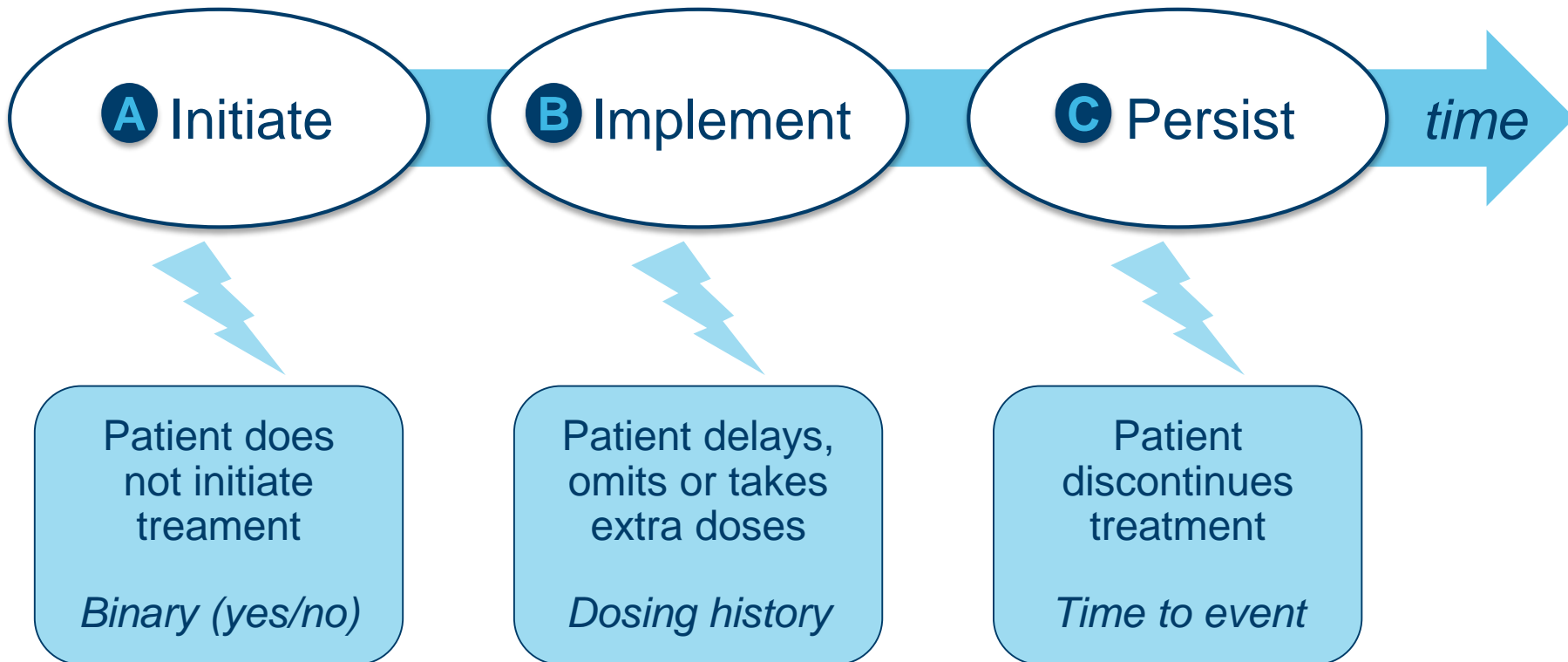


**“Drugs don’t work in patients
who don’t take them.”**

– C. Everett Koop, former US Surgeon General

Medication adherence: ABC Taxonomy

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

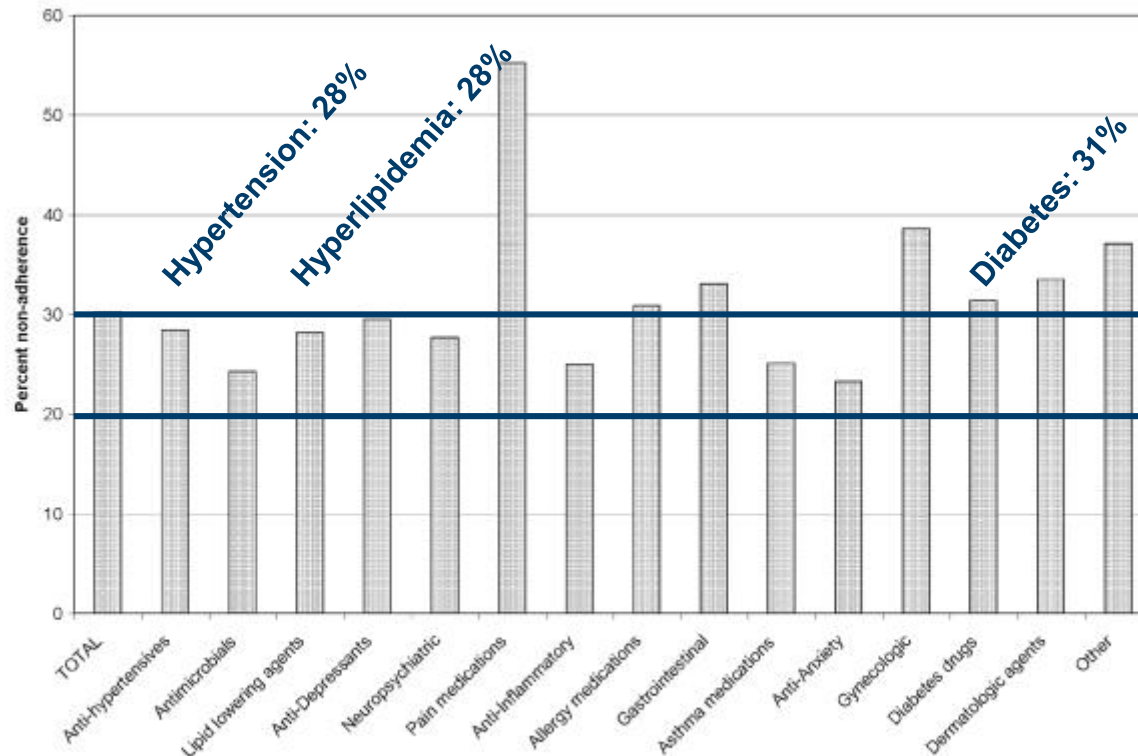
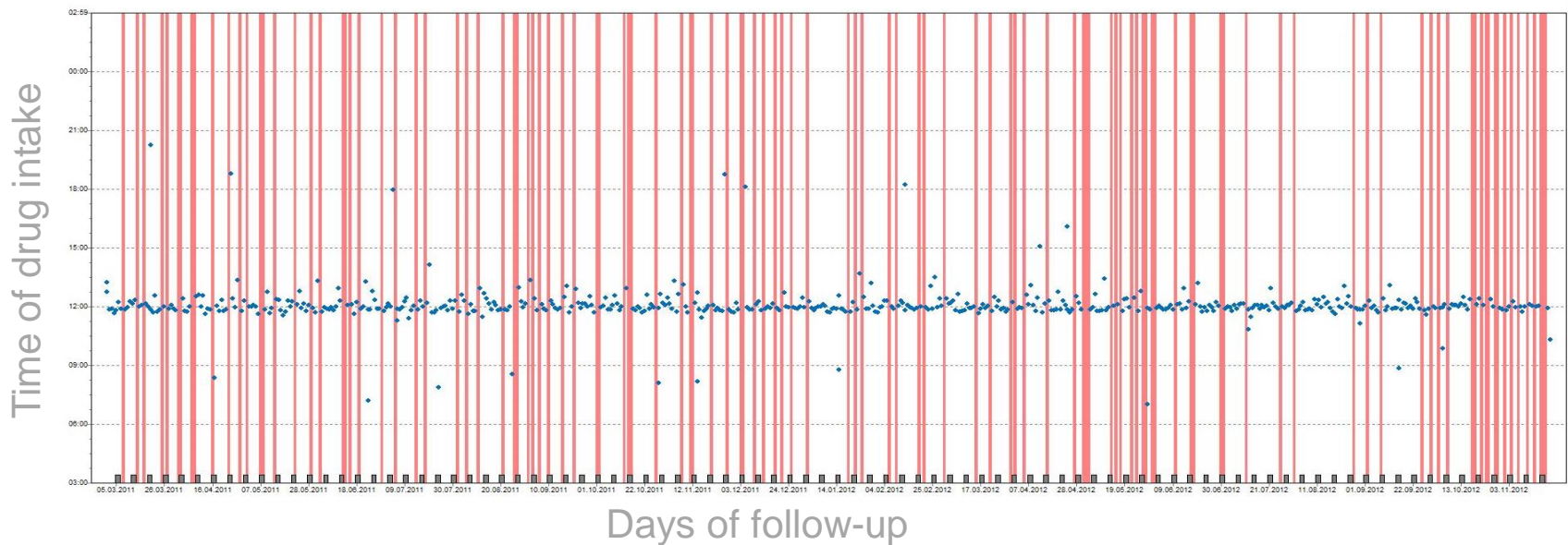


Figure 1. Primary non-adherence to newly prescribed medications. Patients aged 19 and over.

Daily, 15% of patients do not implement as prescribed



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

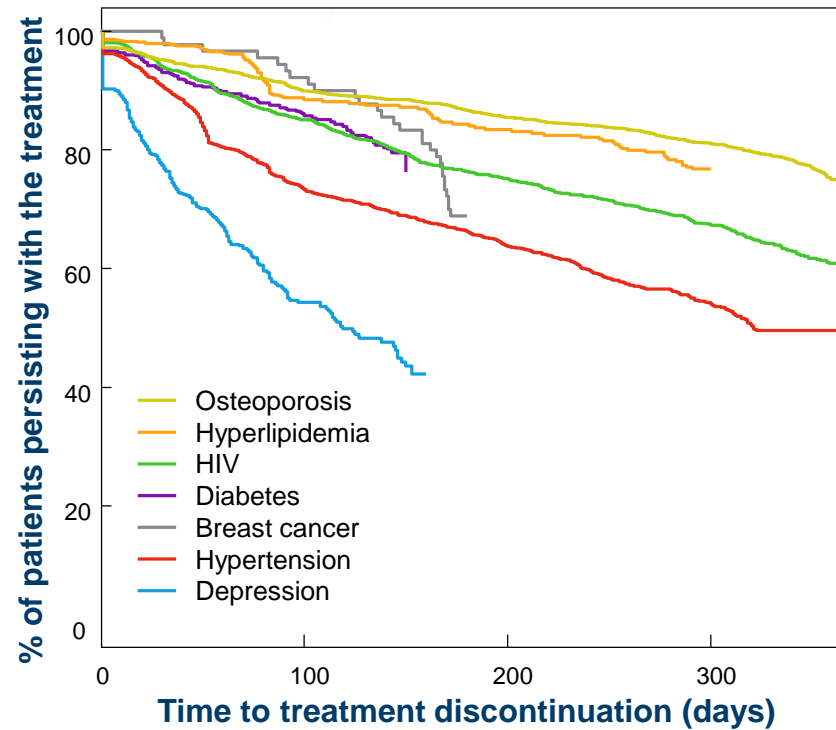
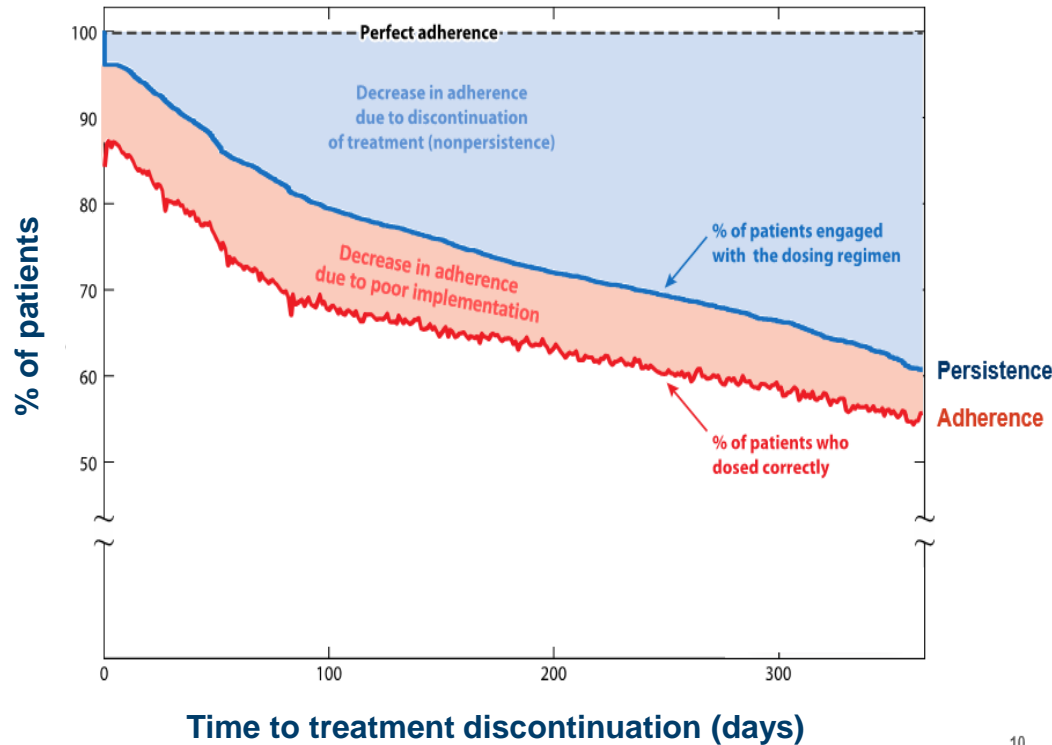
➔ **84% of prescribed doses taken**

How much implementation is enough? **DRUG'S FORGIVENESS**

Overall, 40% of patients will have discontinued treatment by the 12th month

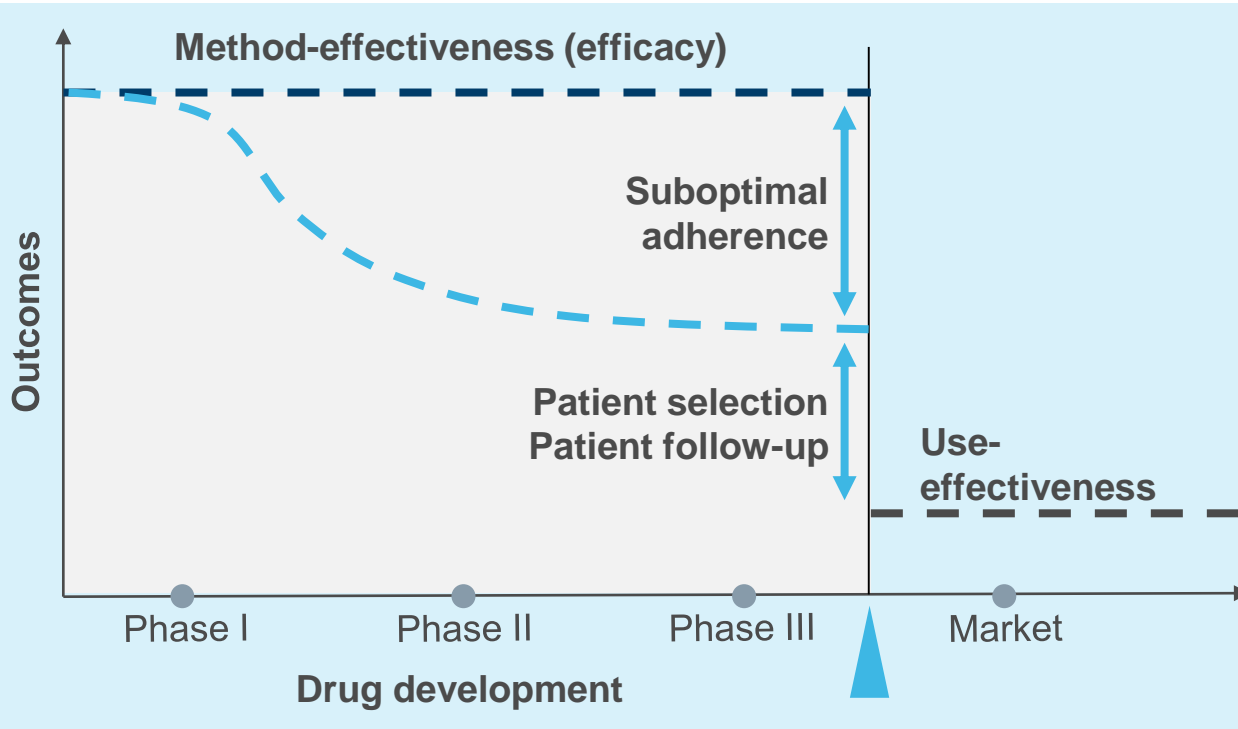


N=16,907 participants from 95 clinical studies



10

The Adherence Gap



Potential consequences of this gap:

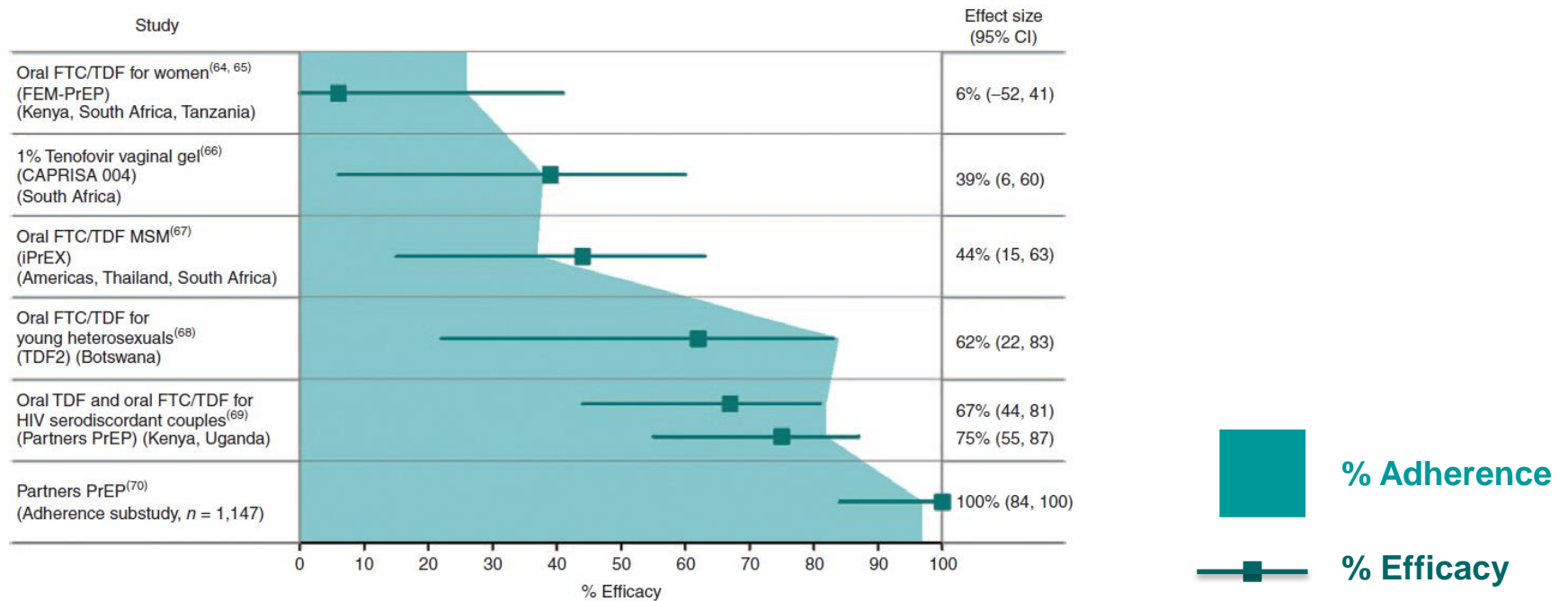
- Risk of failure related to lack of effectiveness
- Poor estimation of toxicity
- Inappropriate dosing regimen

Adherence is Becoming a Regulatory Priority

Draft guidance from the US FDA explicitly addresses adherence strategies

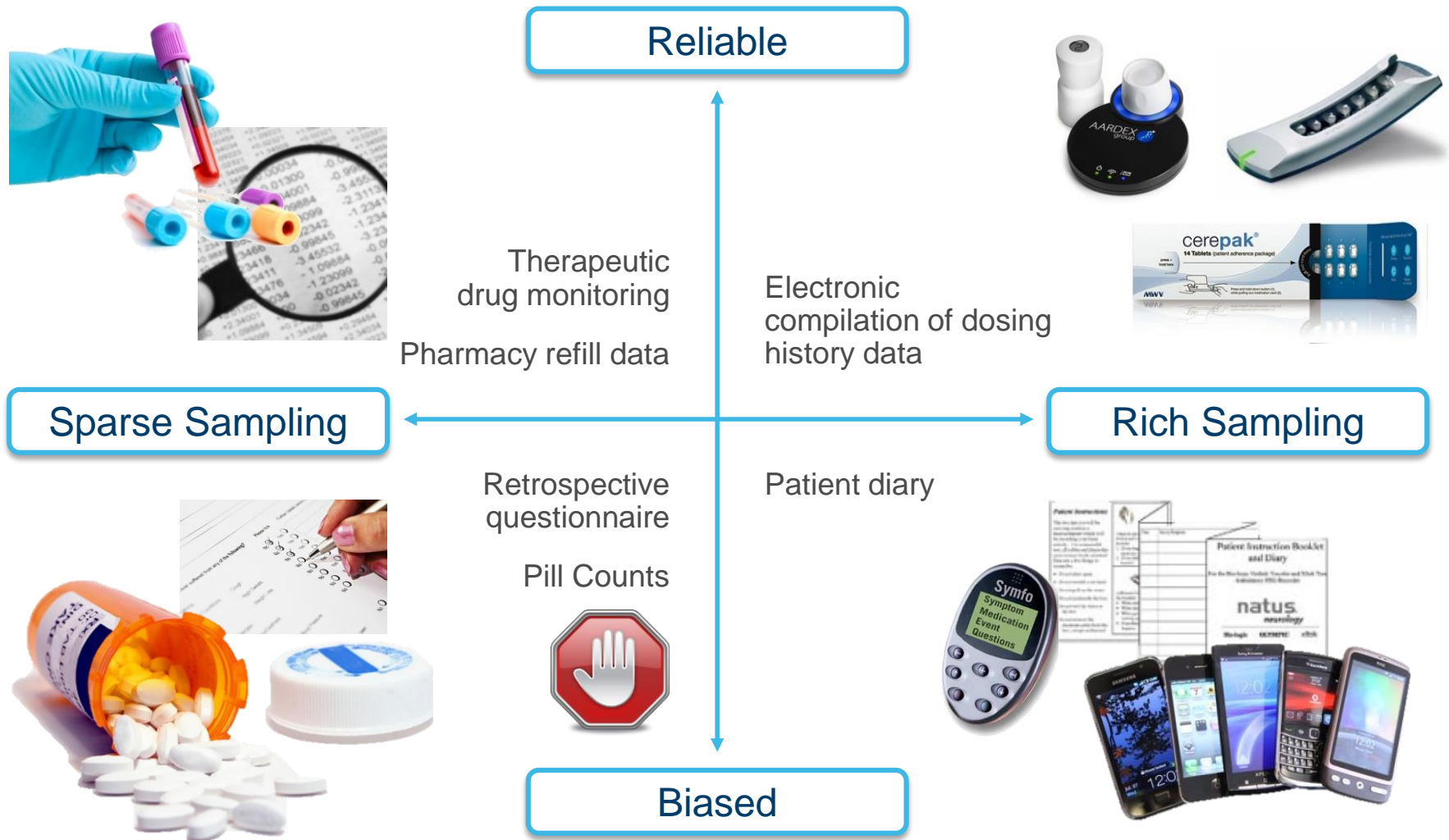
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. Dec 2012

Adherence gap: Seminal example with PrEP



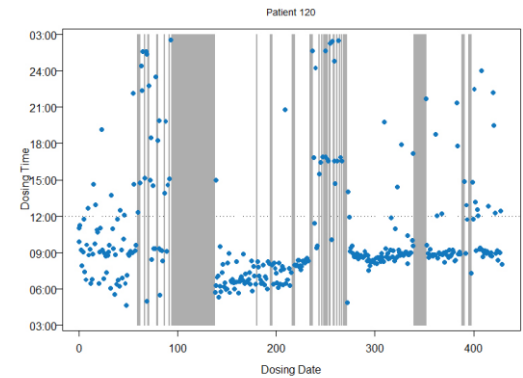
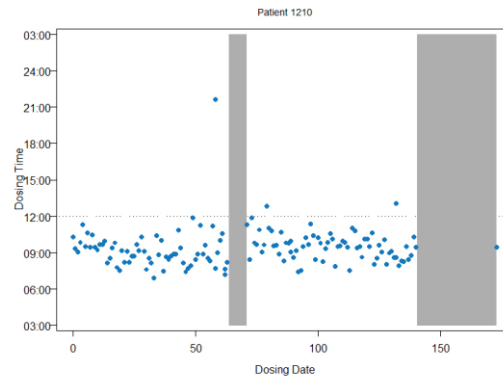
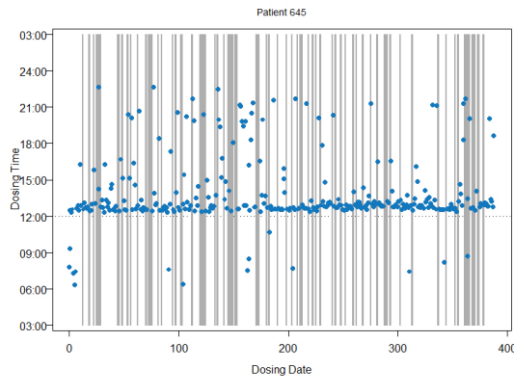
- Adherence based on self-report and pill count not reliable
- Reliability of adherence data should be improved
- No covariate can have a larger impact than not taking the drug
- Adherence data could provide valuable information for both efficacy and safety
- More attention should be paid to adherence data in regulatory review

Adherence Measurement Methods

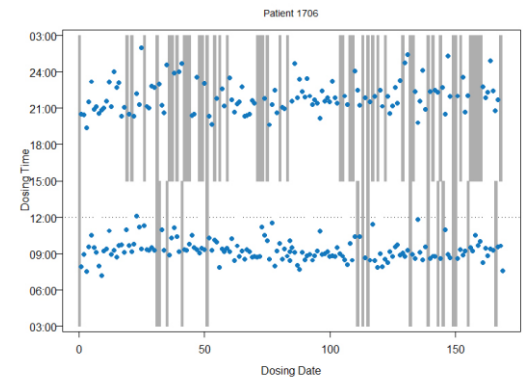
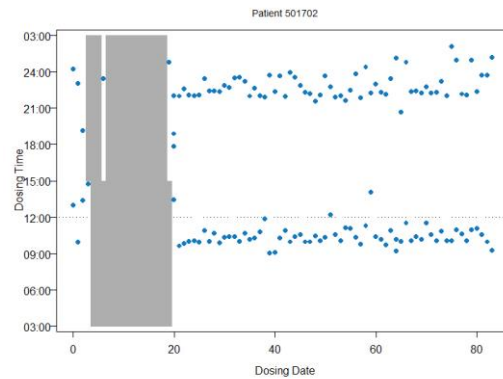
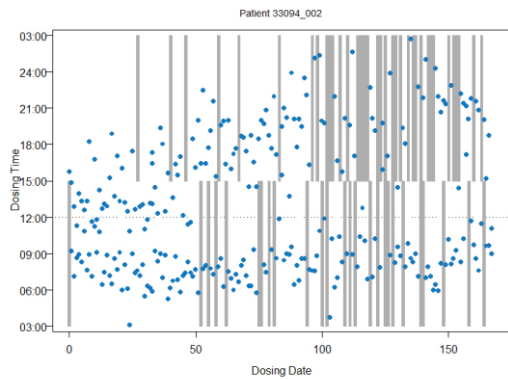


Each of these 6 patients took the same percentage (81%) of prescribed doses

Once daily dosing

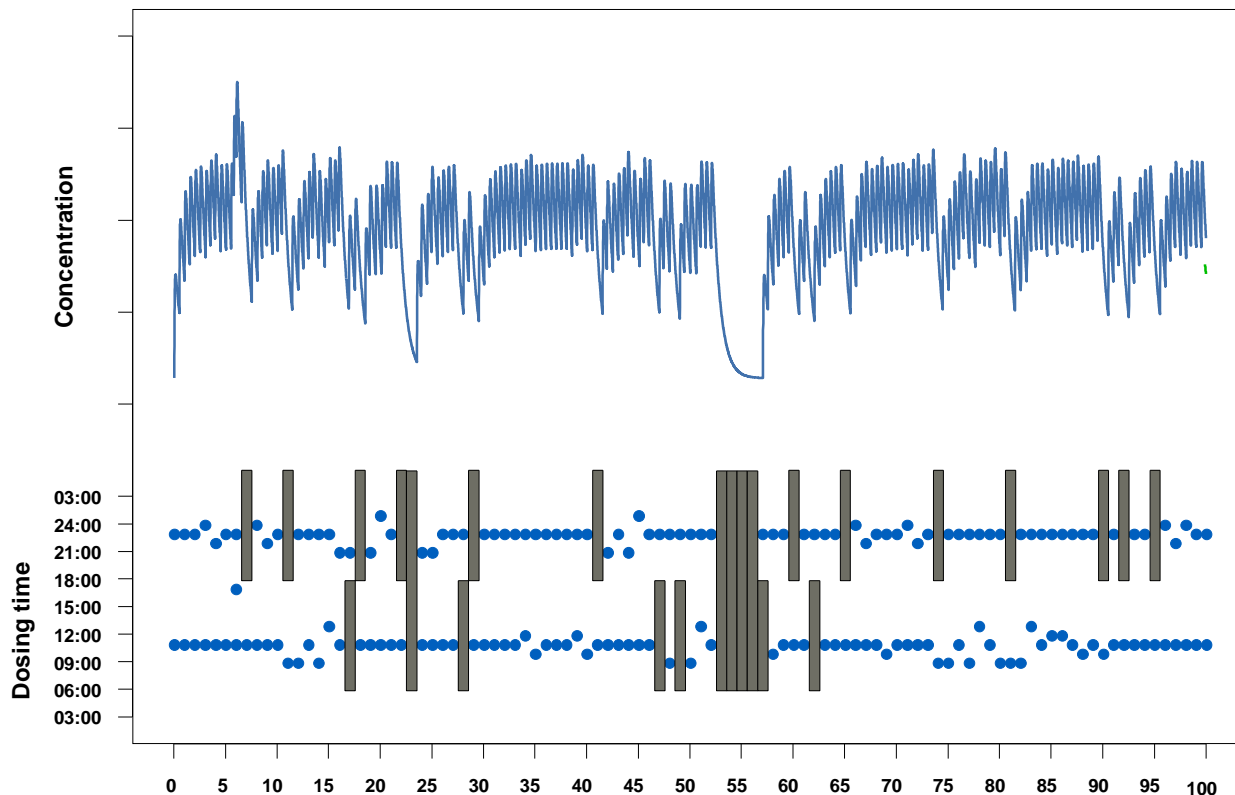


Twice daily dosing



Hi-Fidelity measurement of drug exposure using electronic monitoring of adherence

Medication Event Monitoring Systems (MEMS) & smart packages:
<3% Discrepancies Between Projected and Observed Concentrations



MEMS Bibliometry

703

peer-reviewed
publications

53K

journal
citations

117

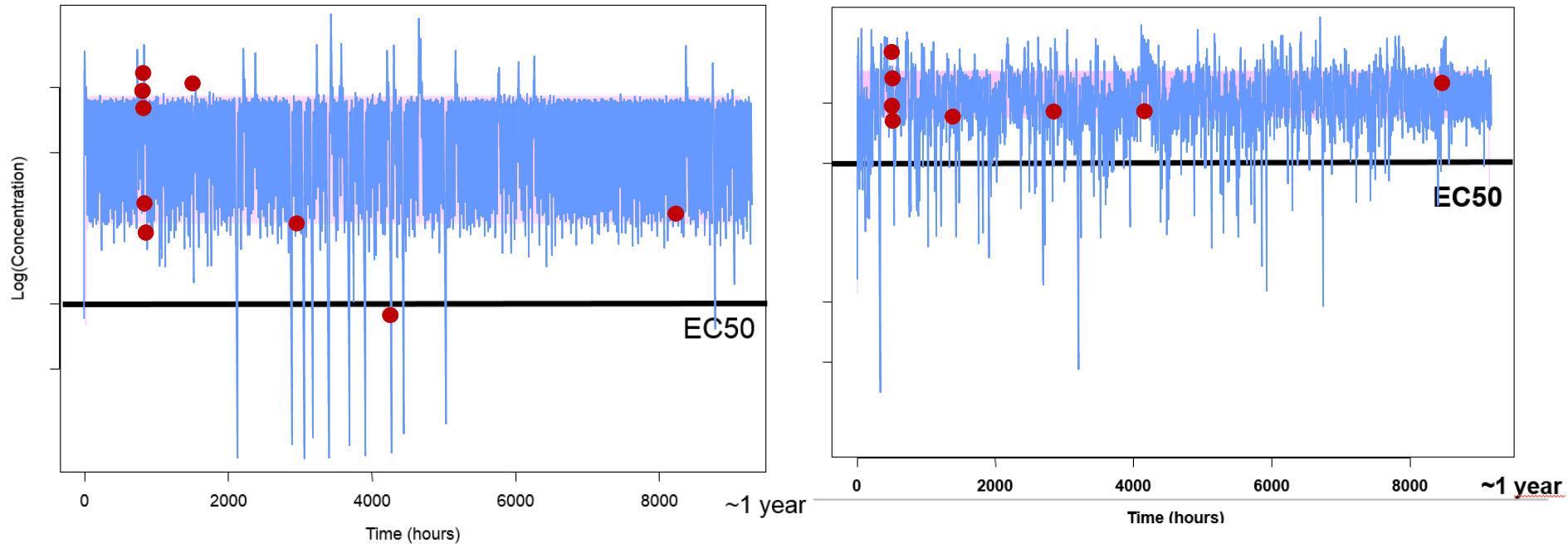
h-index

February 2016, Google Scholar.

Vrijens B et al., *J of Clinical Pharmacol*, 2005, 45: 461-467
Vrijens B, Urquhart J, *Clin Pharmacol Ther*. 2014; 95(6):617-26

The importance of continuous assessment of drug exposure

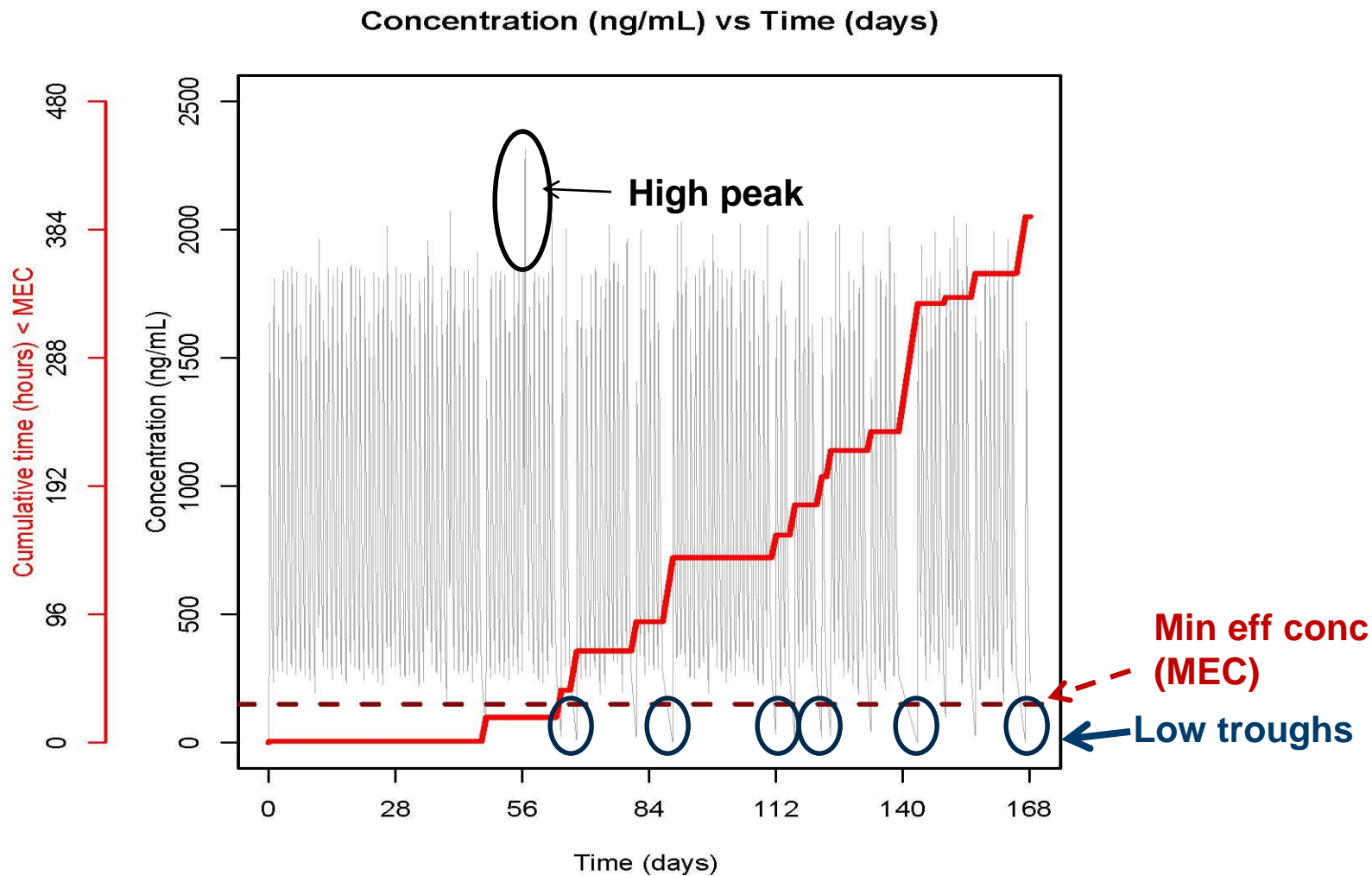
Two examples of long term PK projection based on electronic capture of dosing times



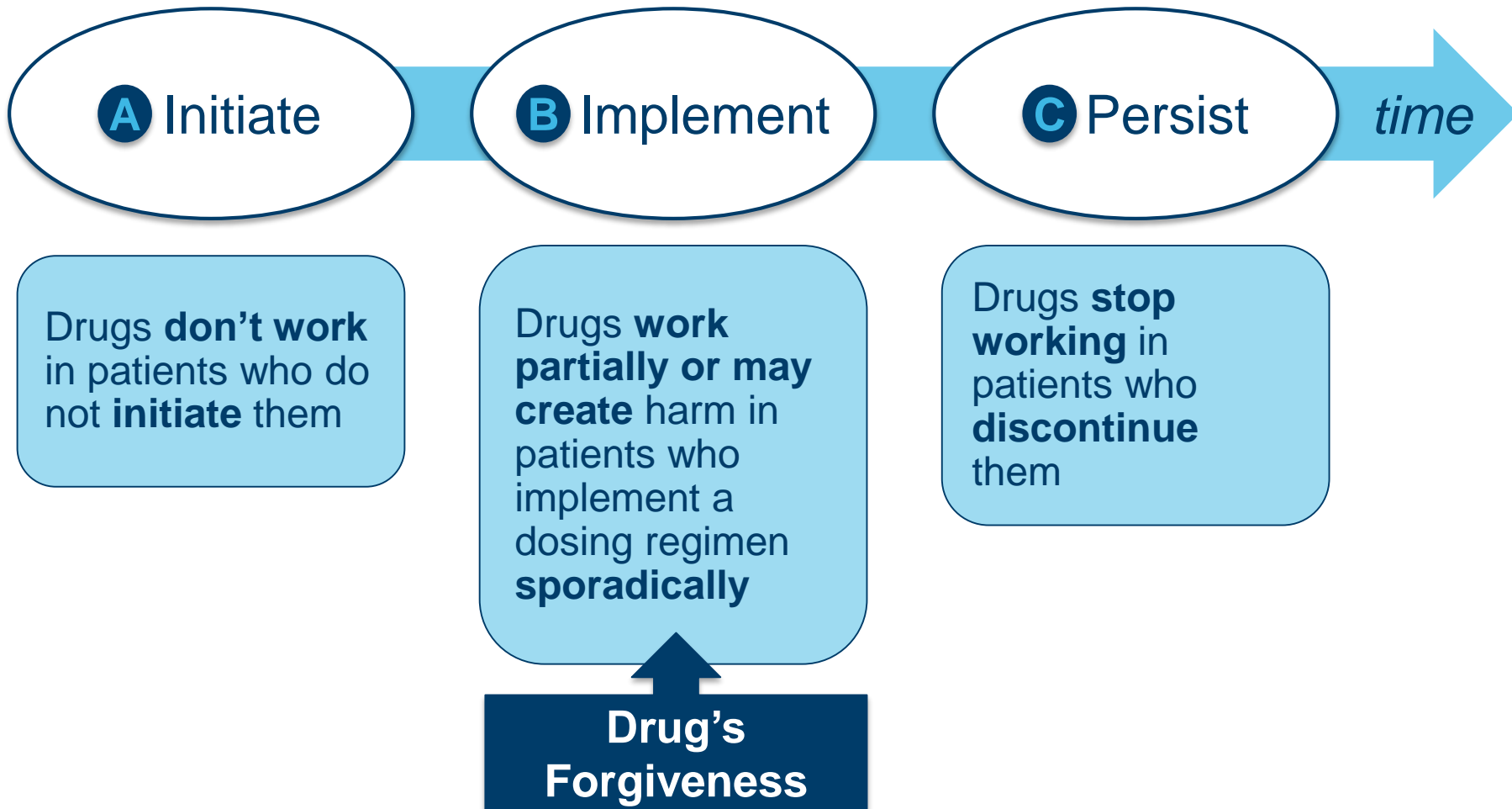
- Measured trough concentrations

Vrijens B et al., *J of Clinical Pharmacol*, 2005, 45: 461-467
Vrijens B, Urquhart J, *Clin Pharmacol Ther*. 2014; 95(6):617-26

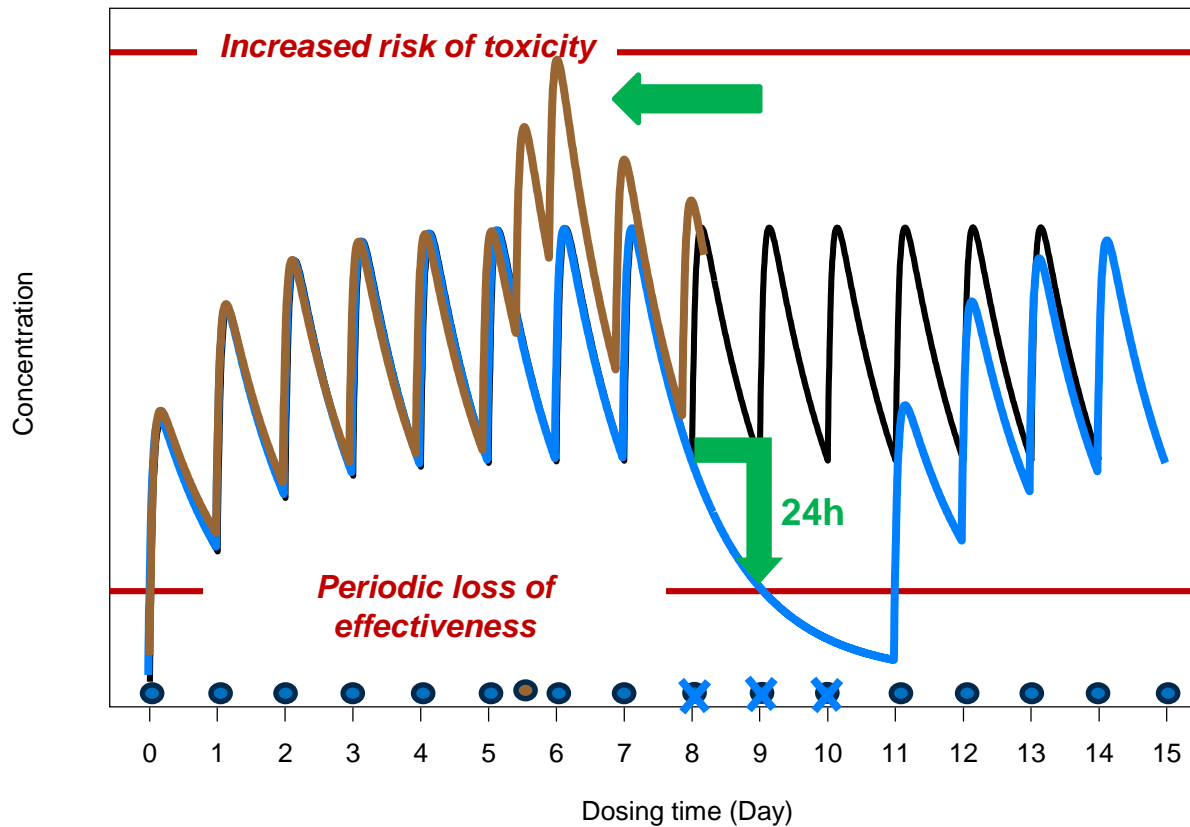
Probing the time-course of drug exposure



Consequences of medication non-adherence



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



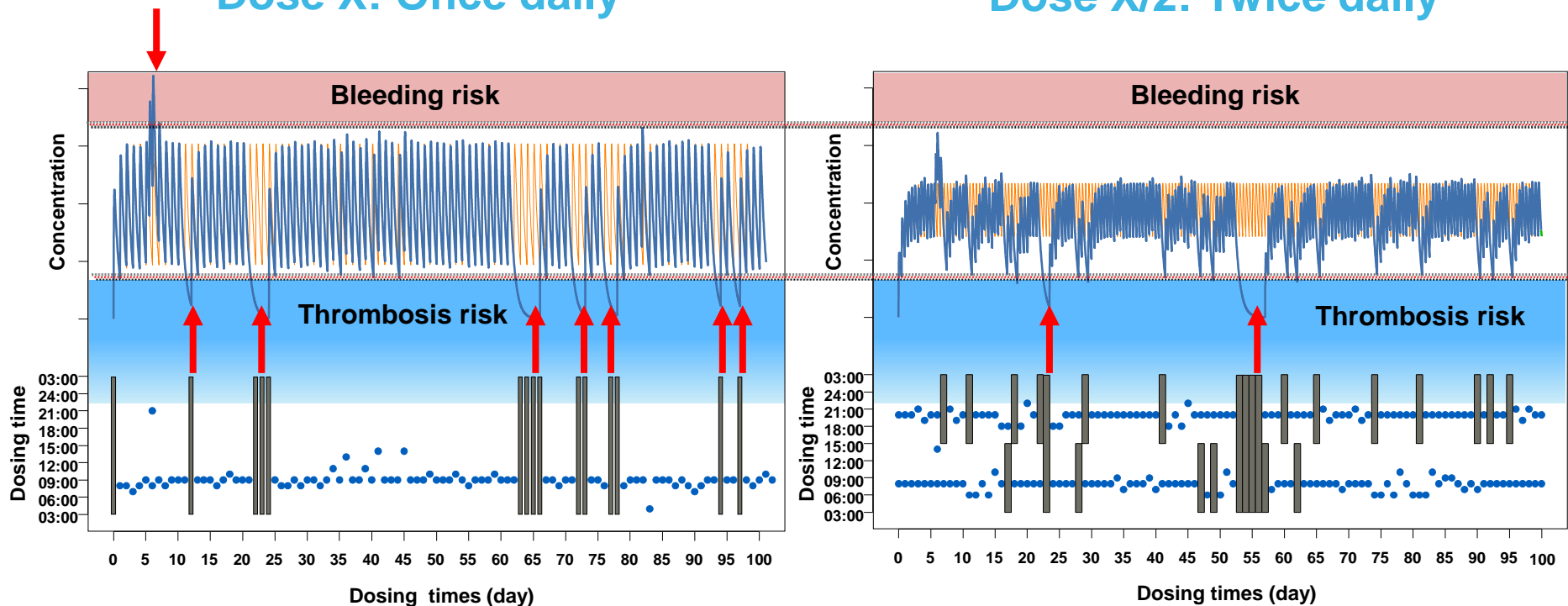
Beyond adherence, think drug forgiveness

The NOACs example:

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

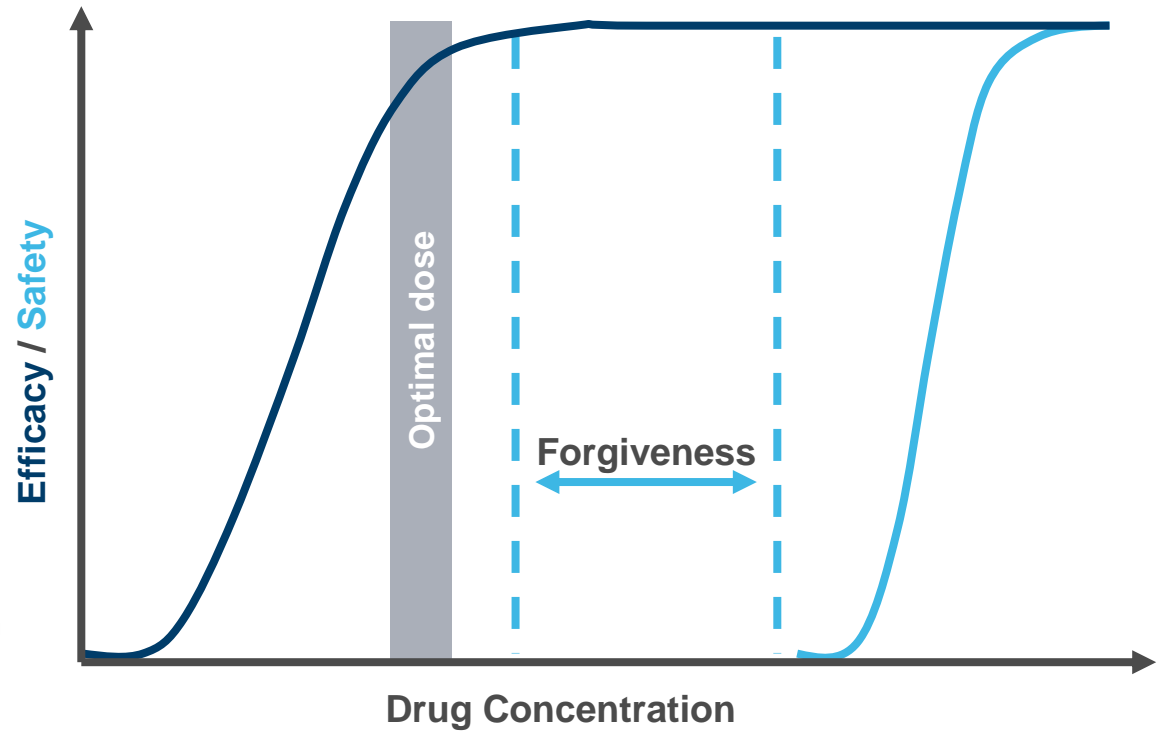
Dose X: Once daily

Dose X/2: Twice daily



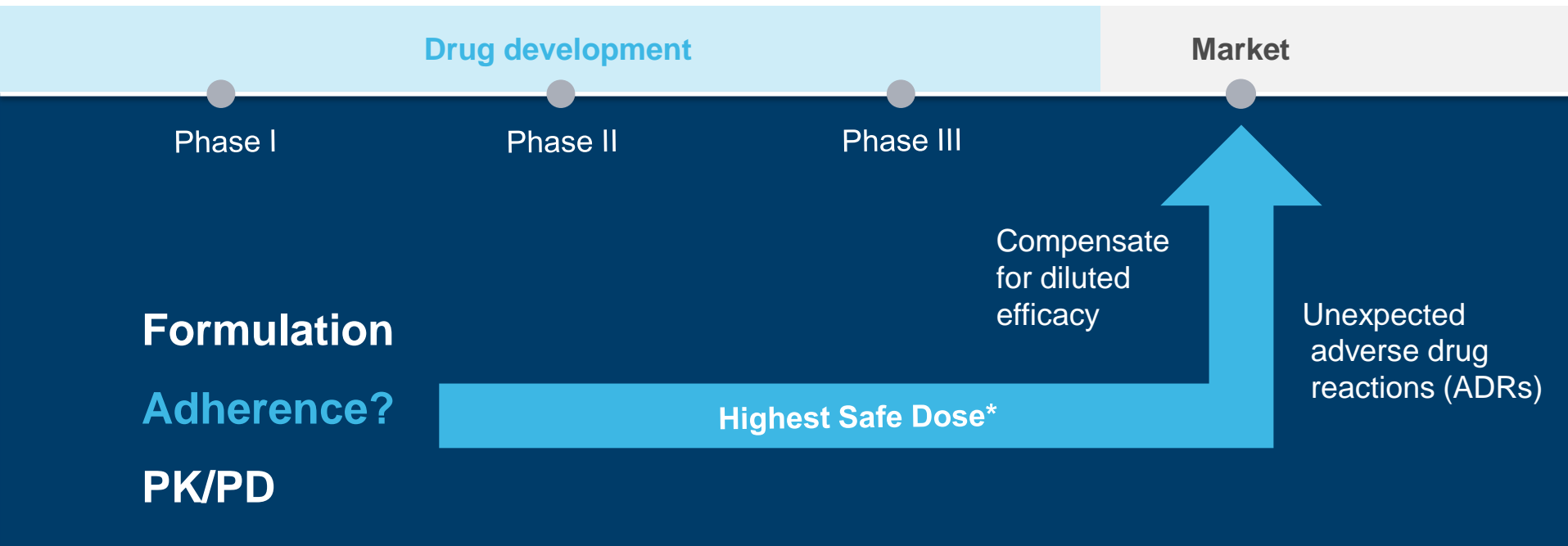
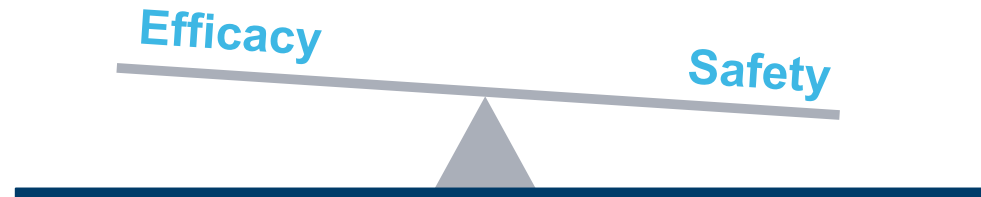
- 15% missed doses
- 15 once-daily missed doses vs. 30 twice-daily missed doses over 100 days

The struthian approach is no longer an option!



Adherence un-informed clinical development

What is the best dosing regimen?



*based on small, controlled, (adaptive) designs

Promising drug that could have been ...

Drug Development

Failed clinical trials due to lack of efficacy

30% attrition

Increased risk of toxicity due to an overestimated dose

30% attrition

Medical Practice

Risk of post-approval dose reduction

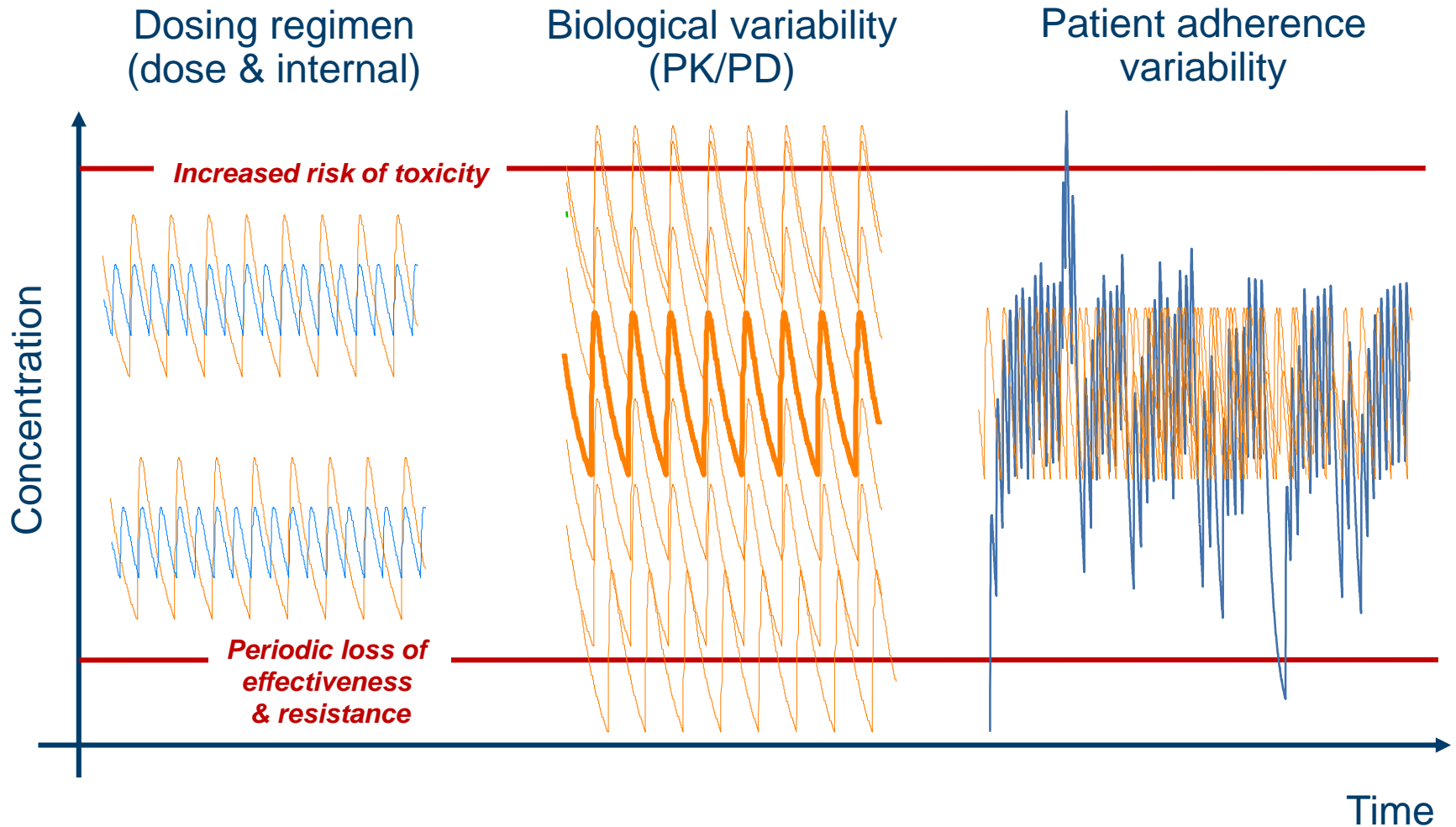
1 in 5: >50% dose reduction^{1,2}

Short persistence:
high churn rates

**50% non-persistence
during the 1st year of
treatment**

1. Cross, J., Lee, H., Westelinck, A. et al. (2002). Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980-1999. *Pharmacoepidemiology and Drug Safety* 11, 439-46.
2. Heerdink, E.R., Urquhart, J. & Leufkens, H.G. (2002). Changes in prescribed drug dose after market introduction. *Pharmacoepidemiology and Drug Safety* 11, 447-453.

Three critical factors to achieve and maintain a successful treatment



Adherence-informed clinical trials

Opportunities

Time Savings

- Better informed benefit/risk and developmental decisions
- Shorter time to set the optimal regimen

Cost Savings

- Greater efficacy and lower variability
(increased power/decreased sample size)
- Fewer post-approval dose-reductions

Improved Therapies

- More informative safety
- More effective dosing regimens

The changing pharma model¹



✓ One dose fits all

- X One dose does not fit all
- Need knowledge at point of care
 - Precision medicine
 - Personalized therapy
 - Individualized treatment
 - Patient-centered care
 - m-health / e-health

Key is being “on treatment”

A Initiation & **C** Persistence
Proportion of Days Covered
PDC >80%

Precise **B** implementation
of the dosing regimen

➔ Medication Adherence is a vital sign to measure and manage

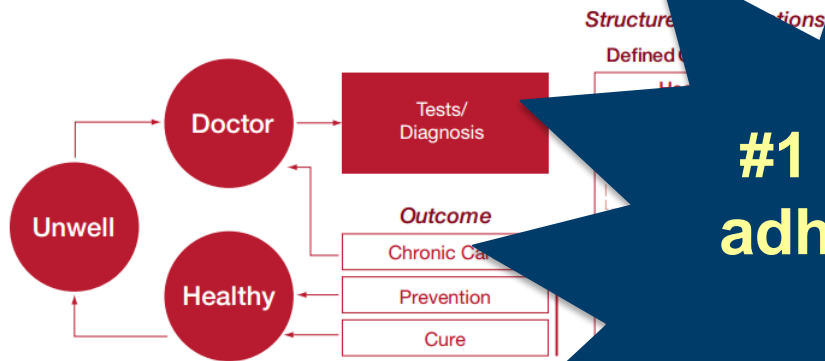
Adherence management is becoming part of care pathways

Pharma 2020: The vision



EHRA Practical Guide on NOACs in NVAF

Figure 7: The development of care pathways will provide greater supply chain predictability



Source: PwC



When a treatment is not working
Think non-adherence!

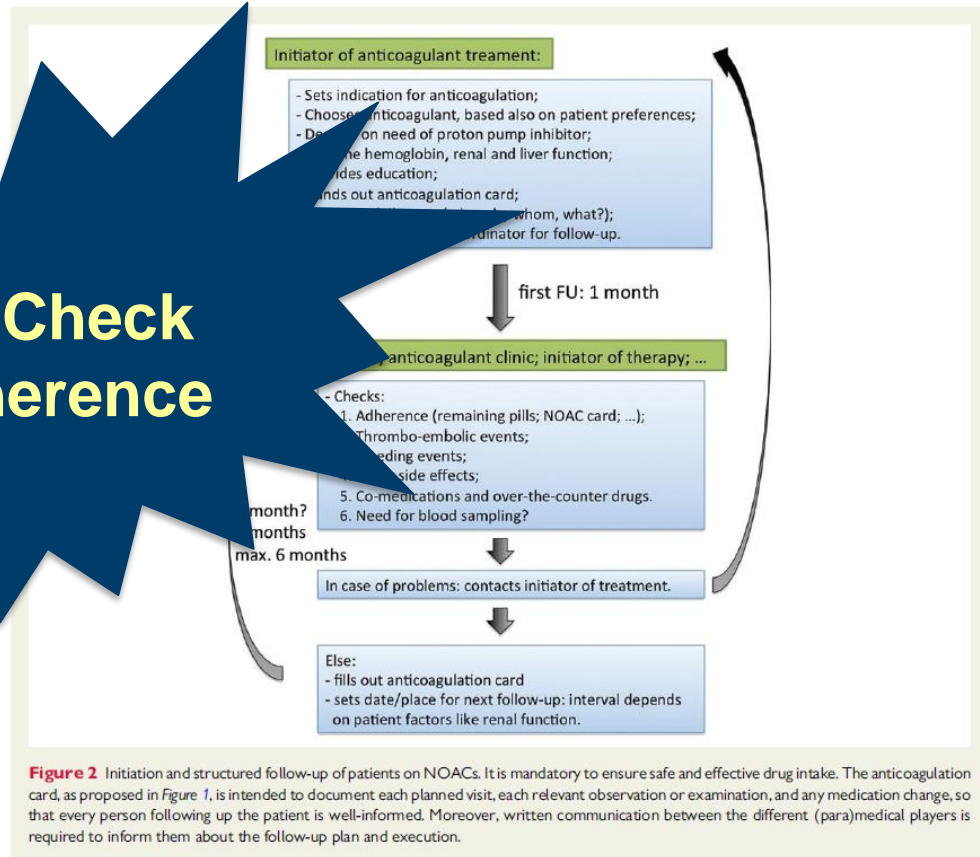
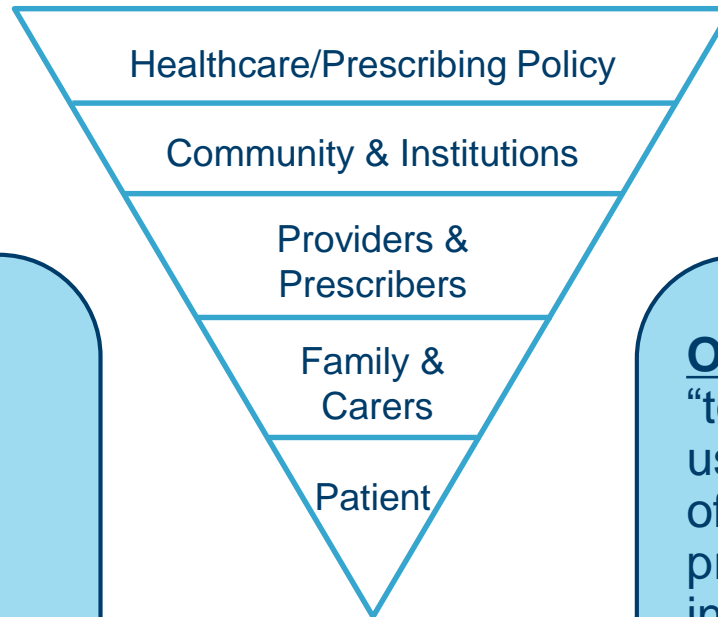


Figure 2 Initiation and structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in Figure 1, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following up the patient is well-informed. Moreover, written communication between the different (para)medical players is required to inform them about the follow-up plan and execution.

Management of adherence: A systems approach



Definition

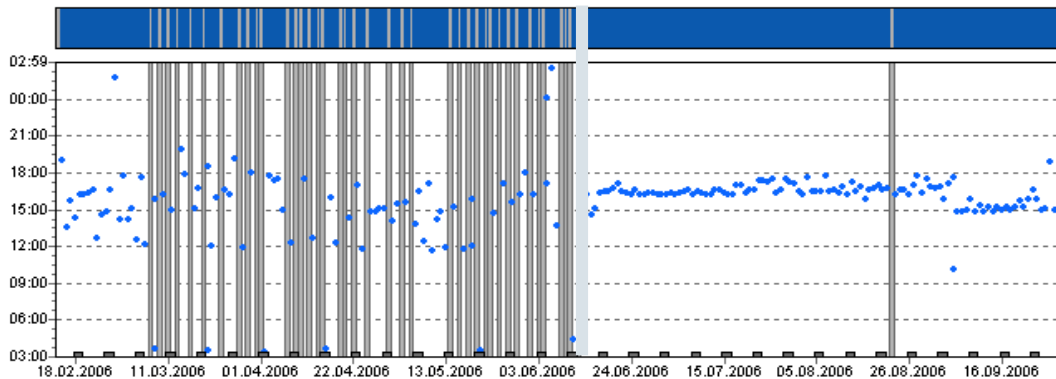
“the process of monitoring and supporting patients’ adherence to medications by healthcare systems, providers, patients and their social networks”

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”

Patients' awareness of their adherence patterns changes behavior

Improved medication adherence

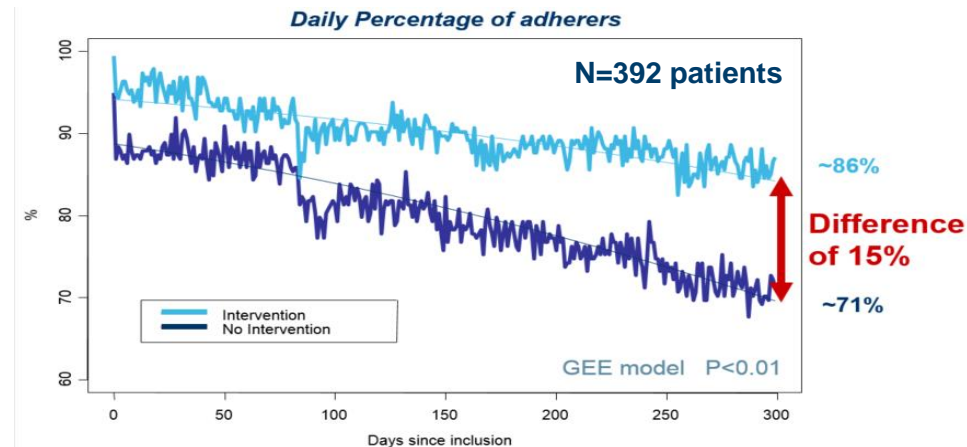


Example of a successful intervention

Focused discussion between a **pharmacist** and patient based on reliable and detailed adherence data

EU-sponsored study confirms that showing patients their own dosing errors is the most effective means to improve adherence

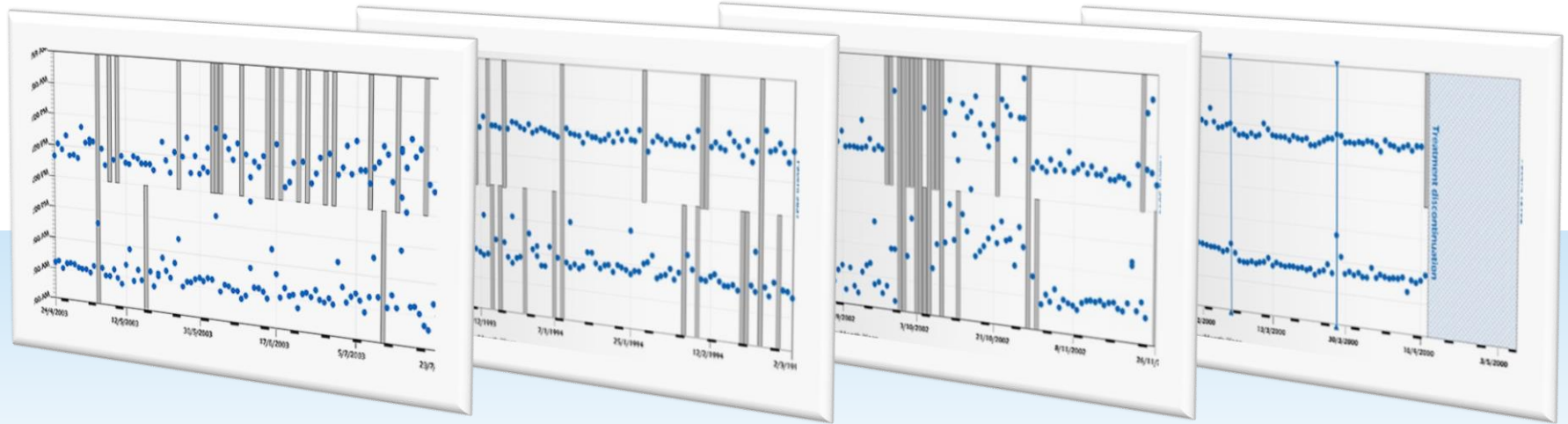
Demonceau et al, Drugs; April 2013.



“What Can Be Measured Can Be Managed”

–Deming, WE

Each of the 4 patients took 75% of prescribed doses during a 3-month period



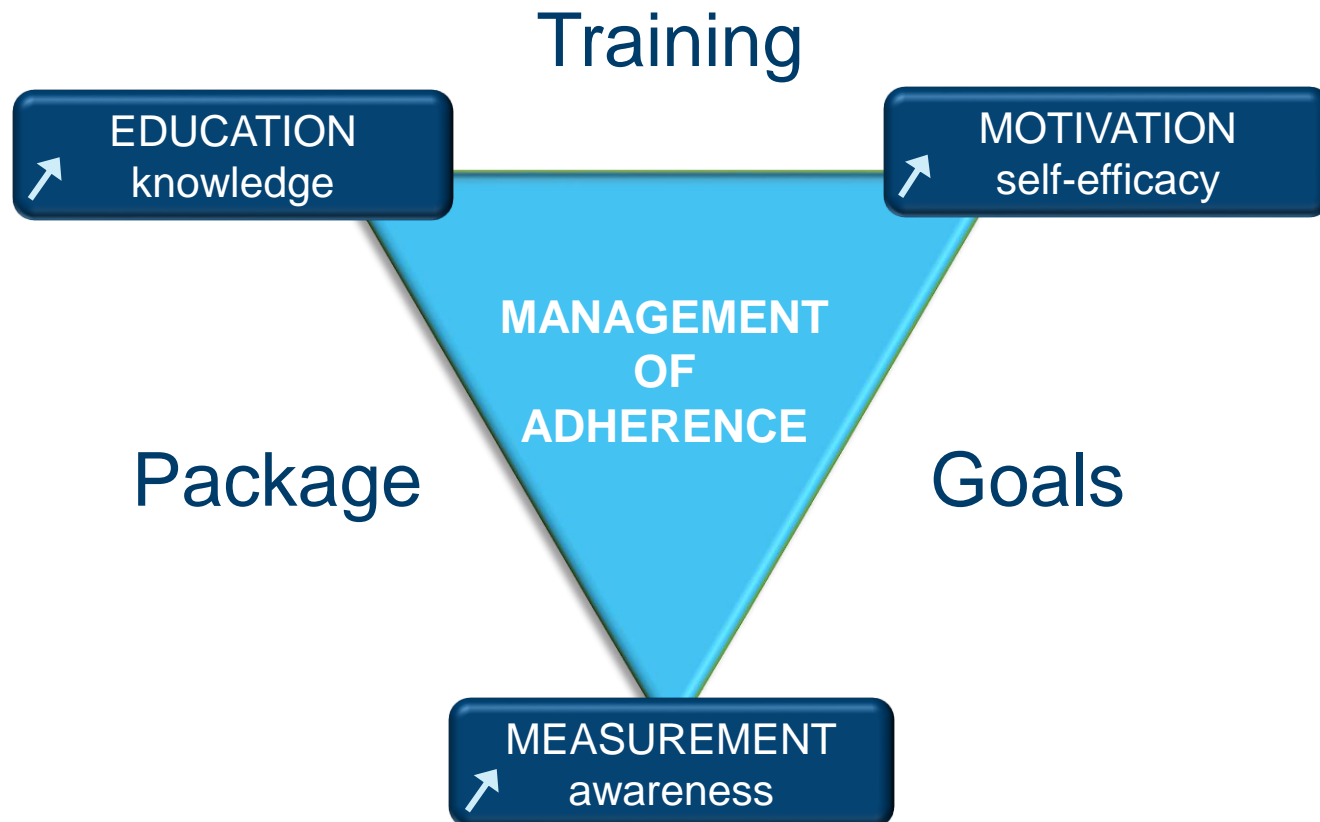
Problem with Evening Dose

Sporadic Dosing

Drug Holiday

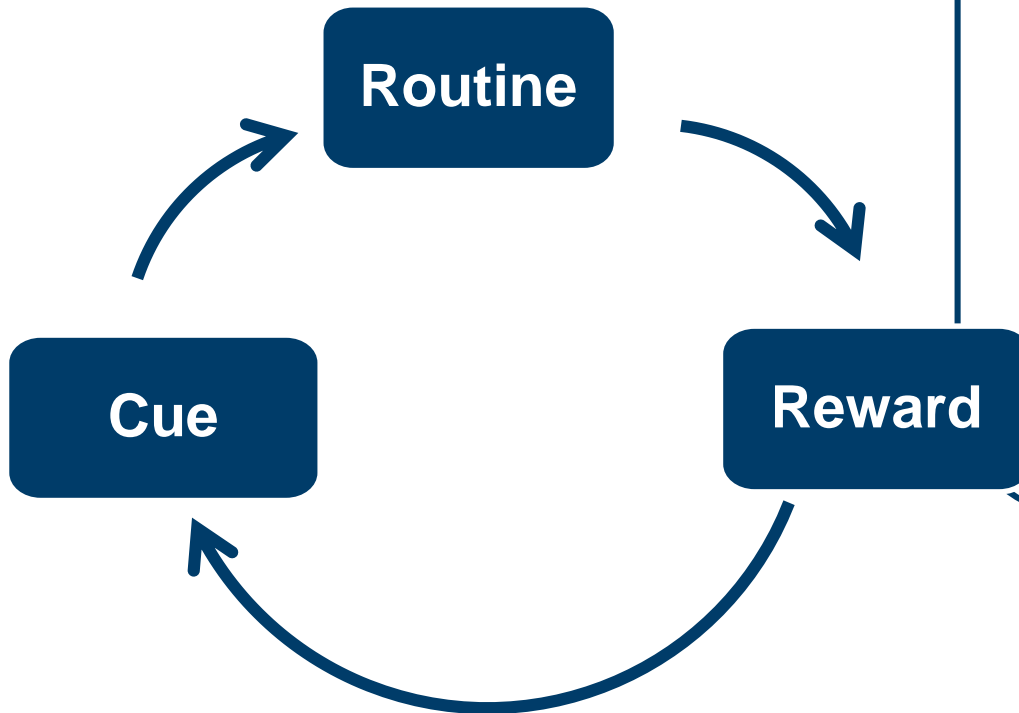
Early Discontinuation

Elements to change patients' behavior



Measurement is also the cornerstone for medication habit building

The habit loop has 3 stages

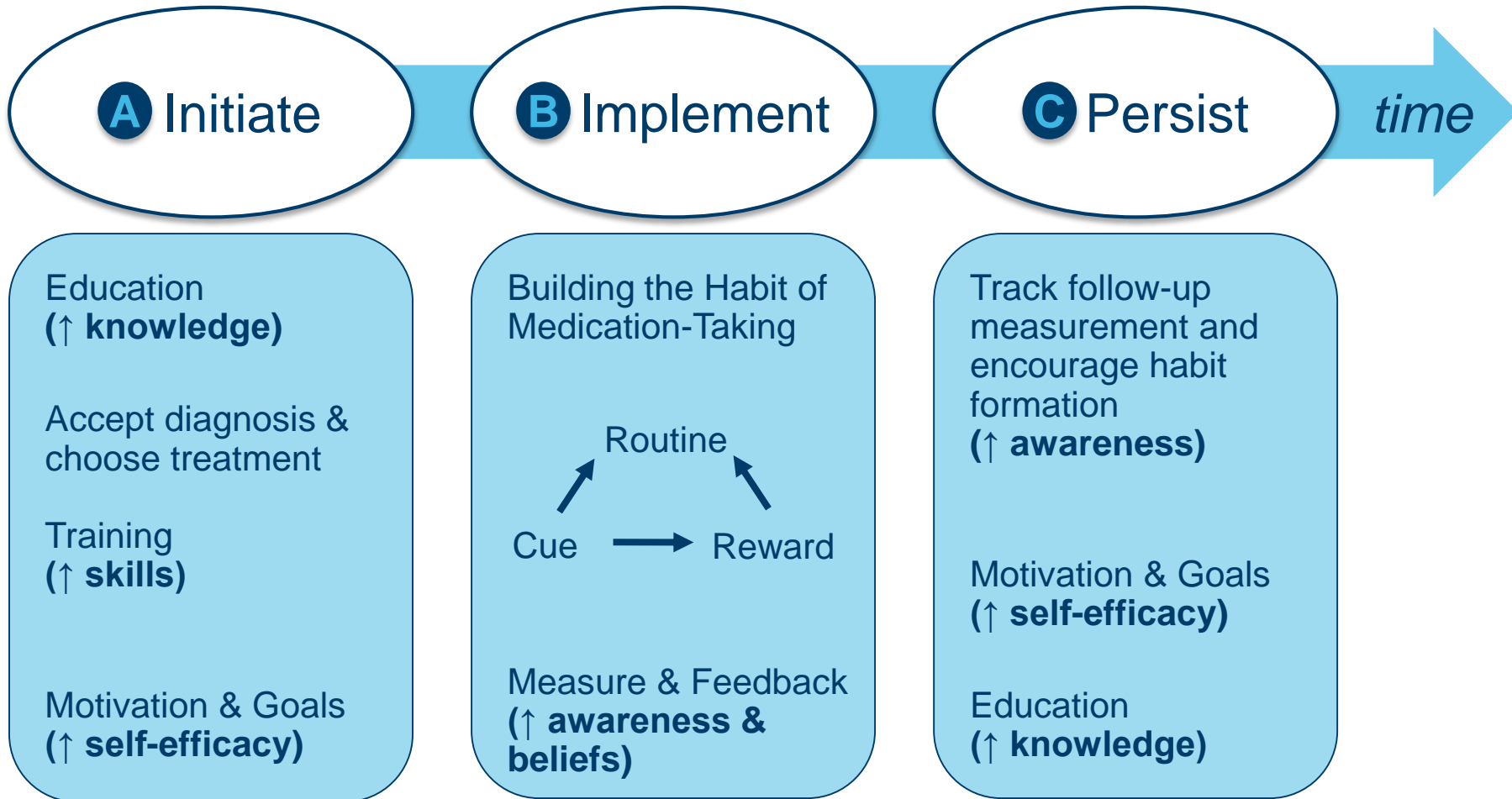


To design or improve a patient's habit of adhering to medications, the first step is making the patient aware of the habit by:

1. Analyzing the habit loop
2. Write down plans and goals
3. Measure & assess achievements

There is not one formula but hundreds!

There is not one solution to manage medication adherence: it's hard work!



Overview of assessment methods of adherence in ambulatory patients



Direct methods (PK/PD)	Requires sampling after prescription	Sampling is too sparse	Subject to white coat adherence
Self-report	Desirability bias	Recall bias	Desirability bias
Pill counts	Easily censored by patient	Only an aggregate summary	Easily censored by patient
Prescription & refill databases	Gold standard if both databases combined	Only an aggregate summary	Gold standard but retrospective
Electronic monitoring	Gold standard in CT; needs activation	Gold standard	Gold standard in CT; needs patient engagement

Packaging is an under-used opportunity to manage effectively medication adherence

E-prescription and pharmacy refill data



Scalability

Calendared blisters and package activated adherence programs: self-measure



Dosing regimen IMPLEMENTATION and habit building

Smart packages – dosing history data

- In clinical trials & research
- At treatment initiation in specialty pharmacy
- At treatment failure
- When an implementation problem is suspected



Patient Adherence is a Big Systems Problem With Many Elements

Healthcare Professionals

1. Better collaboration between HCPs
2. Adherence measure & feedback
3. Think continuity of care
4. Manage polypharmacy
5. Build Medication taking Habit Strategies

Patients

1. Empowerment
2. Self-management
3. Adopt new care models and monitoring technologies

Regulators & Healthcare policy

1. Raise awareness
2. Support education of HCPs
3. Incentivize performance
4. Promote integrated care models
5. At treatment failure, check adherence before dose escalation
6. Set-up the regulatory framework for individualized therapy
7. Data policy for adherence measures
8. Support research in adherence-related sciences
- 9.

Pharma Industry

1. Optimize drug development
2. Think individualized therapies rather than one dose fits all
3. Move from selling a chemical pill to providing a system
4. Improve the package

Family and Carers

1. Special attention to elderly, adolescents, and children
2. Caution with depression and associated diseases
3. Patient associations

High-Fidelity measurement of medication adherence is the **missing link** in precision medicine

LONGER-TERM GOALS

Create a research cohort of **> 1 million American volunteers** who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.



Pioneer **a new model for doing science** that emphasizes **engaged participants, responsible data sharing, and privacy protection.**

Research based upon the cohort data will:

- Advance **pharmacogenomics**, the right drug for the right patient at the right dose
- Identify new targets for **treatment and prevention**
- Test whether **mobile devices** can encourage healthy behaviors
- Lay **scientific foundation** for precision medicine for **many diseases**

Now that we have the ABC taxonomy, ... let's state the 123 conclusions

1 The Problem

Poor adherence to treatments for chronic diseases is a long-neglected worldwide problem of striking magnitude

Its consequences are: biased clinical study results, poor outcomes of drug treatment, emergence of drug resistance, added costs of health-care

2 The Opportunity

The advent of uniquely powerful medicines and reliable means to measure adherence bring patient nonadherence into clear view

Achieving satisfactory adherence may have far greater impact than any other maneuver to improve medical treatments

3 The Action

Health systems must evolve to meet the challenge of achieving satisfactory adherence to therapeutic drug regimens

Patient-tailored and measurement-guided intervention are required to achieve sufficient adherence to therapeutic drug regimens

Thank you for your attention

20th ESPACOMP meeting will be held
In **Lisbon**, Portugal, on the
18th and 19th November 2016
www.ESPACOMP.eu

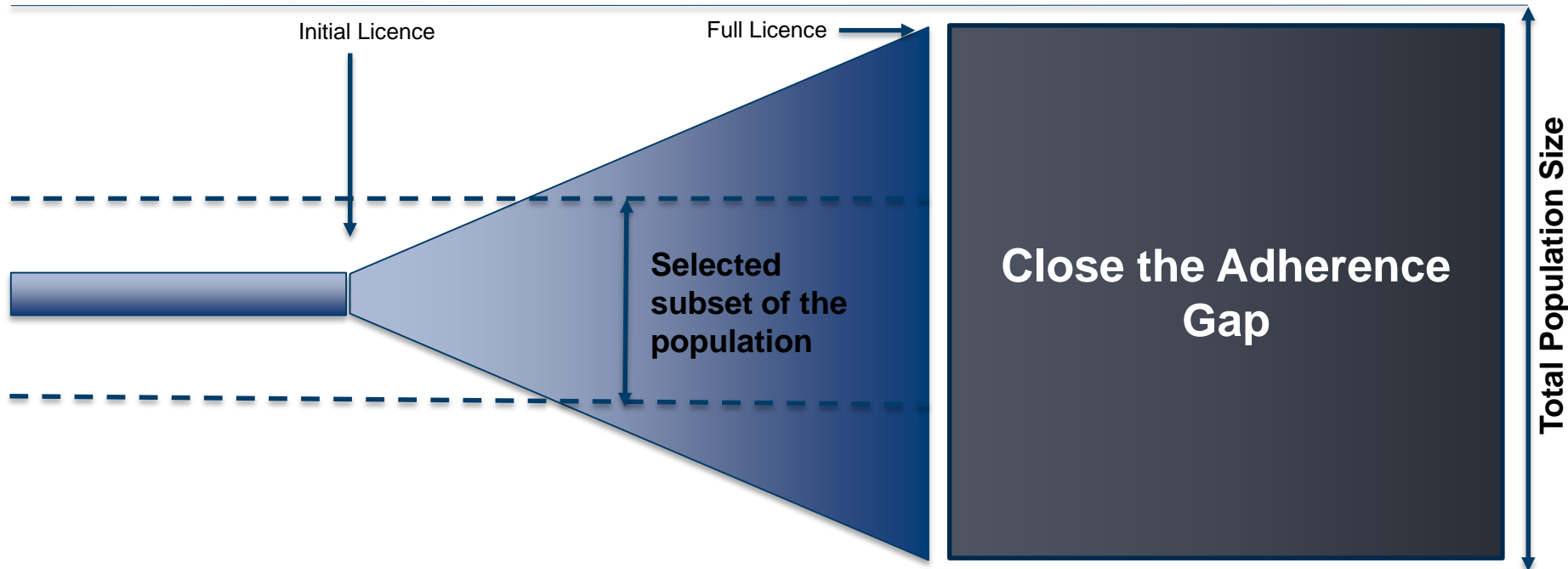


#ESPACOMP2016

Optimizing Drug Development: Towards the Future

Drug development

Medical Practice



Manage Adherence to Medications

- Maximize drug exposure
- Estimate method effectiveness (full efficacy)

Get more insights into Patient Adherence in the Population of interest

- Initiation / Implementation / persistence
- Study drug's forgiveness
- Go beyond ITT analysis
- Individualize therapy

Provide appropriate solutions for treatment individualization & patient adherence

- Not necessarily the same than in drug development
- Go beyond the pill and secure appropriate comparative effectiveness

Adapted from Vrijens & Urquhart, CPT, 2014

Eichler HG et al. Clin Pharmacol Ther 2012; 91: 426-37