November 2016

Madication Adherence: State of the Art

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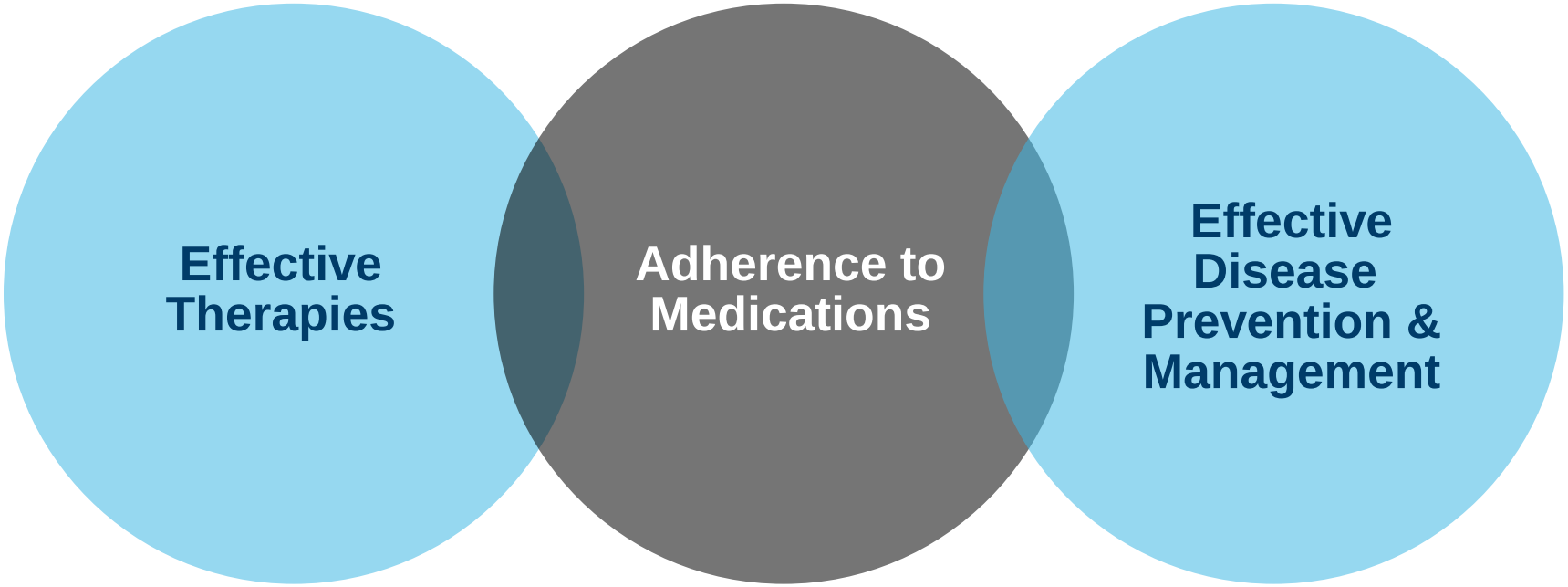
Chief Science Officer, WestRock Healthcare
Associate Professor of Biostatistics
University of Liège, Belgium

WestRock

Adherence is Key to Therapeutic Success

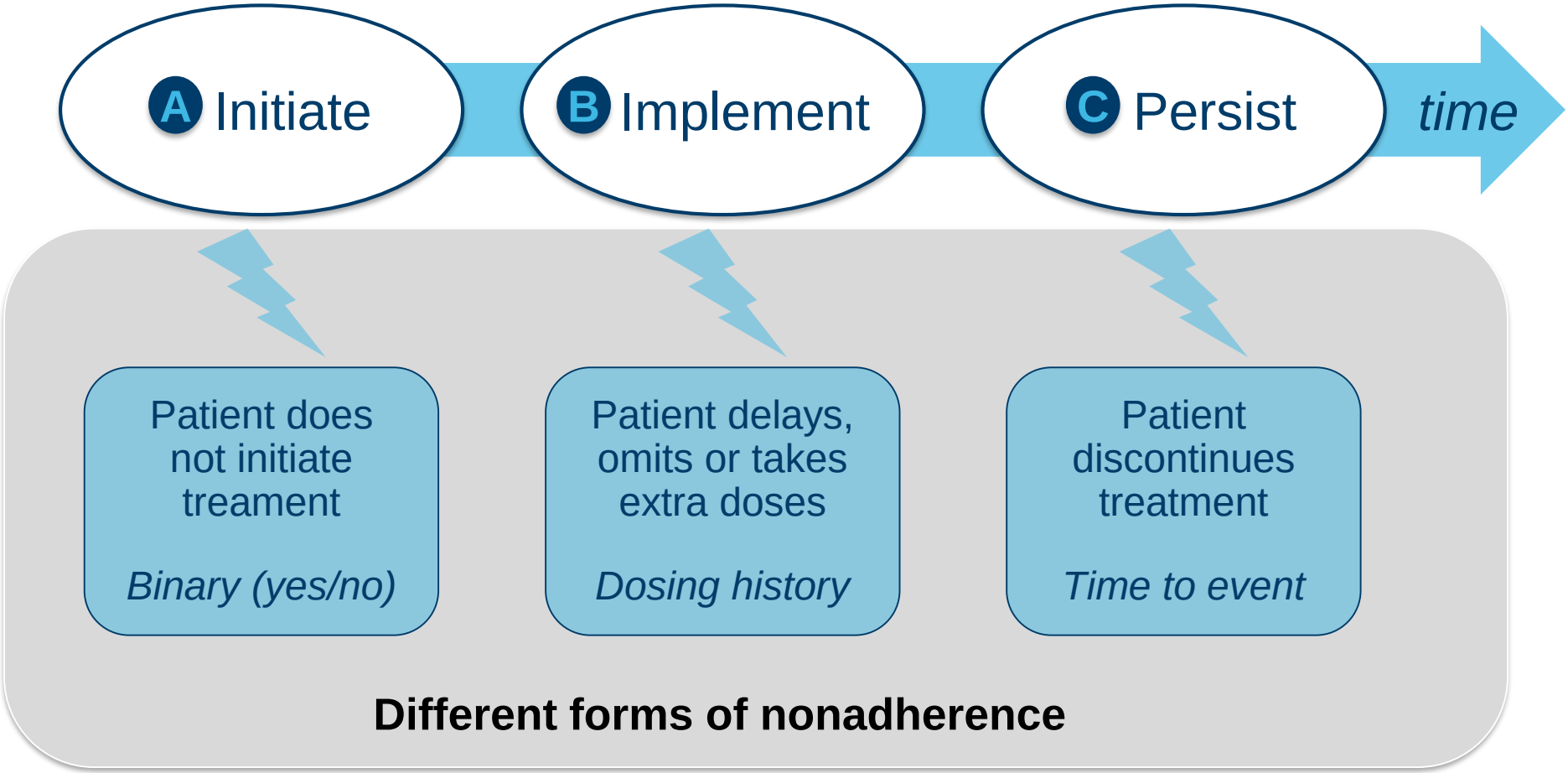


“Drugs don’t work in patients who don’t take them.”

– C. Everett Koop, former US Surgeon General

ABC Taxonomy: Medication Adherence

The process by which patients take their medications as prescribed



EU-sponsored research

Vrijens et al., Br J Clin Pharmacol 2012;73:691-705.

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

A Initiate

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

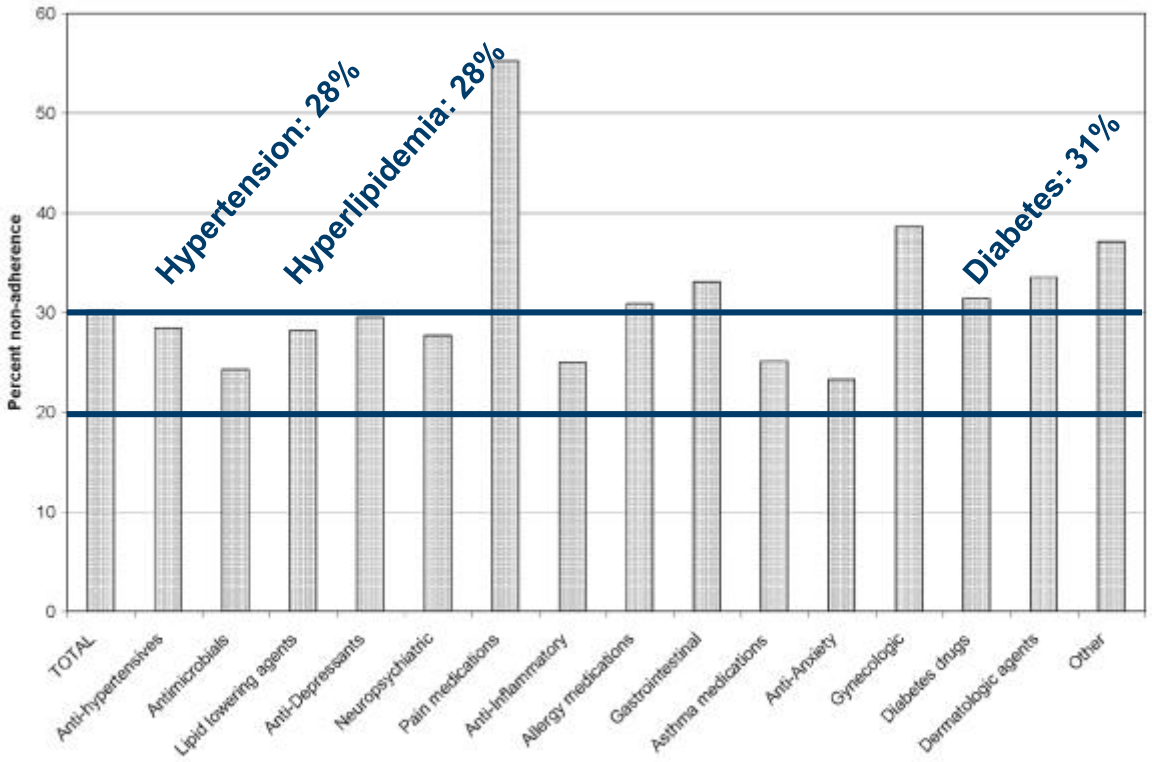
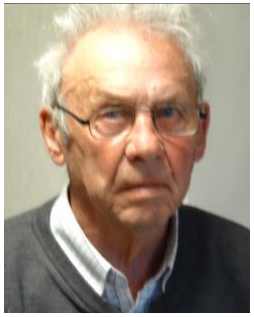


Figure 1. Primary non-adherence to newly prescribed medications. Patients aged 19 and over.

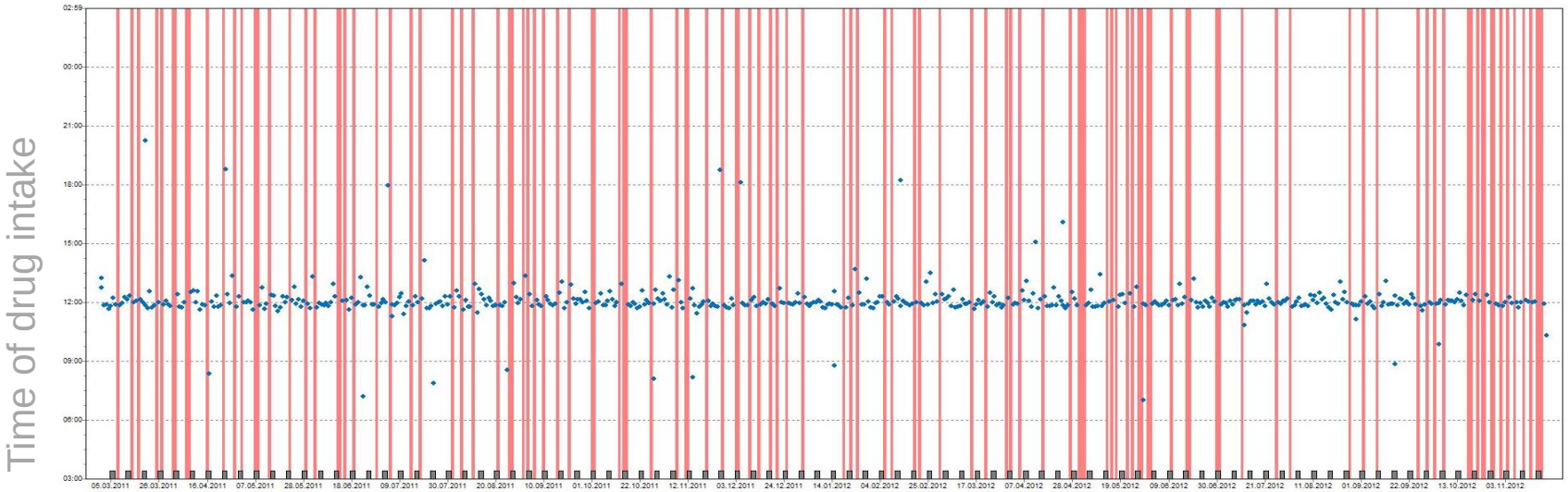
M Fischer et al., J Gen Intern. Med, 25(4):284-90, 2010.

Daily, 15% of patients
do not implement as prescribed

B Implement



Case Study: Dosing History Data over 2 years (2011-2012)



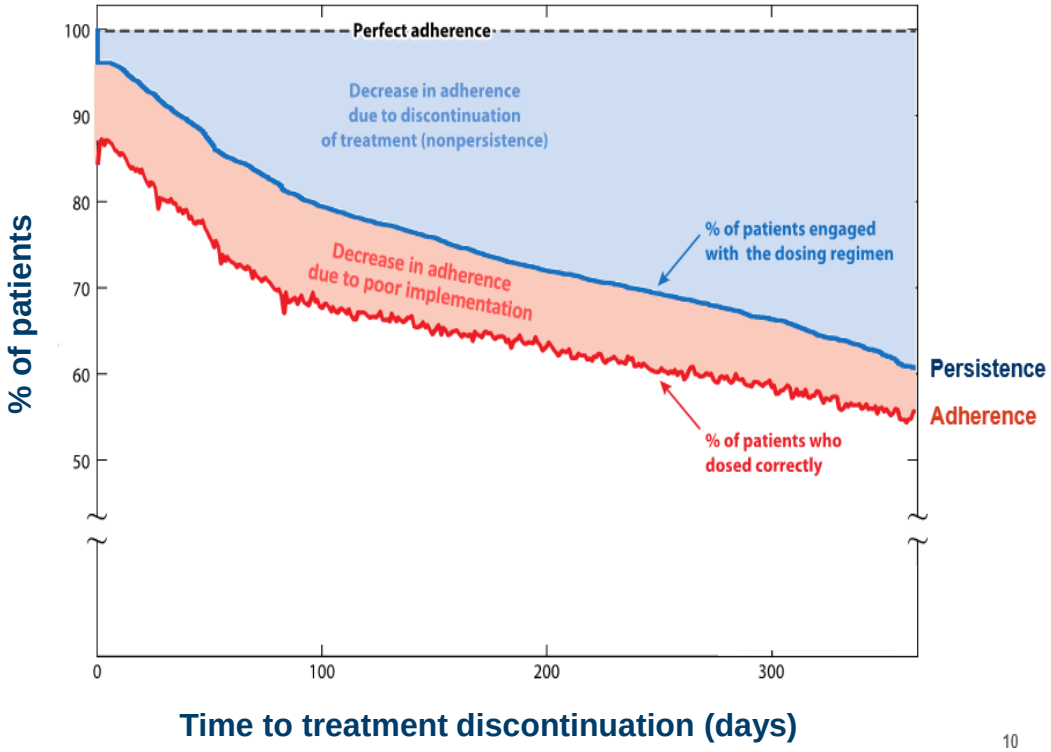
Follow-up: 632 days

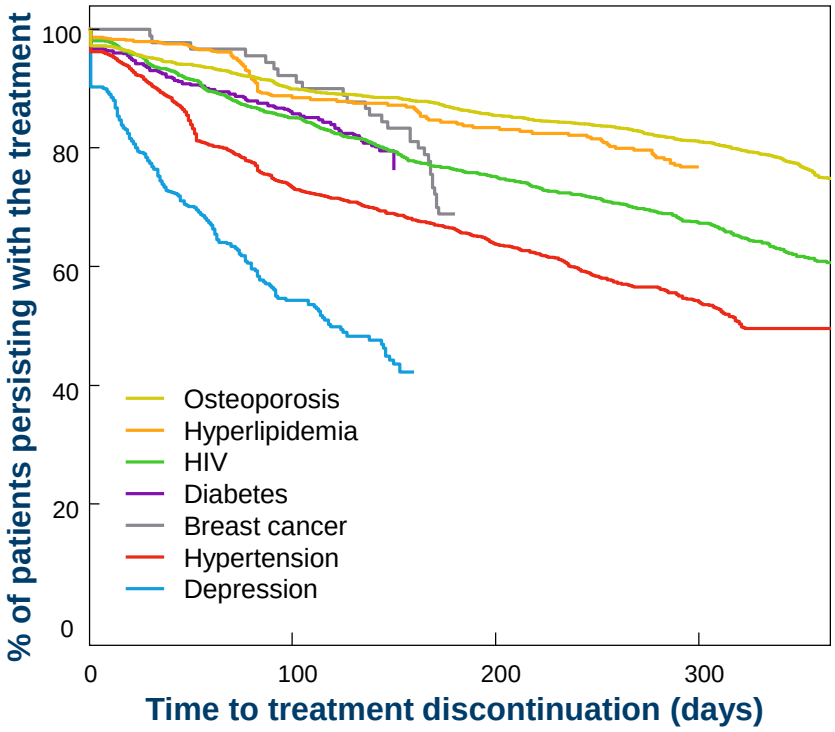
14 days (2%) with double dose
115 days (18%) no doses

➔ **84% of prescribed doses taken**

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

N=16,907 participants from 95 clinical studies with electronic monitoring of adherence





Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301

Medication adherence: summary

The process by which patients take their medications as prescribed

25% of patients **do not initiate** a new prescription

Large differences between:

- Diseases/drugs
- Centers
- HC systems
- Drug dev/practice

Daily, **15%** of patients **do not implement** as prescribed

Patient attribute

Implementation decreases with:

- Food requirements
- Complexity of treatment

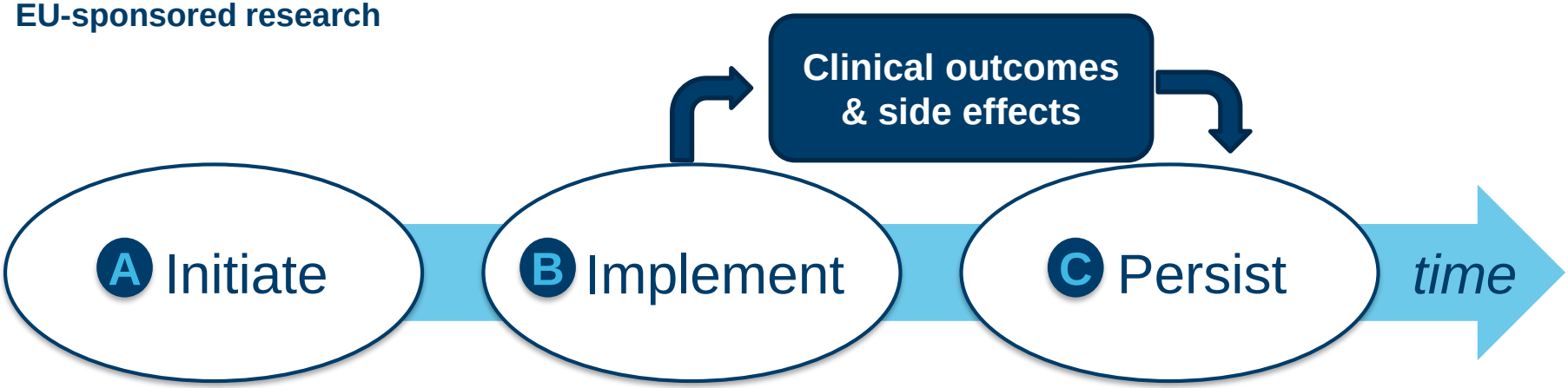
During the first year, **40%** of patients **have discontinued** treatment

Large differences between:

- Diseases/drugs
- Centers
- HC systems
- Drug dev/practice

>700 predictors* of Medication Adherence

EU-sponsored research



- ✓ Patient's lack of insight into the illness
- ✓ Patient's lack of belief in benefit of treament
- ✓ Patient's concerns about medication
- ✓ Poor provider-patient relationship
- ✓ Presence of psychological problems (depression)
- ✓ Inadequate follow-up or discharge planning
- ✓ Cost of medication

- ✓ Presence of cognitive impairment
- ✓ Complexity of treatment
- ✓ Alcohol abuse
- ✓ Family conflict or disorganisation
- ✓ Unability to build Medication Taking Habits

Changes over time

- ✓ Missed appointments
- ✓ Previous behavior & experiences

- ✓ Patient's lack of insight into the illness
- ✓ Patient's lack of belief in benefit of treament
- ✓ Patient's concerns about medication
- ✓ Poor provider-patient relationship
- ✓ Presence of psychological problems (depression)
- ✓ Inadequate follow-up or discharge planning
- ✓ Cost of medication

** Kardas et al., Front Pharmacol. 2013; 25;4:91.*

Overview of assessment methods of adherence in ambulatory patients

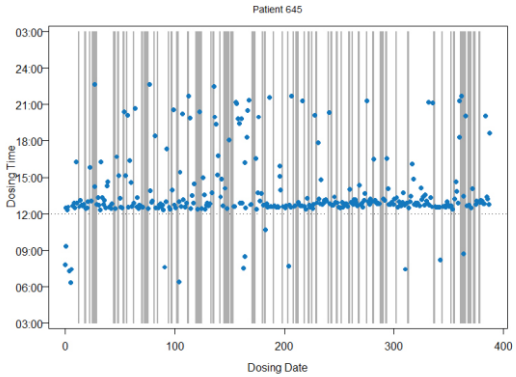
	A Initiate	B Implement	C Persist
Direct methods (PK/PD)	Requires sampling after prescription	Sampling is too sparse	Subject to white coat adherence
Self-report	Desirability bias	Recall bias	Desirability bias
Pill counts	Easily censored by patient	Only an aggregate summary	Easily censored by patient
Prescription & 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

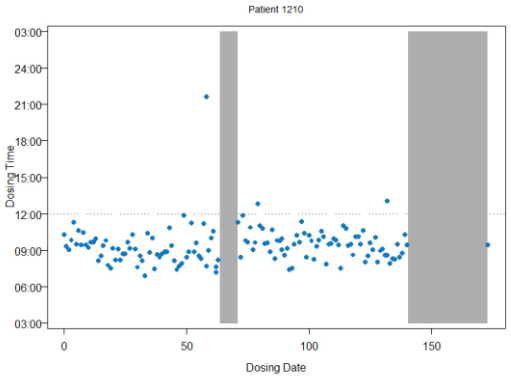
Vrijens B, Heidbuchel H, Europace, 17(8):1317-8, 2015

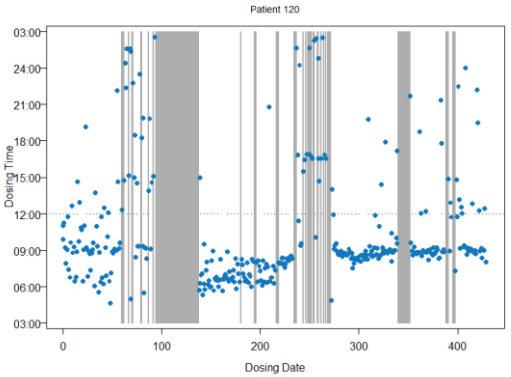
Pre-electronic methods are sparse

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

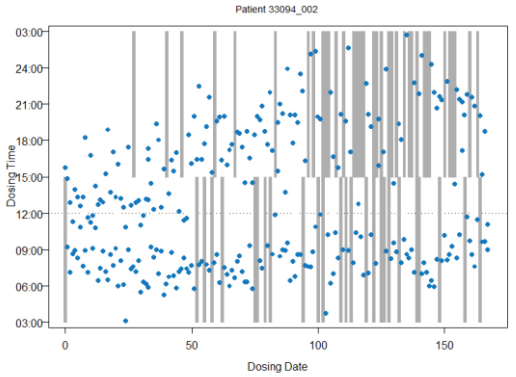
Once daily dosing

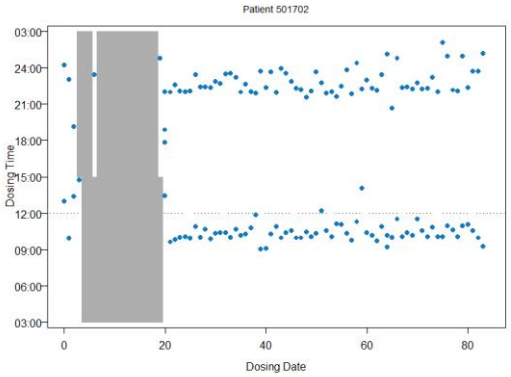


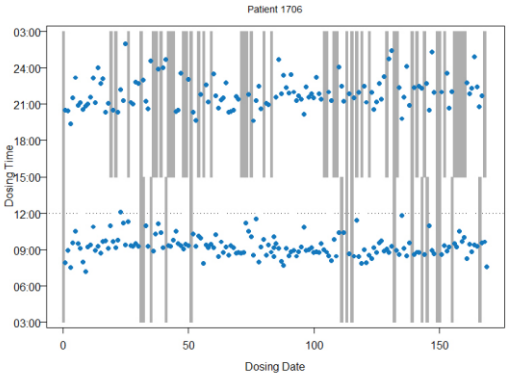




Twice daily dosing

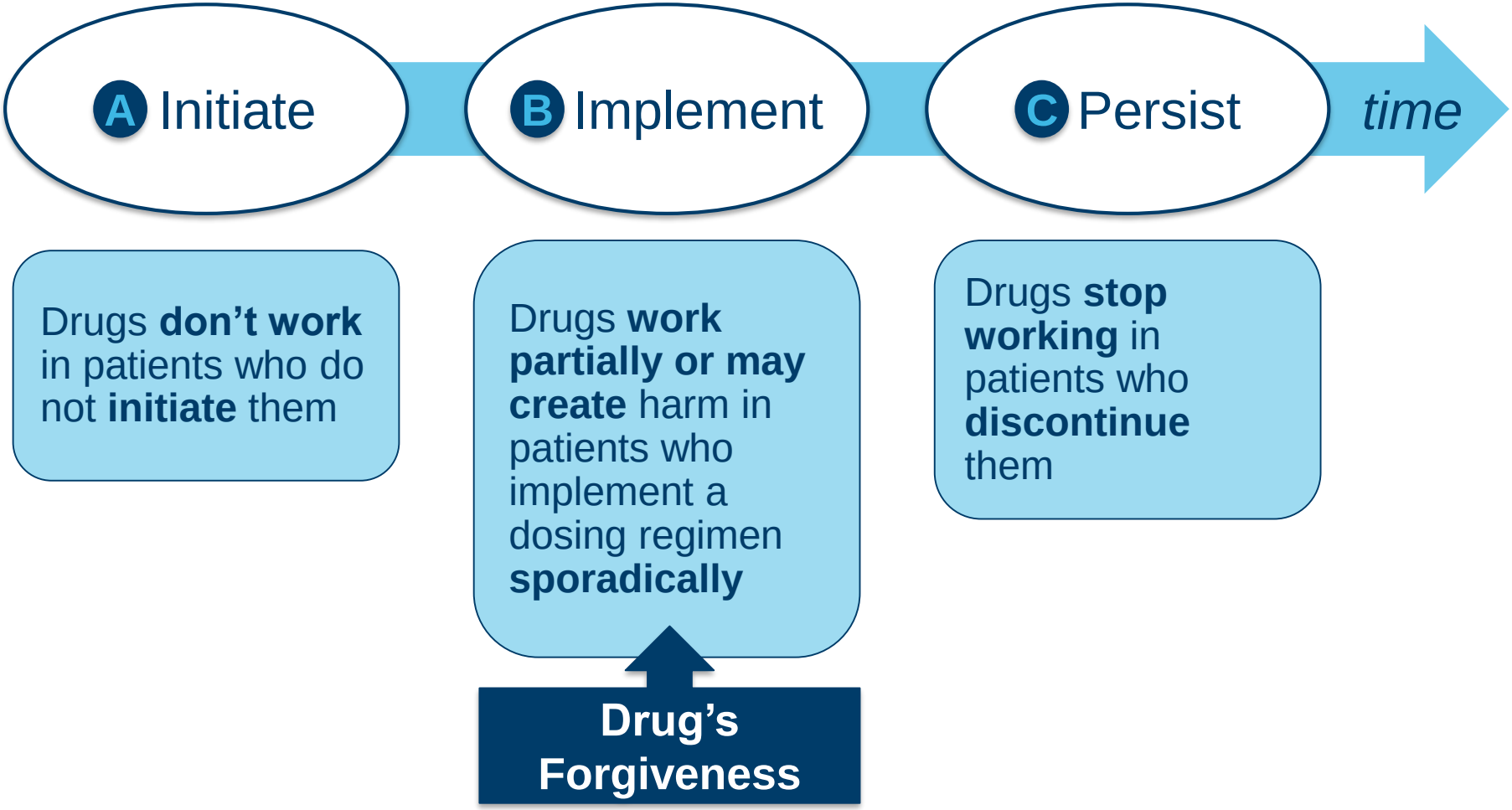






Vrijens B, Drug Utilization Research: Methods and Applications, First Edition, John Wiley & Sons, Ltd., 2016

Consequences of medication non-adherence



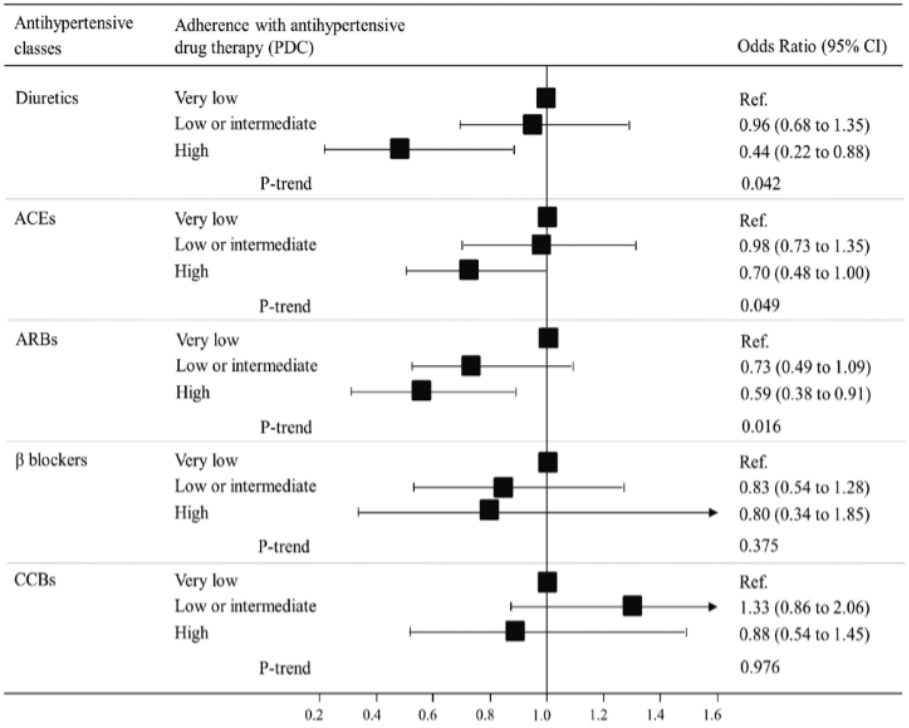
Adherence With Antihypertensive Drug Therapy and the Risk of Heart Failure in Clinical Practice

Giovanni Corrao, Federico Rea, Arianna Ghirardi, Davide Soranna, Luca Merlino, Giuseppe Mancia

Case control study; N=76'017; 2005-2012

Table 2. Effect of Adherence With Antihypertensive Drug Therapy and of Other Factors on the Risk of Hospitalization for Heart Failure

Effect	OR*	95% CI
Adherence with antihypertensive therapy		
Very low	1.00	Reference
Low	0.83	0.63–1.10
Intermediate	0.73	0.55–0.98
High	0.66	0.52–0.83
P trend	<0.001	



Adherence definition based on PDC:

- Very low: ≤ 25%
- Low: 26-50%
- Intermediate: 51-75%
- High: >75%

~ Persistence

PDC=proportion of days covered by treatment

Corrao et al, Hypertension, 2015, 66(4):742-9

MEDICATION ADHERENCE & SPENDING

By M. Christopher Roebuck, Joshua N. Liberman, Marin Gemmill-Toyama, and Troyen A. Brennan

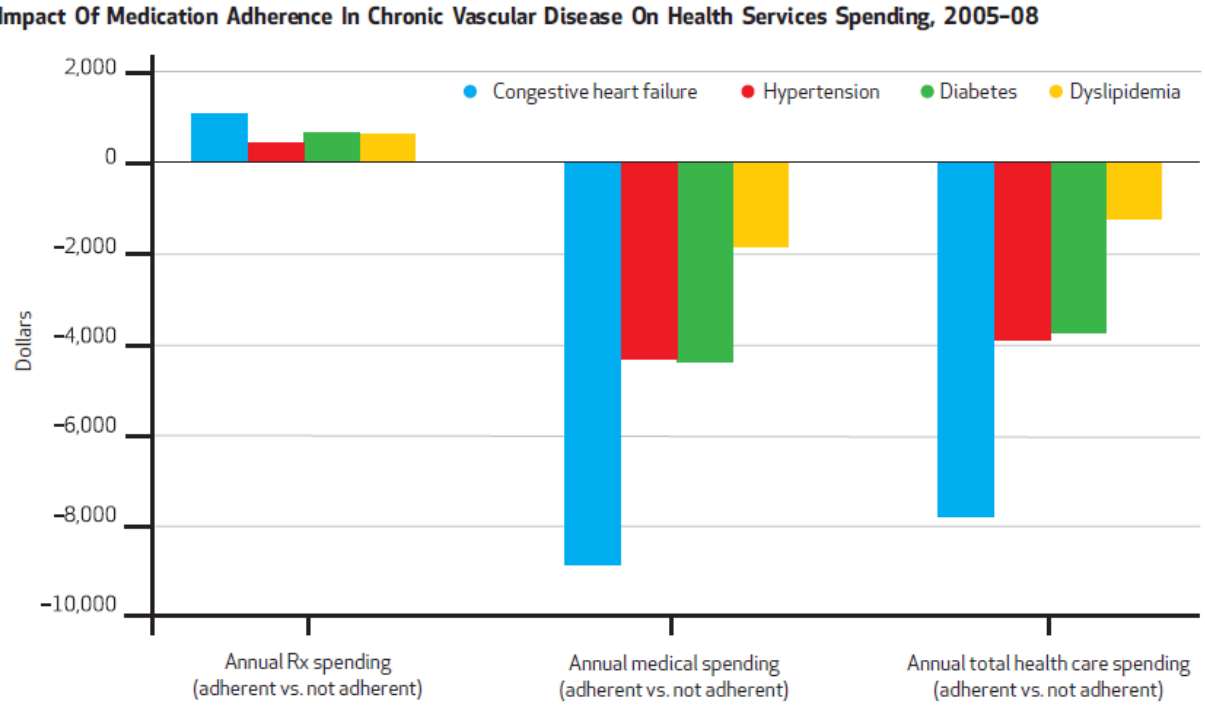
Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending

CVS claims data; N=>150'00; 2005-2008

Adherence definition based on MPR:

Adherent ≥80%
Non-adherent <80%

~ Persistence



MPR=medication procession ratio

Health Affairs, January 2011

What do we know about the patients who did not persist?

Patients who discontinue therapy
e.g. PDC<80%

Patients who persist with therapy
e.g. PDC>80%

- Do they have comparable medical conditions?
- Did they get the right prescription?
- Did they initiate the treatment?
- Did they implement adequaltely?
- Did they experience side effects?
- Were they satisfied with the outcome?

Is a brute force the solution to medication adherence?

Medisafe.com

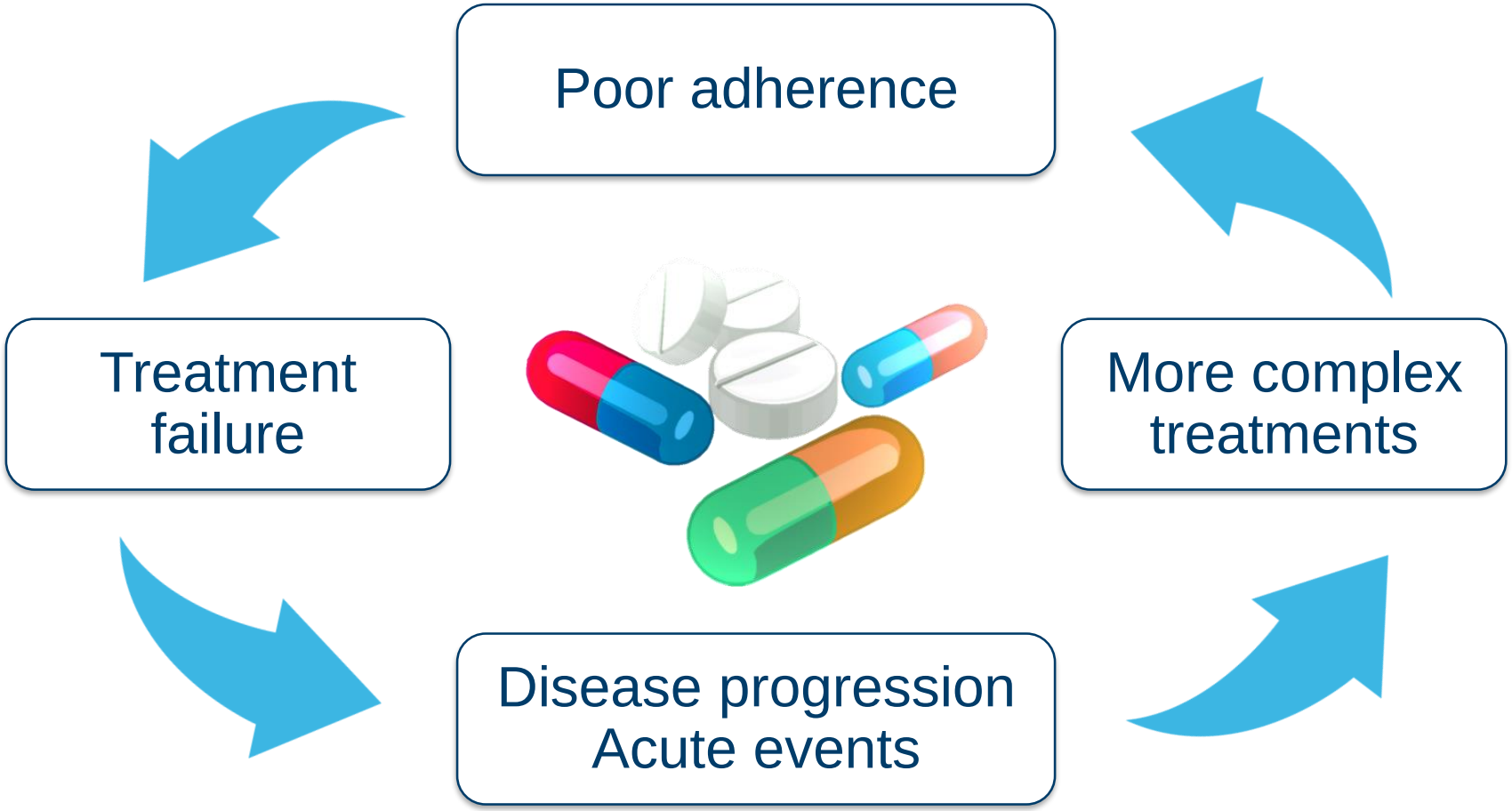
Proteus.com

Time based reminders
Intrusive
Reminds that patients are sick
Creates dependences
Virtual prison
Totalitarist view

AIcure.com

Vaica.com

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



The changing pharma model[1]

✓ 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

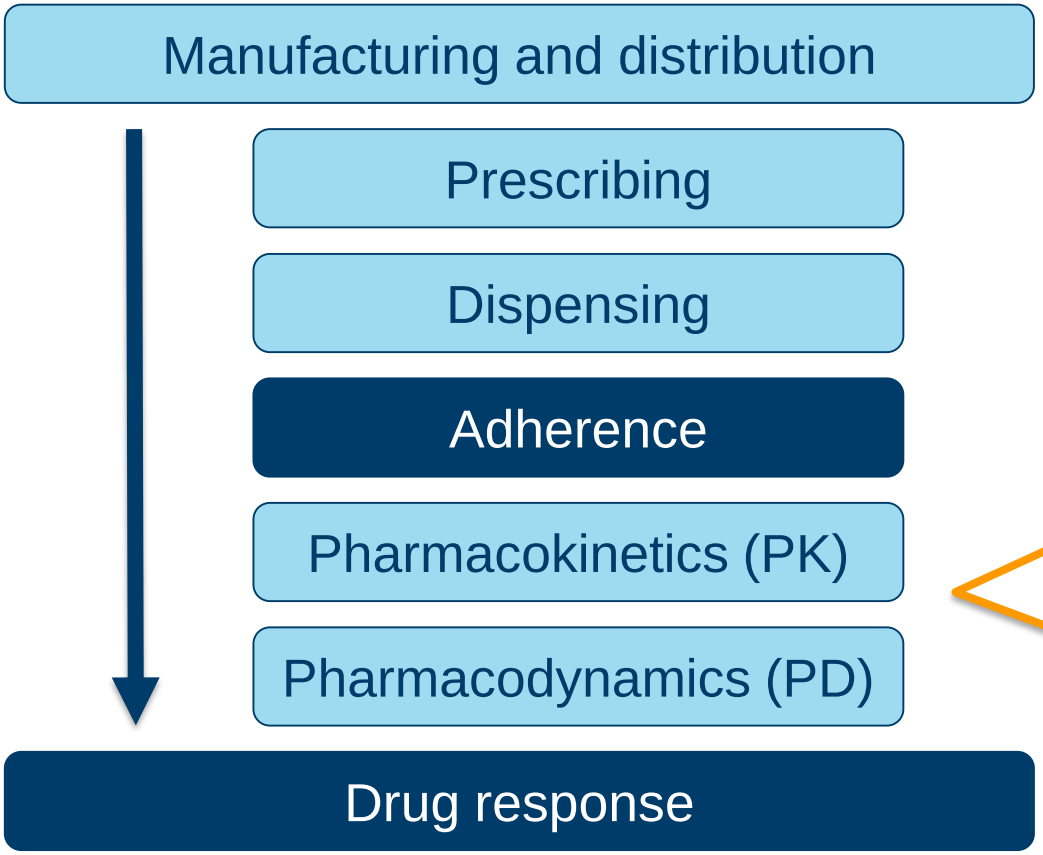
Key is being "on treatment"
A Initiation & C Persistence
Proportion of Days Covered
PDC >80%

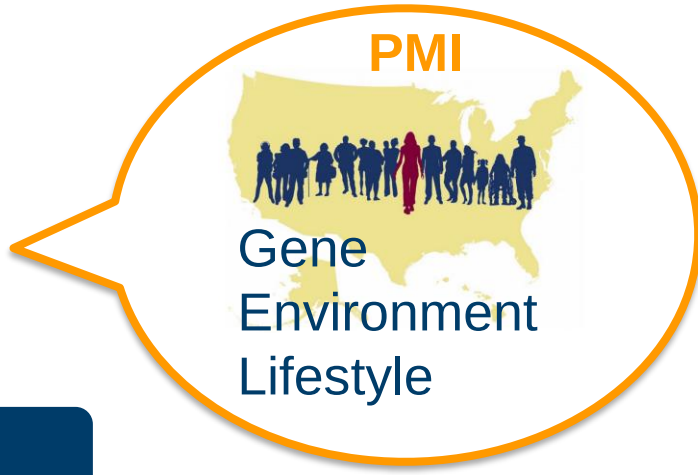
Precise B implementation
of the dosing regimen

➔ **Medication Adherence is a vital sign to measure and manage**

1, Tufts CSDD, 2012

Variable adherence is a major source of variance in drug response



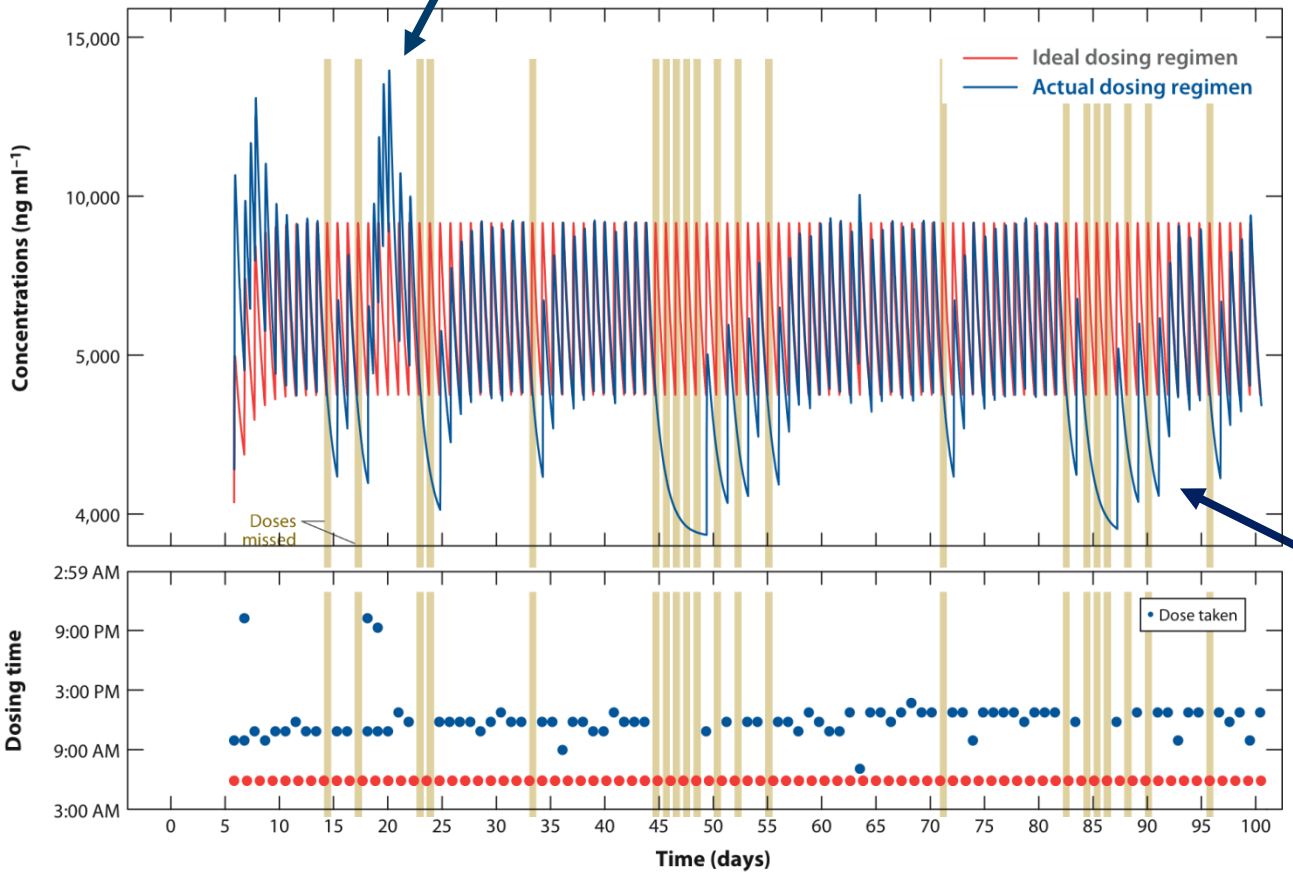


www.nih.gov/precision-medicine-initiative-cohort-program

Harter JJ, Peck CC. Ann N Y Acad Sci 1991;618:563–71.

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

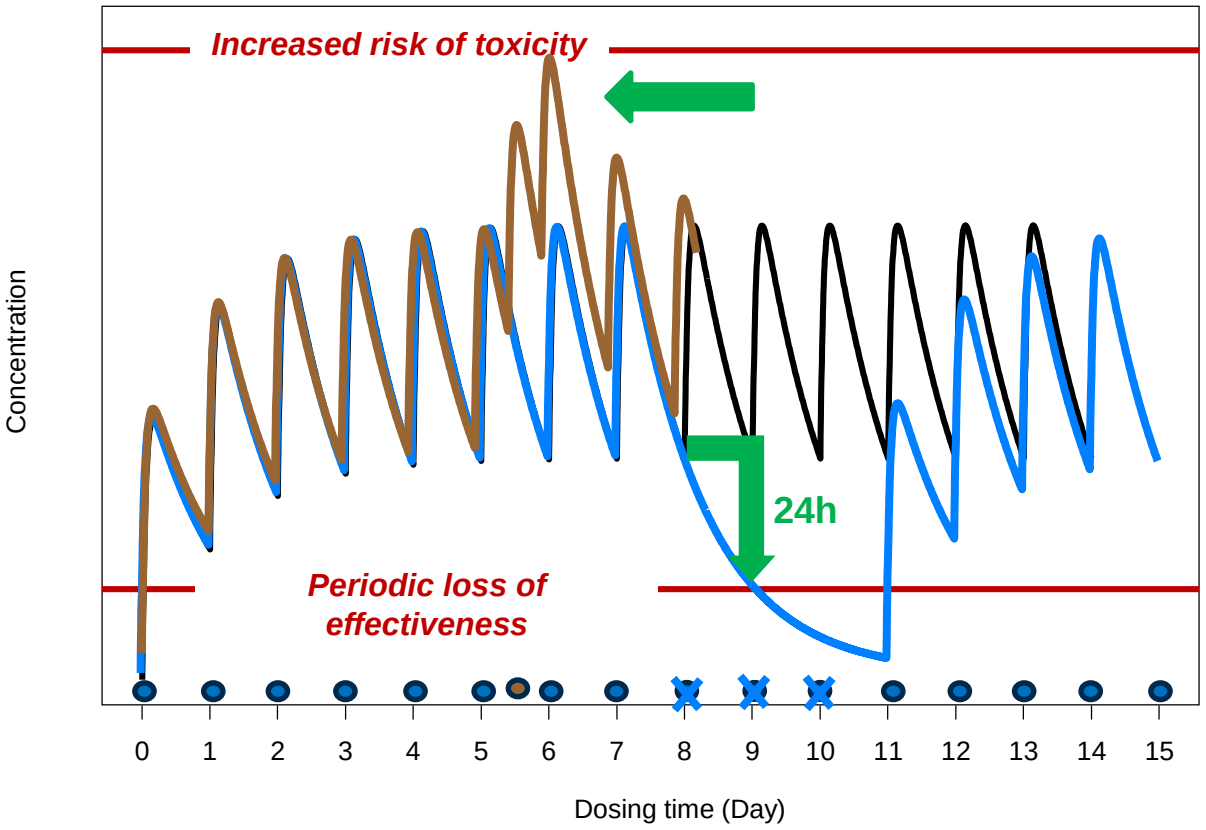
Occasional toxicity



Periodic loss of effectiveness & emergence of drug resistance

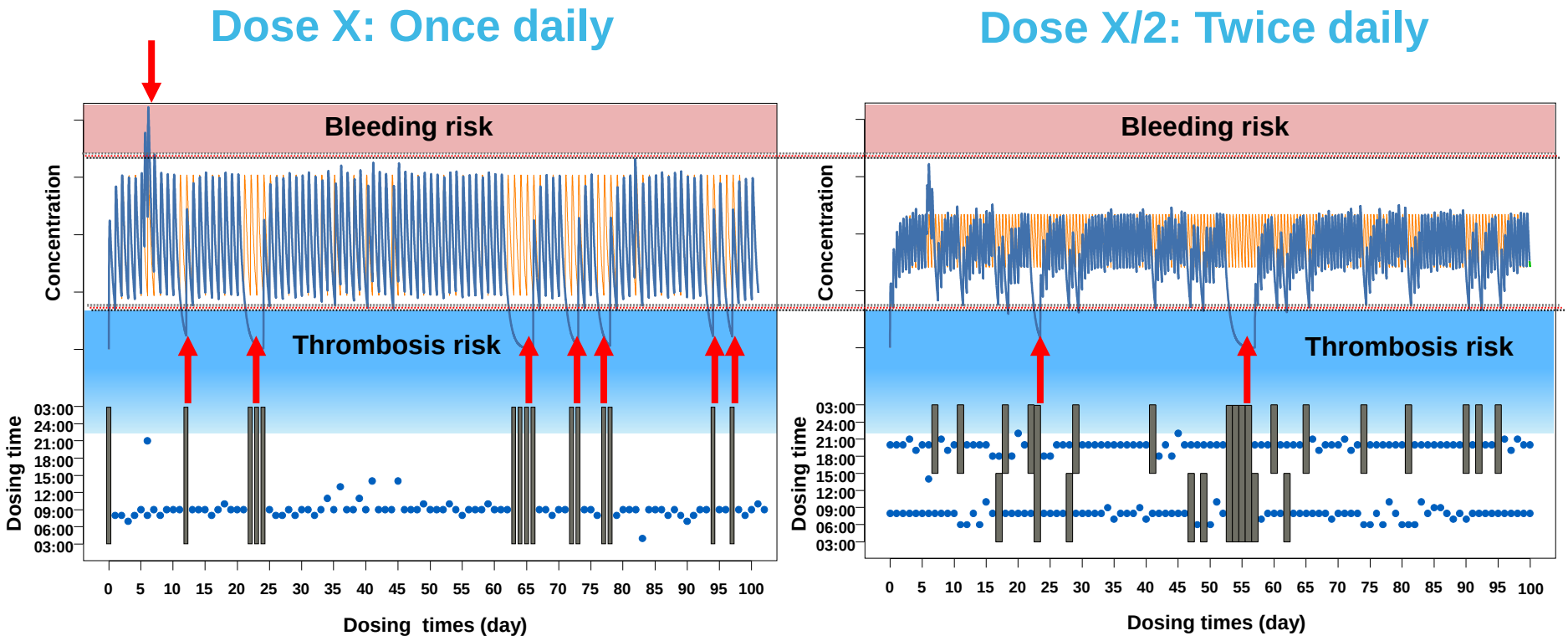
Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301

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



Beyond adherence, think drug forgiveness

The NOACs example:
Drug exposure simulations assuming $T_{1/2}$=12h; T_{max}=3h



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

Vrijens B, Heidbuchel H, Europace, 17(8):1317-8, 2015

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

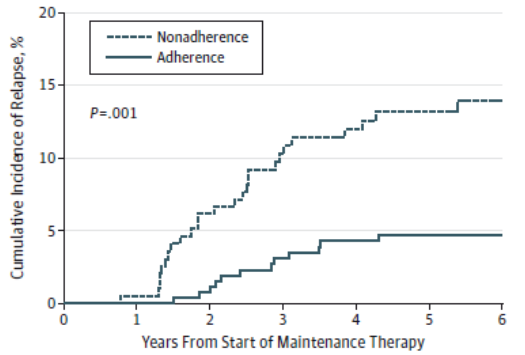
Original Investigation

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

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

Related article

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."[5] 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 AALL0932; clinicaltrials.gov identifier: NCT01190930). 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

thioguanine nucleotide (TGN) metabolite le
polymorphisms (eg, thiopurine methyltrans
measurement of absolute neutrophil counts
drug administration according to circadian ri
transferase levels, physician compliance, and
ence to prescribed therapy).[7] As a result of the
maintenance phase dosing is now based on ti

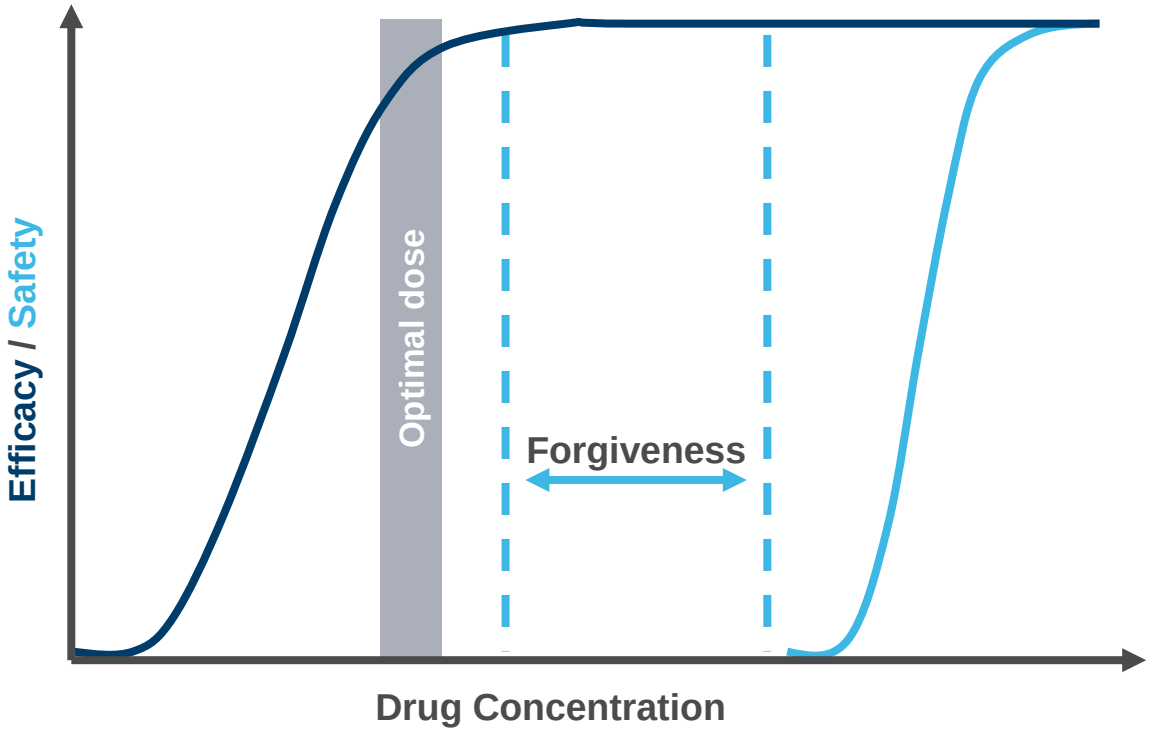
jamaoncology.com

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"

Bhatia S, et al., JAMA Oncol.; 1(3):287-95, 2015.

The struthian approach is no longer an option!



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

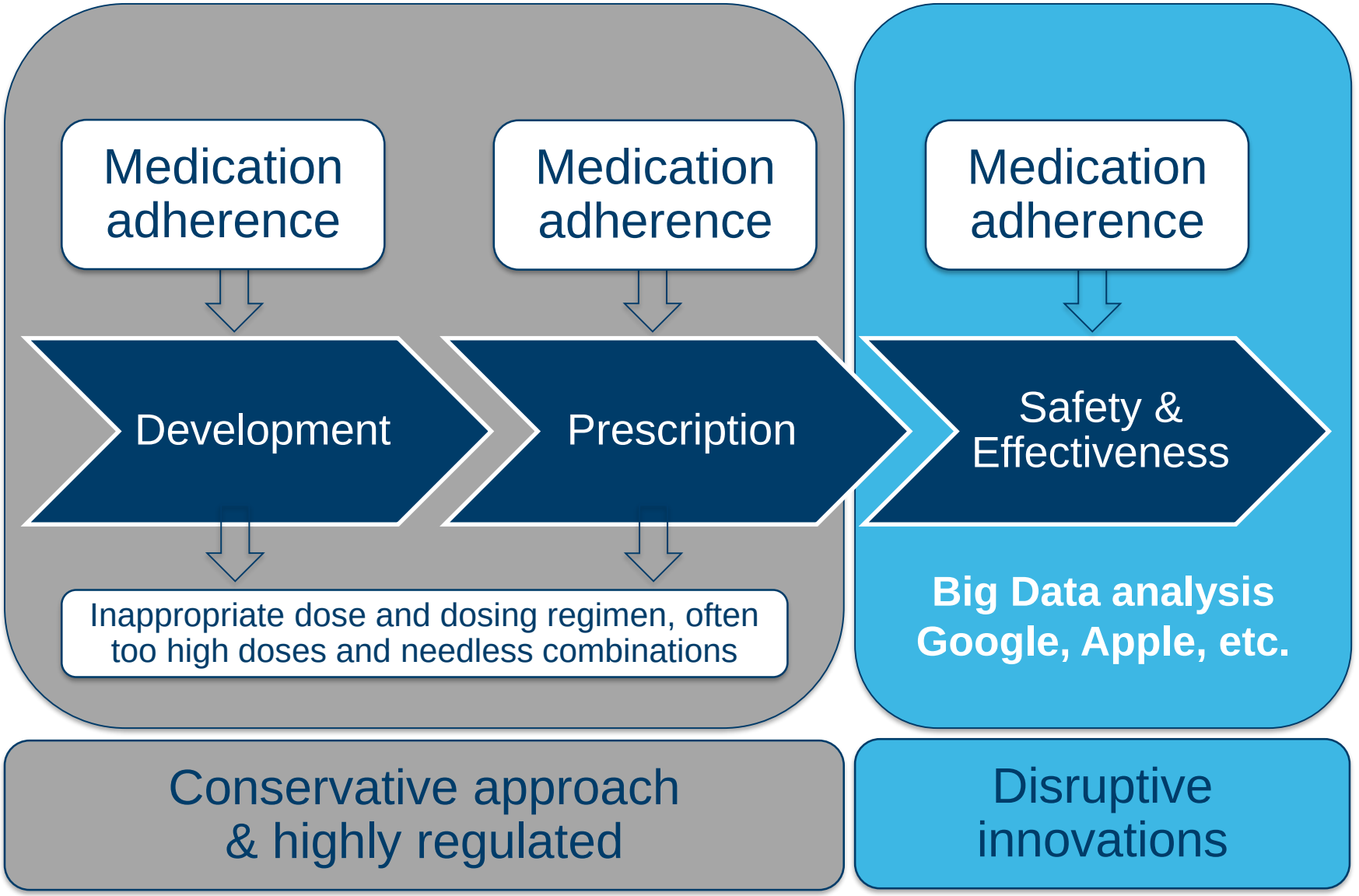
1 in 5: >50% dose reduction[1,2]

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.*

Adherence-informed development and prescription is urgently needed

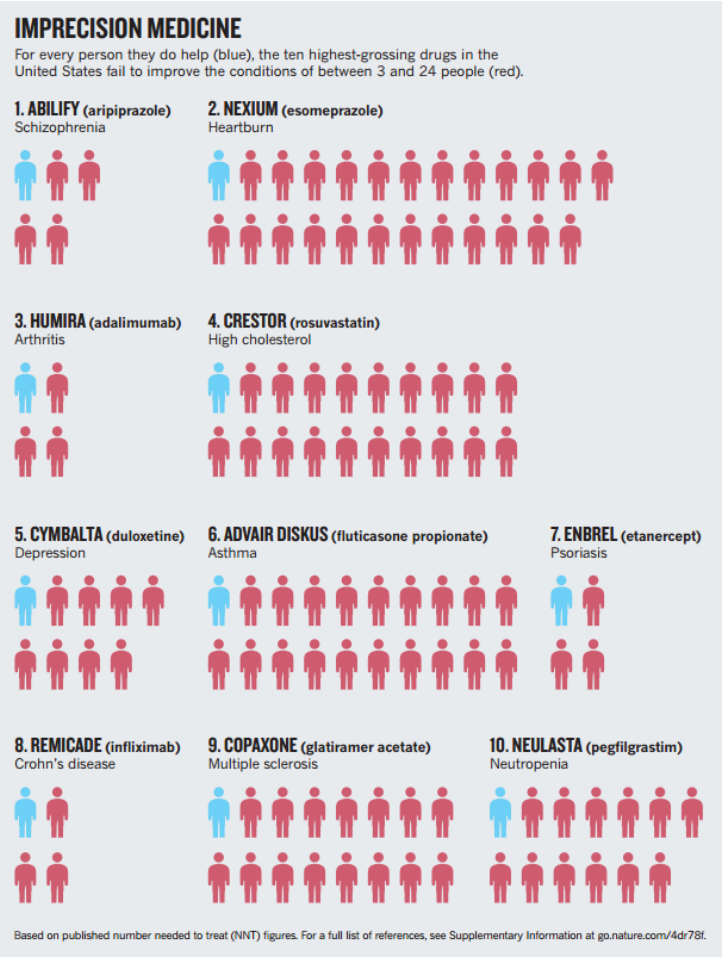


When Treatment is Not Working:
Think Non-Adherence!

ILLUSTRATION BY GREG CLARKE

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.



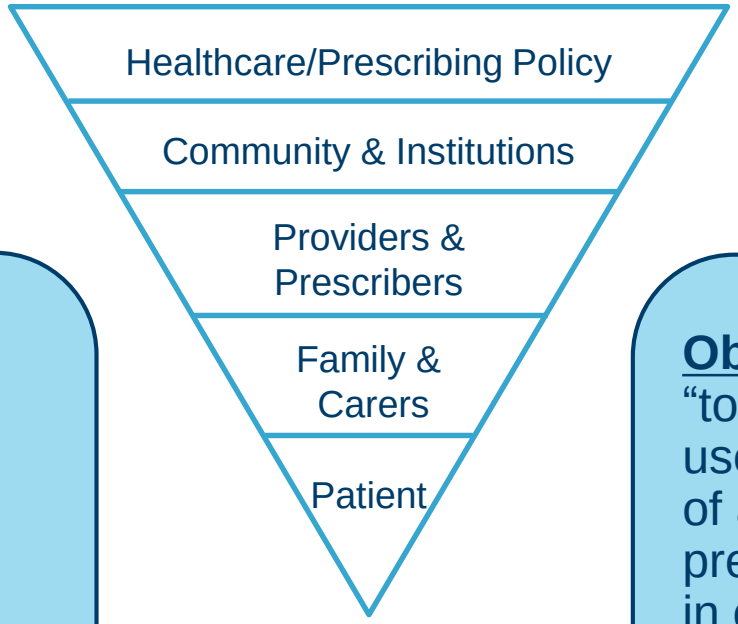
Nature, 30 April 2015.

Non-Adherence Becomes a Threat for the Economic Well Being of a Country

"A $474 billion USD avoidable cost opportunity, or 8% of the world's health expenditure, exists in these areas"

IMS INSTITUTE FOR HEALTHCARE INFORMATICS

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"

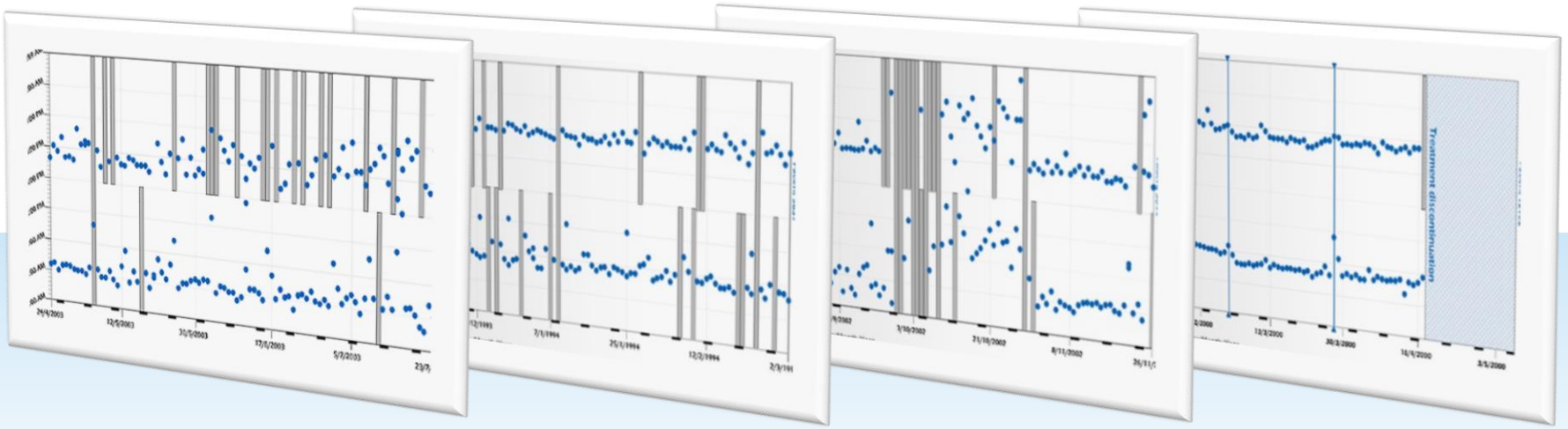
EU-sponsored research

Vrijens B et al., Br J Clin Pharmacol 2012;73:691-705.

“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

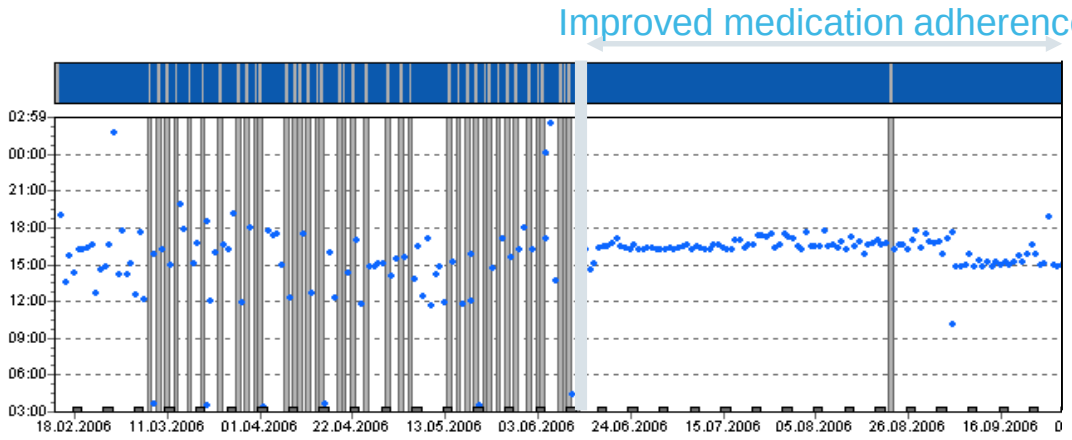
Sporadic Dosing

Drug Holiday

Early Discontinuation

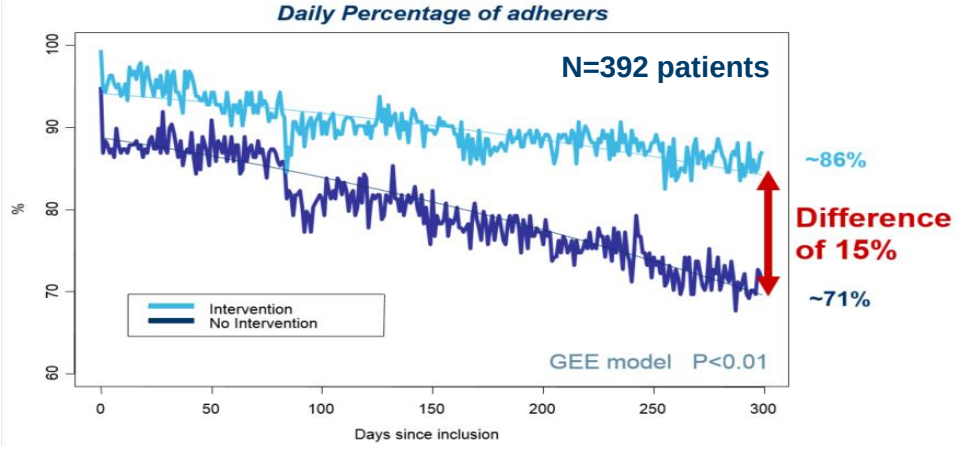
Vrijens B, Urquhart J, White D, 2014, Expert Rev Clin Pharmacol; 7(5):633-44

Patients' awareness of their adherence patterns changes behavior



Example of a successful intervention

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

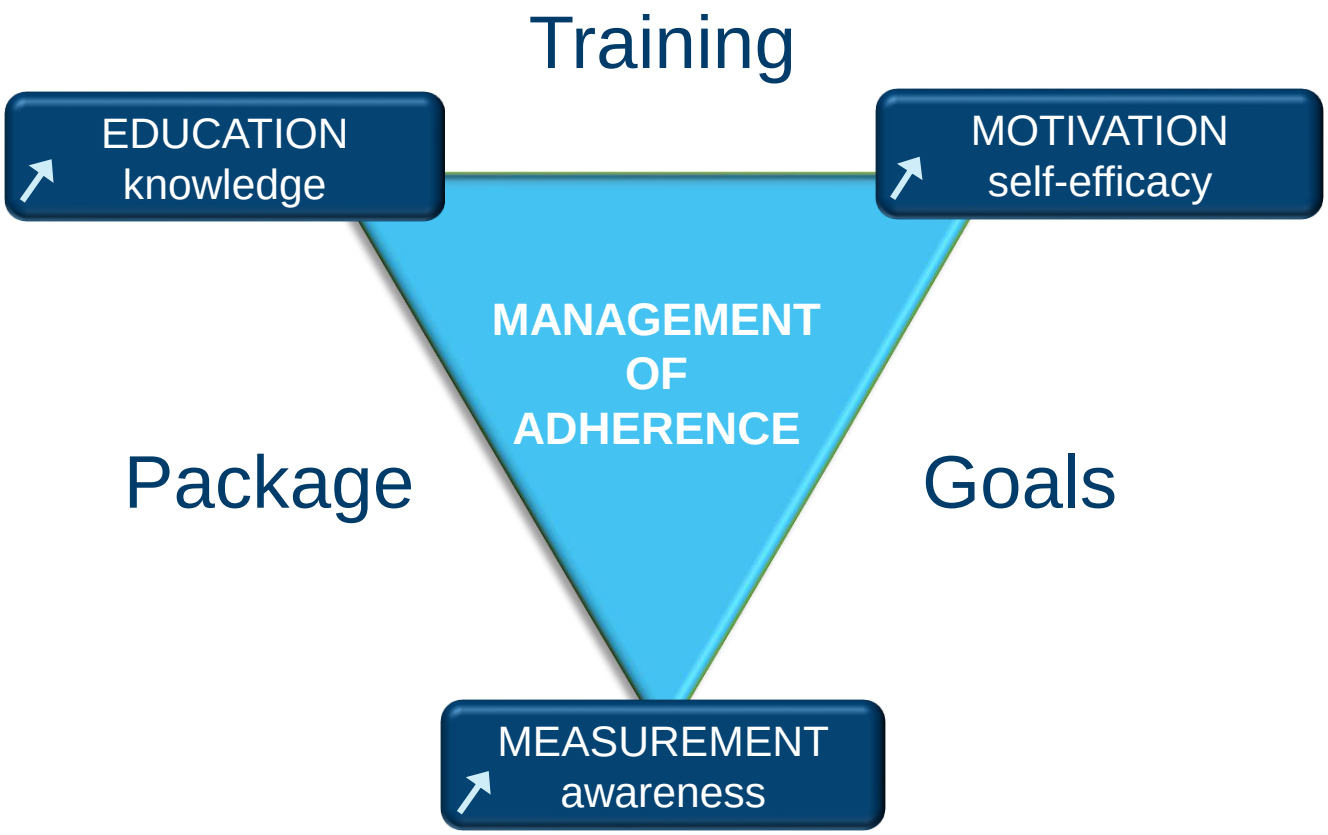


EU-sponsored study confirms that showing patients their own dosing errors is the most effective means to improve adherence

Demonceau et al, Drugs; April 2013.

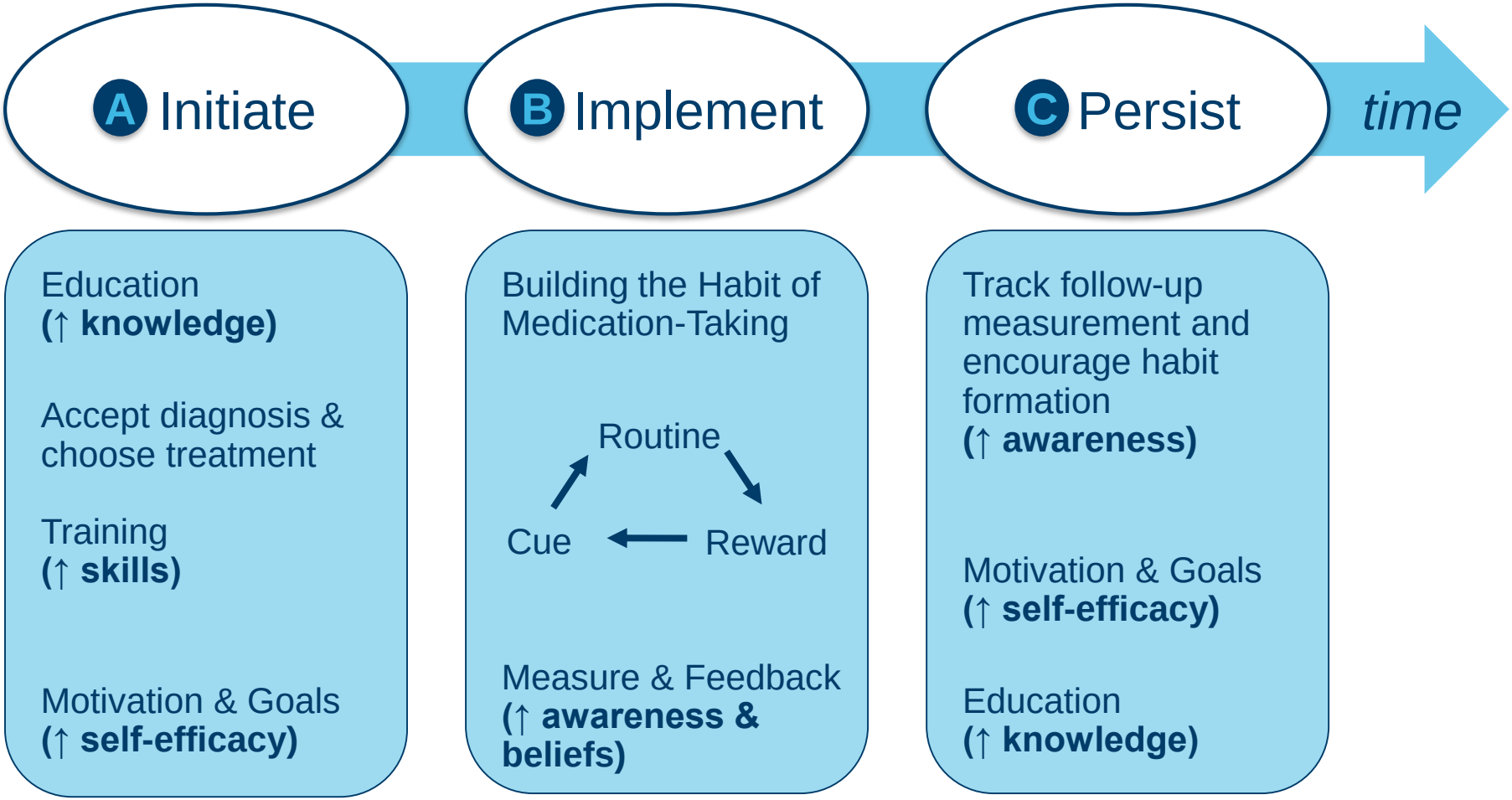
Vrijens B , et al, Pharmacoepidemiol Drug Saf. 2006;15(2):115-21.

Elements to change patients' behavior



Vrijens B, Urquhart J, White D, 2014, Expert Rev Clin Pharmacol; 7(5):633-44

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



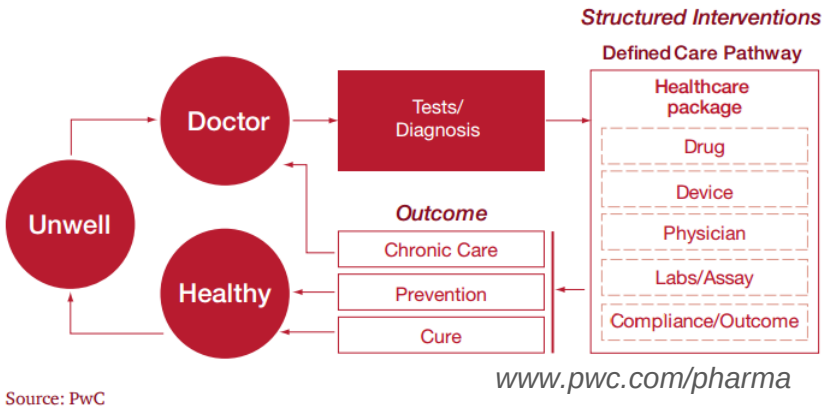
Vrijens B, Urquhart J, White D, 2014, Expert Rev Clin Pharmacol; 7(5):633-44

Adherence management is becoming part of care pathways

Pharma 2020: The vision

pwc

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



Source: PwC

www.pwc.com/pharma

EHRA Practical Guide on NOACs in NVAF

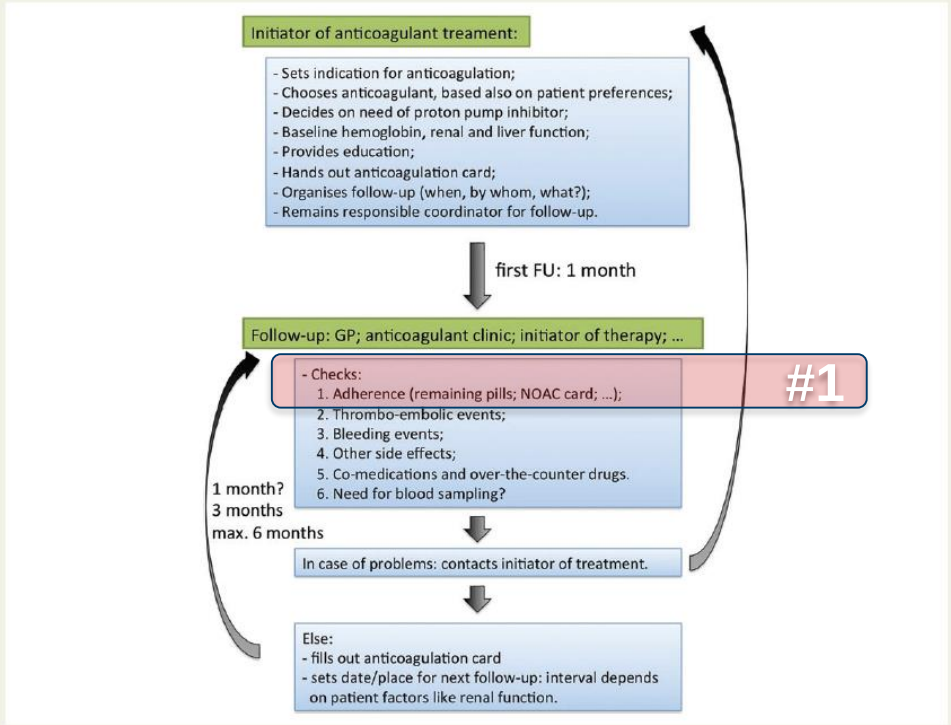
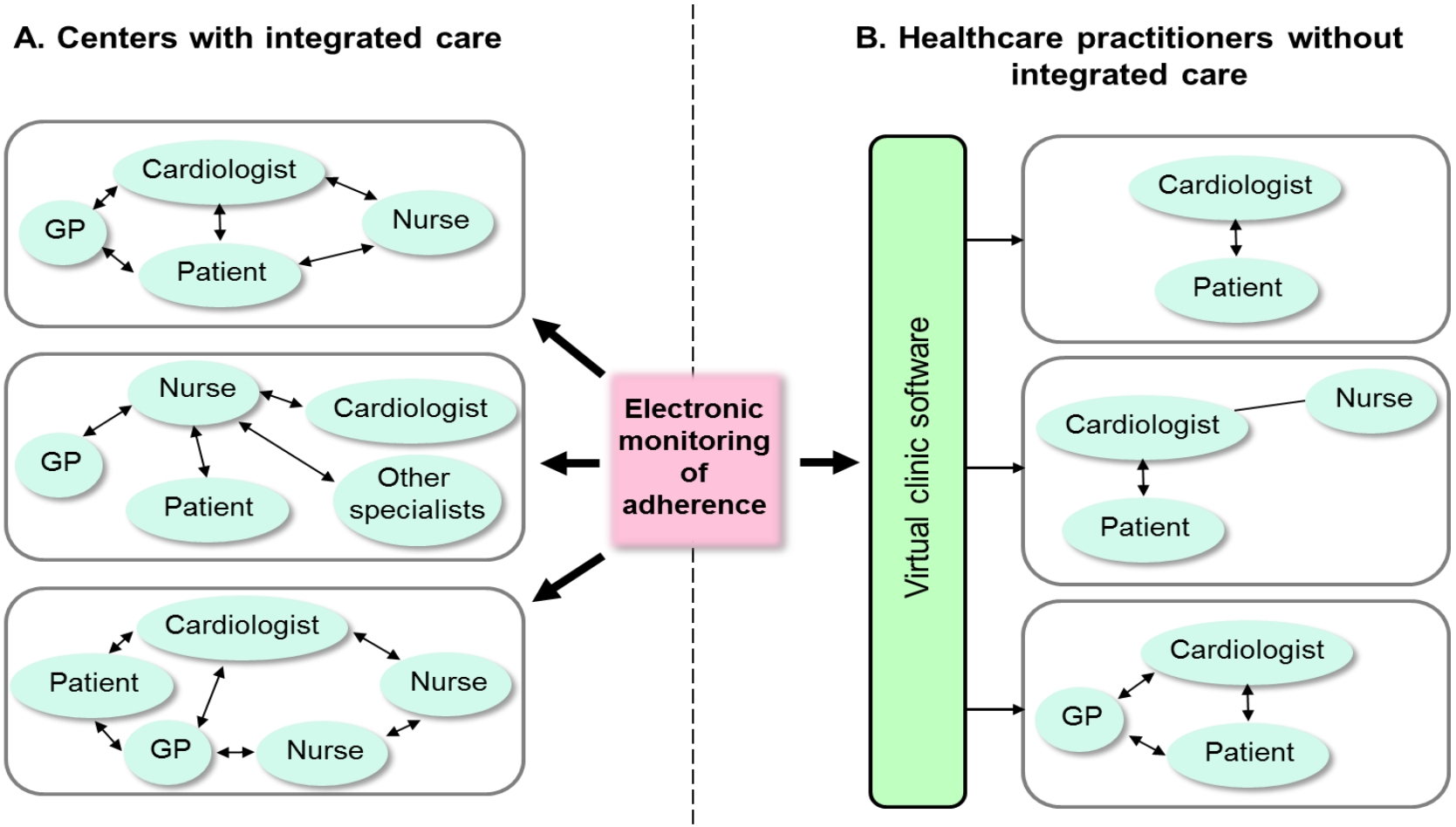


Figure 2 Initiation and structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in *Figure 1*, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every 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.

Heidbuchel et al, Europace. 2015;17(10):1467-507

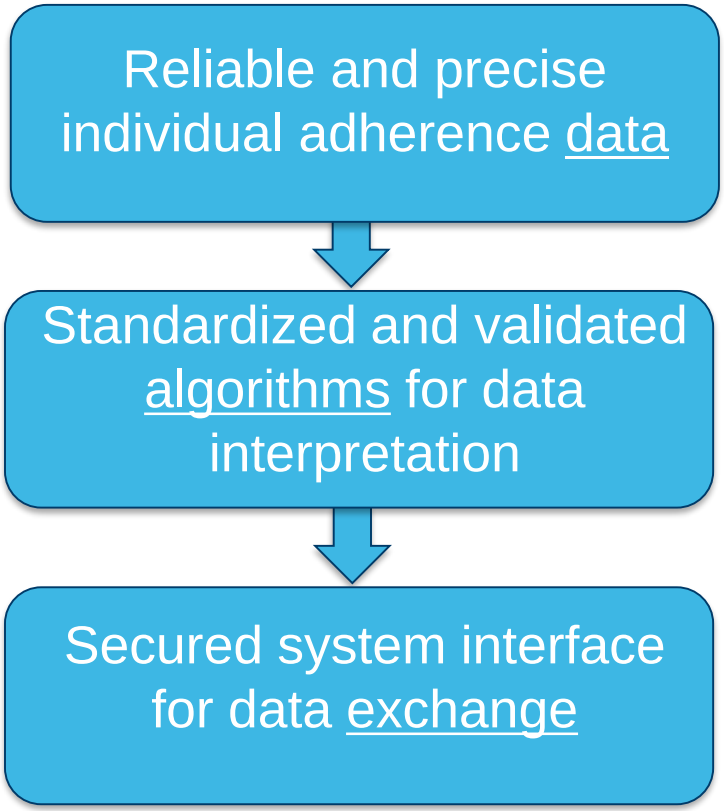
Requires integration into different care systems



Vrijens B, Heidbuchel H, Europace, 17(8):1317-8, 2015

Individualised m-Health interventions integrated in clinical care

High quality & Useful



Cost-Effective

Special Focus on:

- ✓ Key clinical parameters
- ✓ Selected patients
- ✓ Critical time points (e.g. initiation, treatment failure, when a problem is suspected)
- ✓ Medical condition/treatment

The danger is that “point of care” is changing

- ✓ Use internet to get information about health condition
- ✓ Join patient support groups
- ✓ m-Health (devices & apps)
- ✓ Big data analysis / artificial intelligence (AI)

May lead to healthcare cahos

→ Need supervision and integration in clinical care

Big Data & Artificial Intelligence will redesign healthcare as well


Robots invest money better than people

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Investors cool on start-ups that promise silver bullets

Sentiment towards industry sours as backers look harder at what companies offer, says Murad Ahmed

Financial Times, March 16-17, 2016

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