Bridging the efficacy-effectiveness gap

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Self-assessment questions

Answer yes or no

1. I know the difference between efficacy and effectiveness
2. The efficacy-effectiveness gap is often a problem of variability in drug response
3. Patient compliance and off-label use do not contribute to the efficacy-effectiveness gap


MIND THE GAP

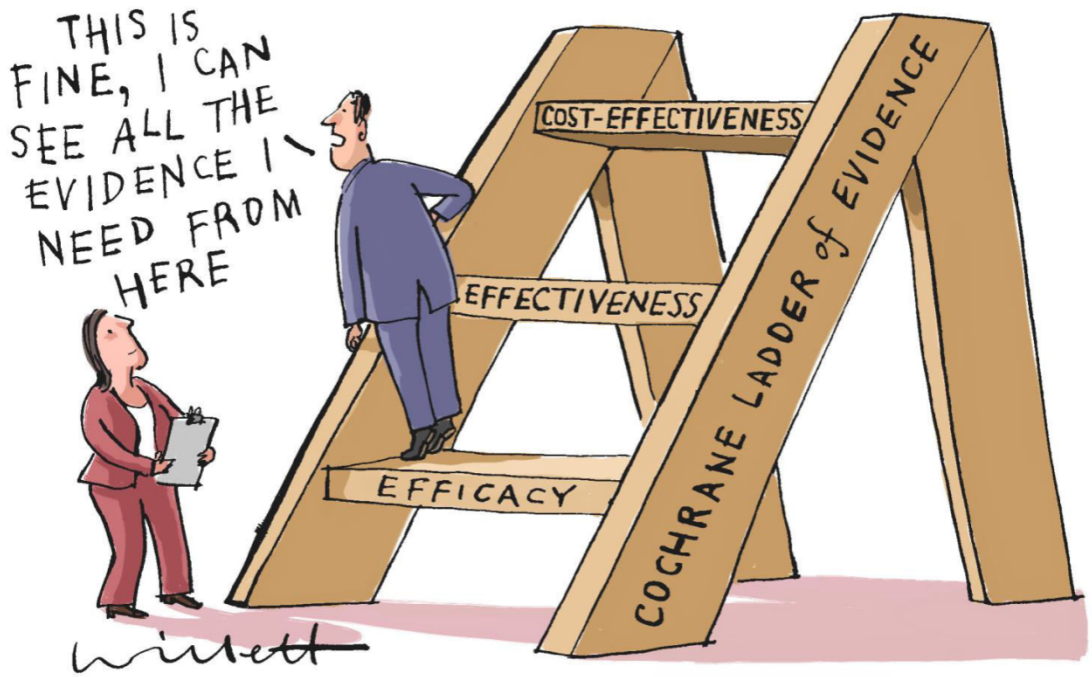
Efficacy versus effectiveness

- **Efficacy** is the extent to which an intervention does more good than harm under ideal circumstances (= clinical trial conditions)

- **Effectiveness** is the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice

Definitions by the EU High Level Pharmaceutical Forum (Oct 2008)

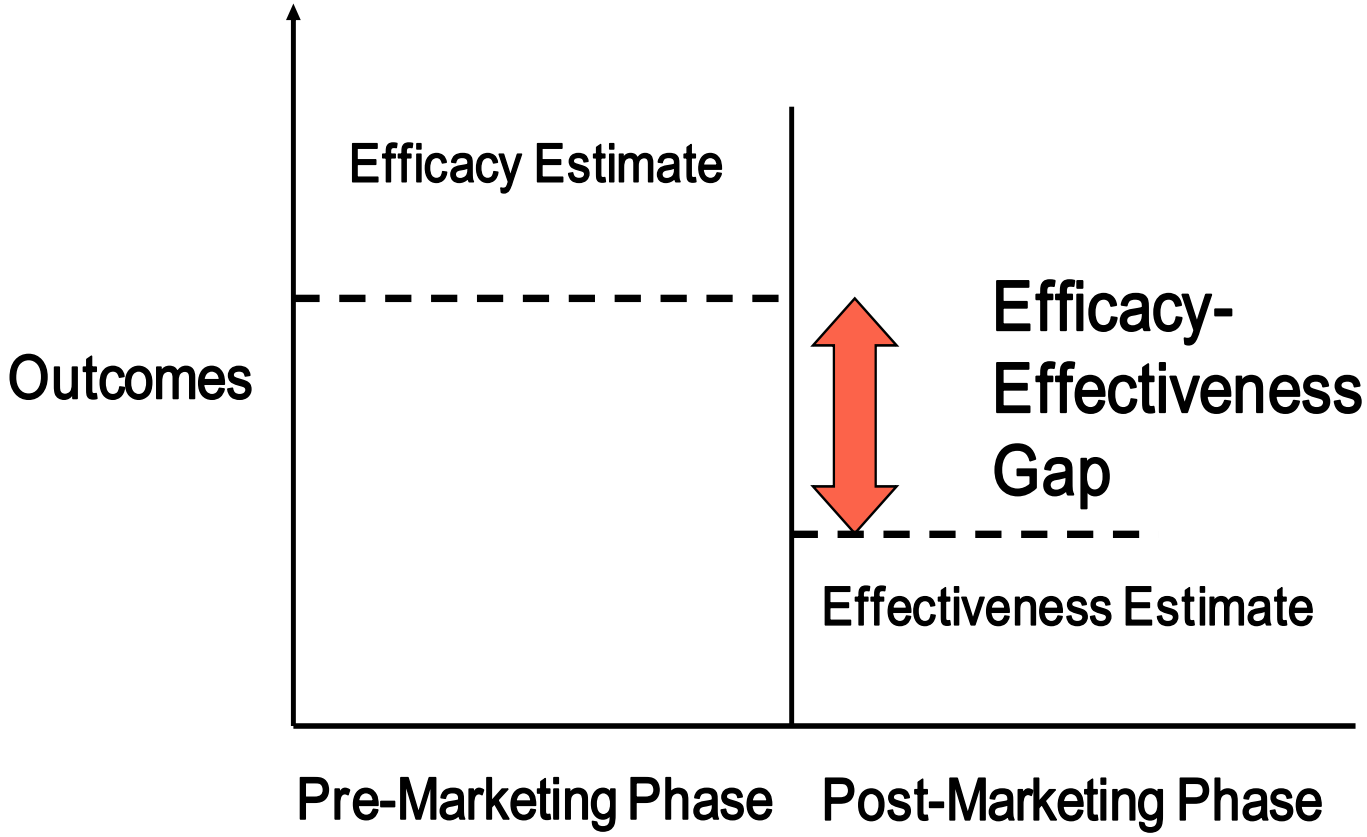
Efficacy versus effectiveness



"Does it work?"

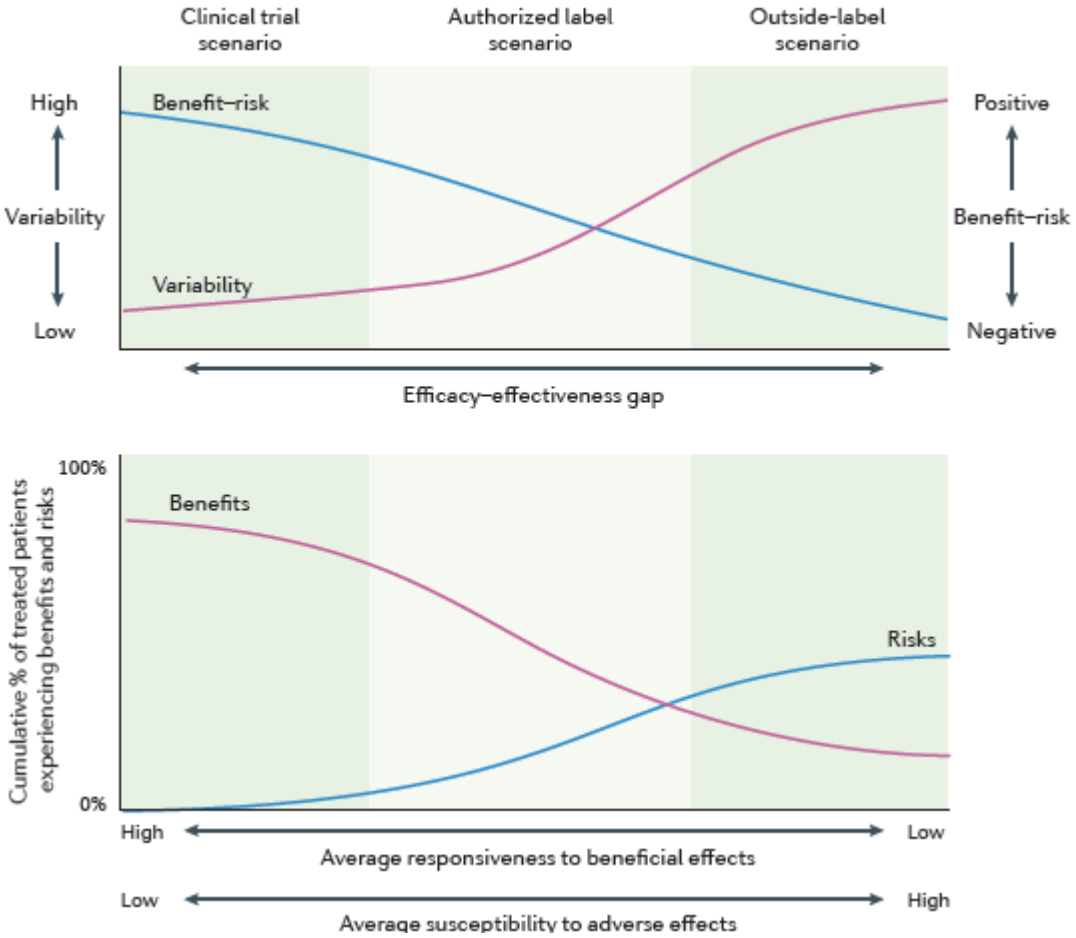
"Can it work?"

Efficacy-effectiveness gap



Eichler HG, Blöchl-Daum B

Benefit-risk of drugs



Eichler HG et al., Nat Rev Drug Discov. 2011 Jul 1;10(7):495-506

What creates the efficacy-effectiveness gap? 3 Paradigms

Paradigm	Description	Themes encompassed
1. The EEG is related to real-life characteristics of the health care system	The ideal effect of the drug is distorted by real-life characteristics of the health care system, related to the physician, the patient, and access to health care resources	• In routine practice, the *physicians'* "behavior" regarding medical guidelines and dissemination of knowledge is not optimal • In routine practice, the *patients' adherence* is not optimal • In routine practice, there are access barriers to health care resources
2. The EEG is related to an issue of the method used to measure the drug's effect	Efficacy and effectiveness studies use different study designs and design parameters, hence the EEG	• Concept of *evidence-based medicine* and *hierarchy of evidence*: the efficacy is the *real* effect of the drug; the RCTs are the criterion standard for measuring the drug's effect • Concept of *pragmatism*: RCTs' lack of generalizability; any direct dissemination of evidence coming from clinical trial into clinical practice is inadequate
3. The EEG is related to an issue of complex interaction	The drug's effect is the result of complex (and multiple) interactions between the biological effect of the drug and "real-life" contextual factors, hence the EEG	• Some contextual factors are (significantly) interacting with the drug's biological effect ("drivers of effectiveness") • An imbalance in the distribution of these factors between efficacy and effectiveness studies may cause an EEG

EEG, efficacy-effectiveness gap; RCT, randomized controlled trial.

Nordon C et al., Value Health, 2016 Jan;19(1):75-81

Examples of Issues, the case for oncology.

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13
BMJ 2017; 359 doi: https://doi.org/10.1136/bmj.j4530 (Published 04 October 2017)Cite this as: *BMJ* 2017;359:j4530

No survival, QoL gain for many EMA cancer drug approvals.

Between 2009 and 2013, the EMA granted a marketing authorization to **48 anticancer** medications for **68 indications**, but **only 24 – just over a third – had evidence they provided an OS** gain over existing treatments, best supportive care, placebo, or as an add-on therapy, with the magnitude of gain ranging from **1.0 to 5.8 months**.

Oncology GAPS and extrapolation

- C3POMab approved for a specific setting with phase II trial, surrogate endpoint.
- Nobody knows how it‘s use will affect it‘s effectiveness in later stages of disease.
- Should we use it?

Study Designs (such as comparator)
and parameters (such as surrogate outcomes):

- **allow for regulatory aprovals**
- **Increase the EEG**

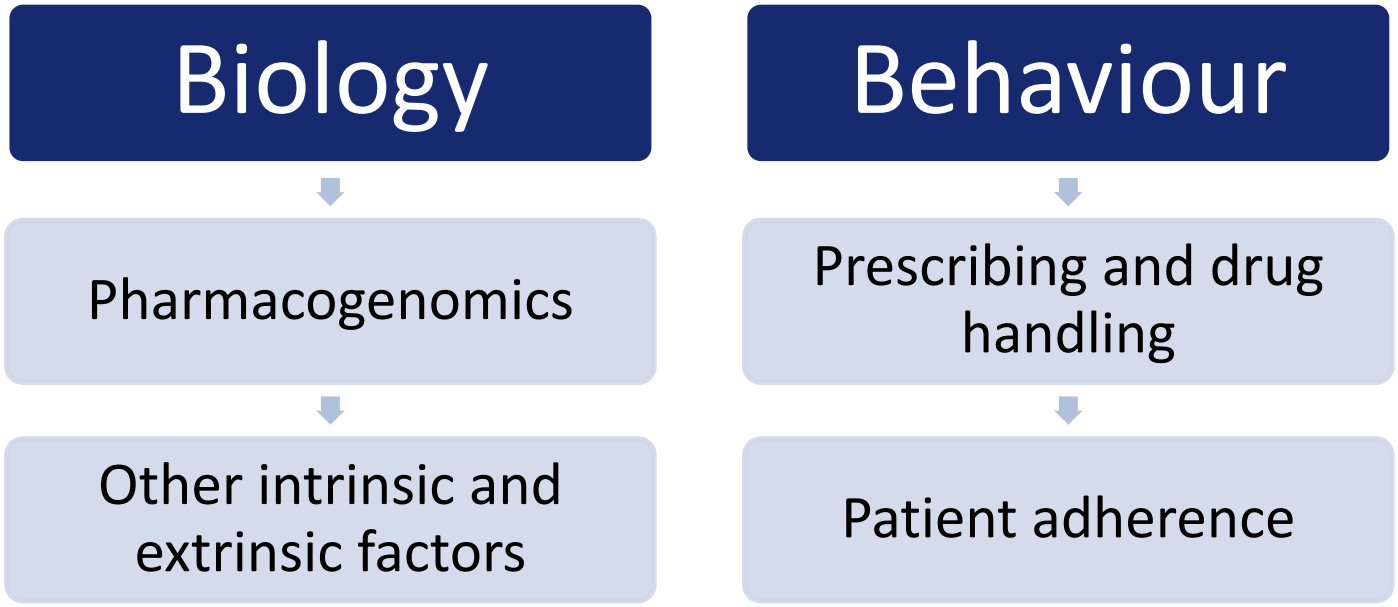
What actually creates the efficacy-effectiveness gap?

Patient – Drug - Doctor

Can we conceptualise the efficacy – effectiveness gap?

A problem of VARIABILITY

Sources of variability in drug response



Biology

↓

Pharmacogenomics

A substantial fraction of variability in efficacy or toxicity
can be explained on the basis of a single genomic marker

TRASTUZUMAB (Herceptin®)
HER2 +/-

This is increasingly being used in drug designs – “targeted therapy”

Biology

Other intrinsic and extrinsic factors

Co-determination of PK/PD

Intrinsic: age, sex, body weight, comorbitities, baseline severity of disease

Extrinsic: environmental influences (pollution, sunlight), co-medication, food

INFLIXIMAB
High BMI > lower response

Behaviour

Prescribing and drug handling

Drugs approved for defined indications and conditions > OFF-LABEL-USE

What's in the label? How did it get there?

Behaviour

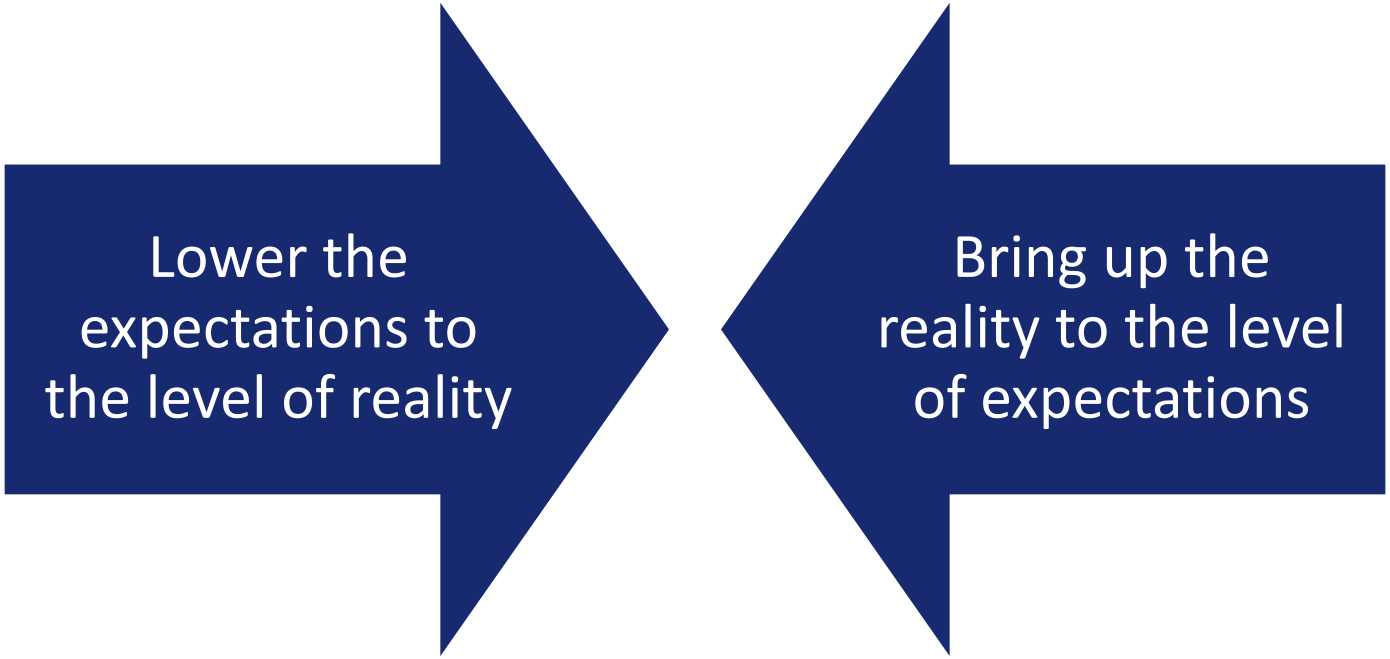
Patient adherence

„Drugs don‘t work in patients who don‘t take them.“
(Koop‘s Law)

Poor adherence (compliance) to prescribed drug regimens:
e.g. fluctuations in dose-timing;
omitting a single-day‘s dosing;
repeat drug holidays;
non-persistence

Bridging the efficacy-effectiveness gap - A serious challenge

2 Ways



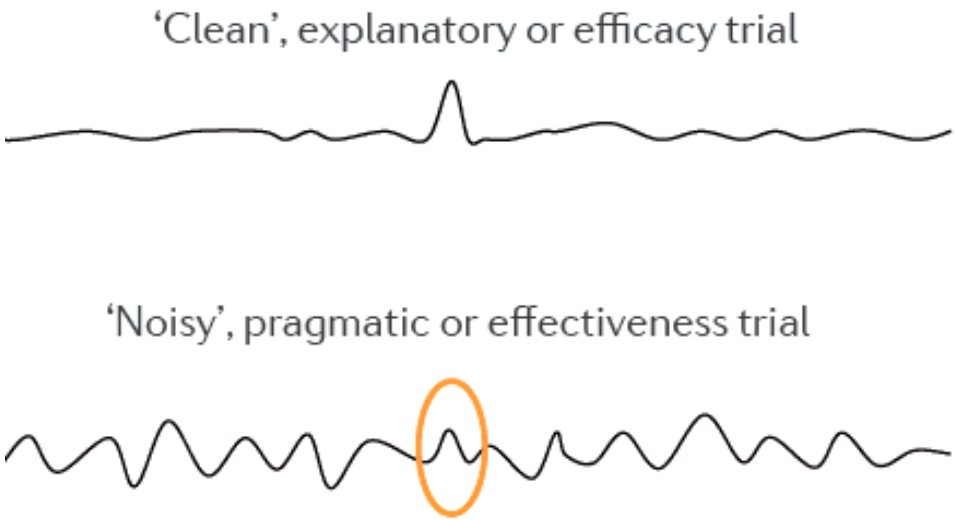
Way 1:

Lower the expectations to the level of reality

Regulators demand pre-marketing studies that fully represent clinical reality and then base licensing decisions on effectiveness information

- Regulatory RCT should be internally valid and must be externally valid („pragmatic“ clinical trials or effectiveness trials)(endpoints, compartors, etc.)
- Fewer and broader patient selection criteria
- Less control over patient management

Signal-to-noise ratio in clinical trials



Not the easiest way to do it...
...but is it the best for the patient!?

Eichler HG et al., Nat Rev Drug Discov. 2011 Jul 1;10(7):495-506

Way 2:

Bring up reality to the level of expectations

Every-day practice strictly follows the label (or other adequate evidence sources) and drug regimens are individualized to meet patient‘s needs.

… a drug problem or a healthcare delivery problem?

Which patient for this drug?
Which drug for this patient?

- Quality of prescribing:
  „The right drug, at the right dose,
  at the right time, to the right patient.“
- Biomarker-guided benefit-risk stratification
  Focus on optimised treatment-eligible population
- Post-marketing risk-management plans
- Present information in a useful format to guide drug prescribing

Toys to improve adherence?

Abilify MyCite – the first digital pill

FDA News Release

FDA approves pill with sensor that digitally tracks if patients have ingested their medication

New tool for patients taking Abilify

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release November 13, 2017

Summary FDA approves Abilify MyCite, a pill with a sensor that digitally tracks if patients have ingested their medication

Release

The U.S. Food and Drug Administration today approved the first drug in the U.S. with a digital ingestion tracking system. Abilify MyCite (aripiprazole tablets with sensor) has an ingestible sensor embedded in the pill that records that the medication was taken. The product is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder and for use as an add-on treatment for depression in adults.

The system works by sending a message from the pill's sensor to a wearable patch. The patch transmits the information to a mobile application so that patients can track the ingestion of the medication on their smart phone. Patients can also permit their caregivers and physician to access the information through a web-based portal.

"Being able to track ingestion of medications prescribed for mental illness may be useful for some patients," said Mitchell Mathis, M.D., director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research. "The FDA supports the development and use of new technology in prescription drugs and is committed to working with companies to understand how technology might benefit patients and prescribers."

Inquiries

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As the sensor becomes wet it sends a signal to the arm patch

The mobi
automati
message
member

http://www.thasso.com

Reading recommendation

OPINION

Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response

Hans-Georg Eichler, Eric Abadie, Alasdair Breckenridge, Bruno Flamion, Lars L. Gustafsson, Hubert Leufkens, Malcolm Rowland, Christian K. Schneider and Brigitte Bloechl-Daum

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And what‘s in it for the Hospital Pharmacist?

1. Understand the GAP and it’s causes. Be critical, everything that shines is not gold. Be supportive of effectiveness research
2. Reduce or adapt to variability: look for adequate prescribing (label or other); require adequate biomarkers before dispensing, implement TDM as applicable.
3. Compliance and drug use education: pharmacists do it better

Self-assessment questions

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Self-assessment questions

Answer yes or no

1. I know the difference between efficacy and effectiveness **YES**
2. The efficacy-effectiveness gap is often a problem of variability in drug response **YES**
3. Patient compliance and off-label use do not contribute to the efficacy-effectiveness gap **NO**

If realized…

„Medicine might [indeed become]
a science and not an art.“

Sir William Osler, 1892

Take home messages

- The efficacy-effectiveness gap is to a considerable degree a problem of variability in drug response
- Biological and behavioural sources of variability
- Pre- and post-licensing technologies will need to be harnessed to bridge the efficacy–effectiveness gap
- *There is a ROLE for hospital pharmacists!*