CHARITÉ

Comprehensive Cancer Center | Universitätstumorzentrum


# Clinical Trial Design

SPARK
BIH

Dr. med. Susen Burock

# Declaration of conflict of interest

**Disclosure: None**

# What is a clinical study?

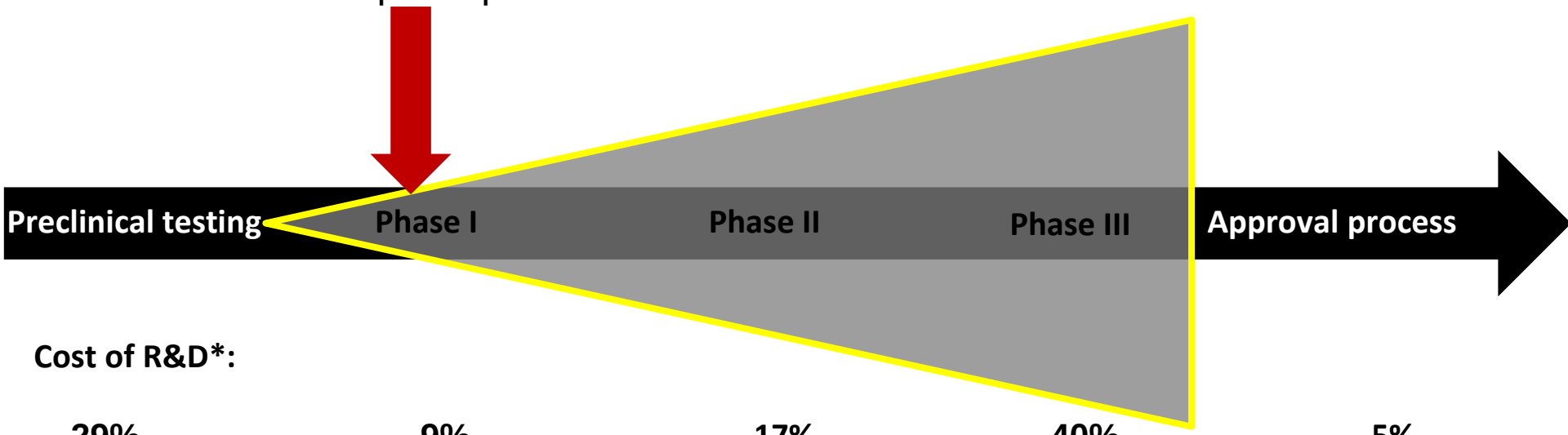
Systematic collection of data to answer one or more questions in terms of

- Prevention
- Diagnosis
- Treatment

It can be a non-interventional study (observation only) or an interventional study (randomized or non-randomized).

# Methodology of clinical trials

Dose-ranging (on healthy volunteers) for safety
20-100 participants




| | | | | |
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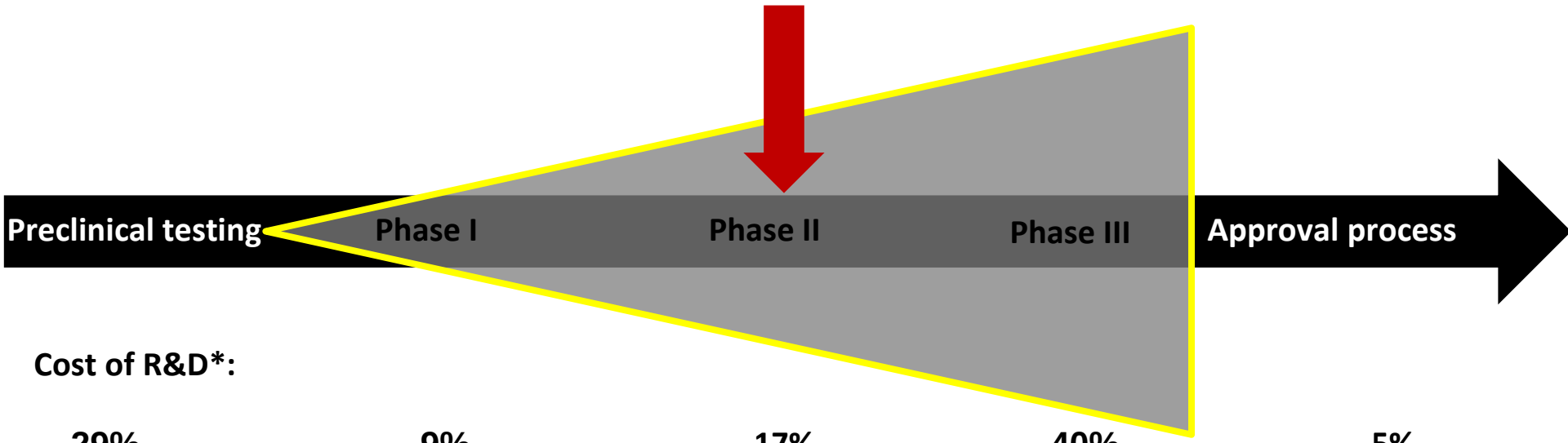
| **Cost of R&D*:** | | | | |
| **29%** | **9%** | **17%** | **40%** | **5%** |
| **Number of compounds** | | | | |
| **250** | **10** | | | **1** |

* Dimasi et al

# Methodology of clinical trials

Efficacy
Side effects
50-300 participants

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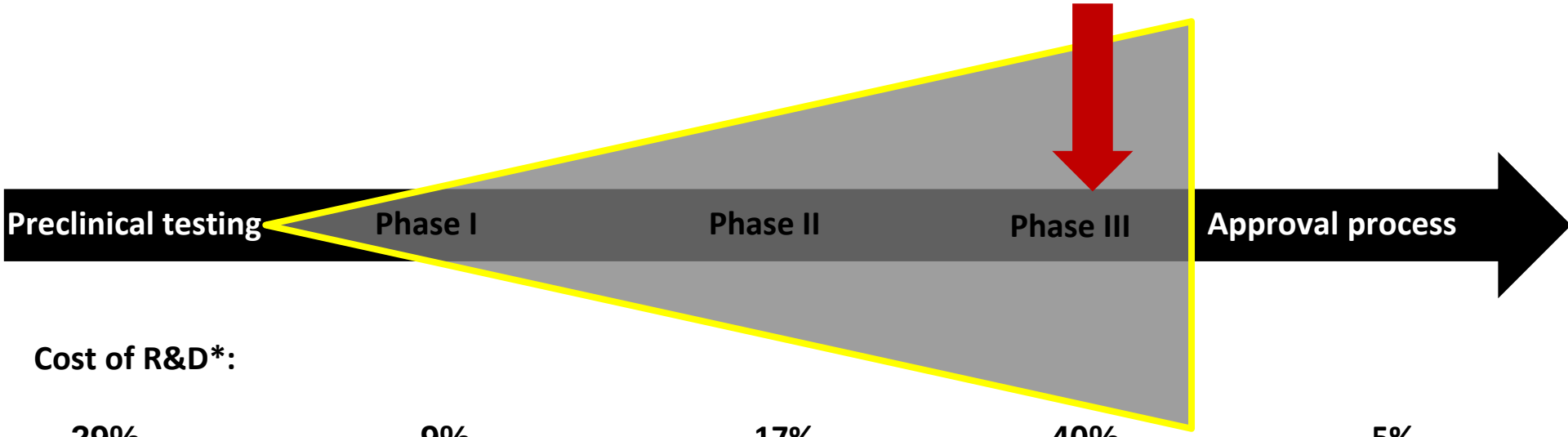
# Methodology of clinical trials

Efficacy
Effectiveness
Safety
Up to a few thousand participants

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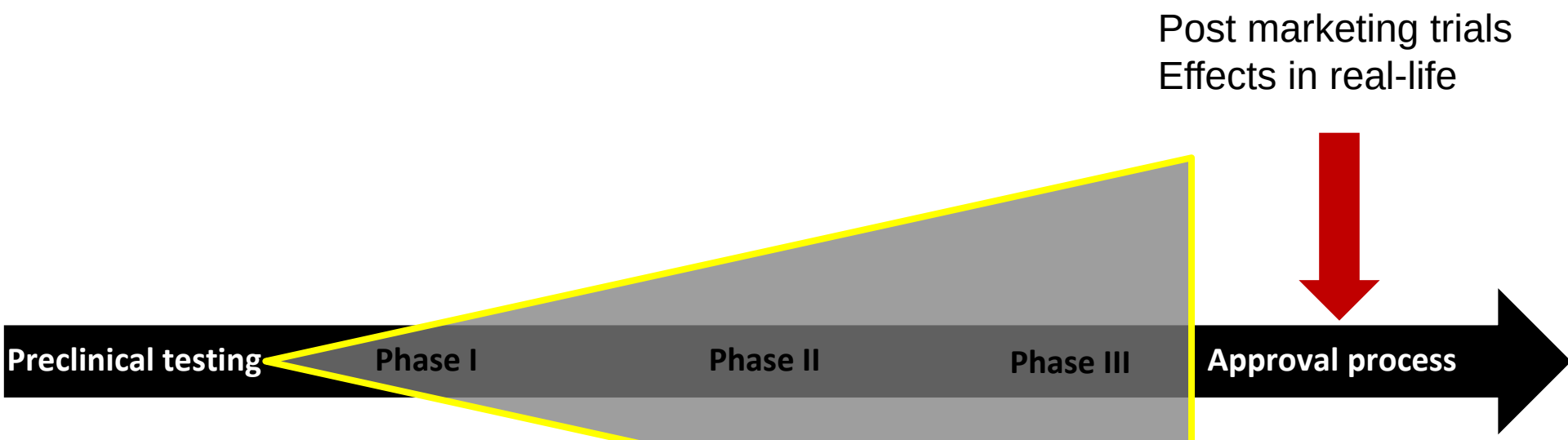


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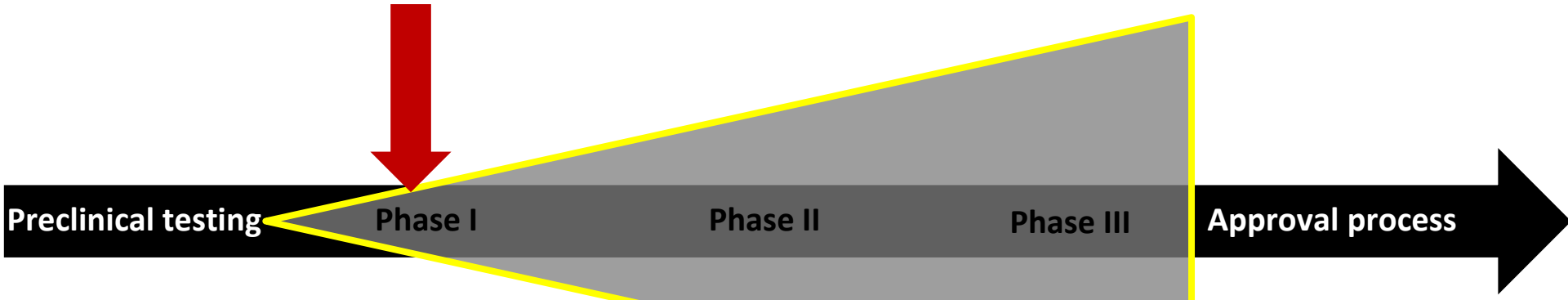


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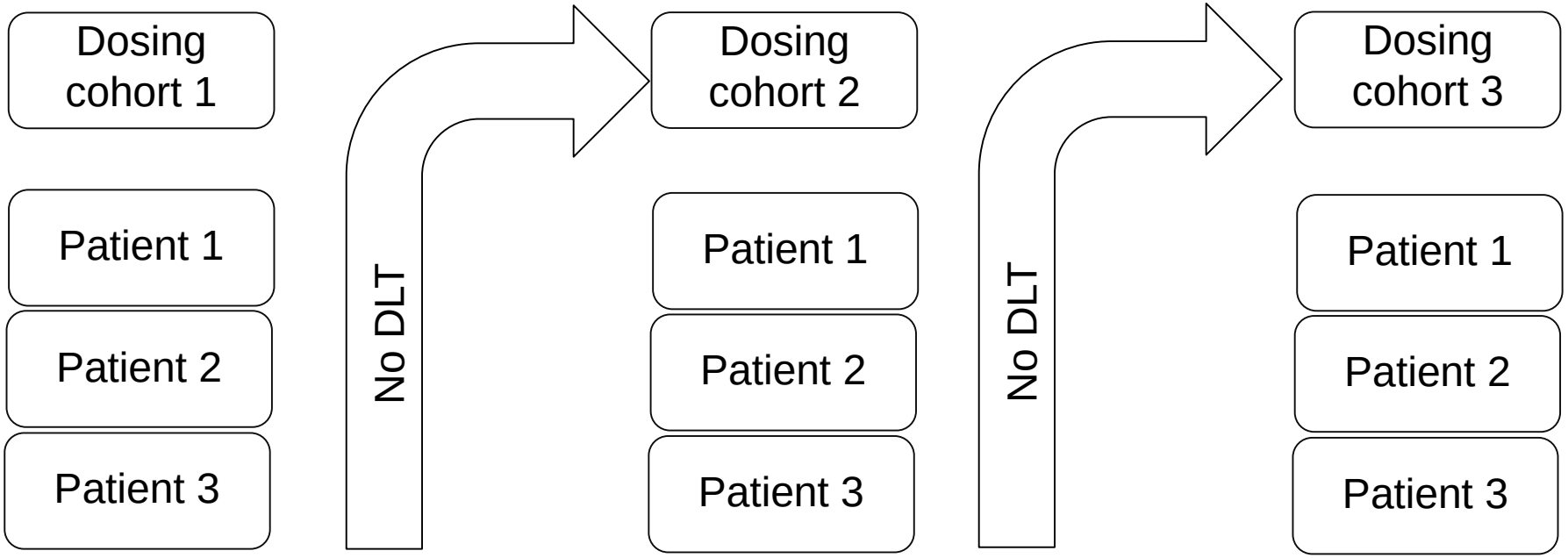
# Clinical trial design

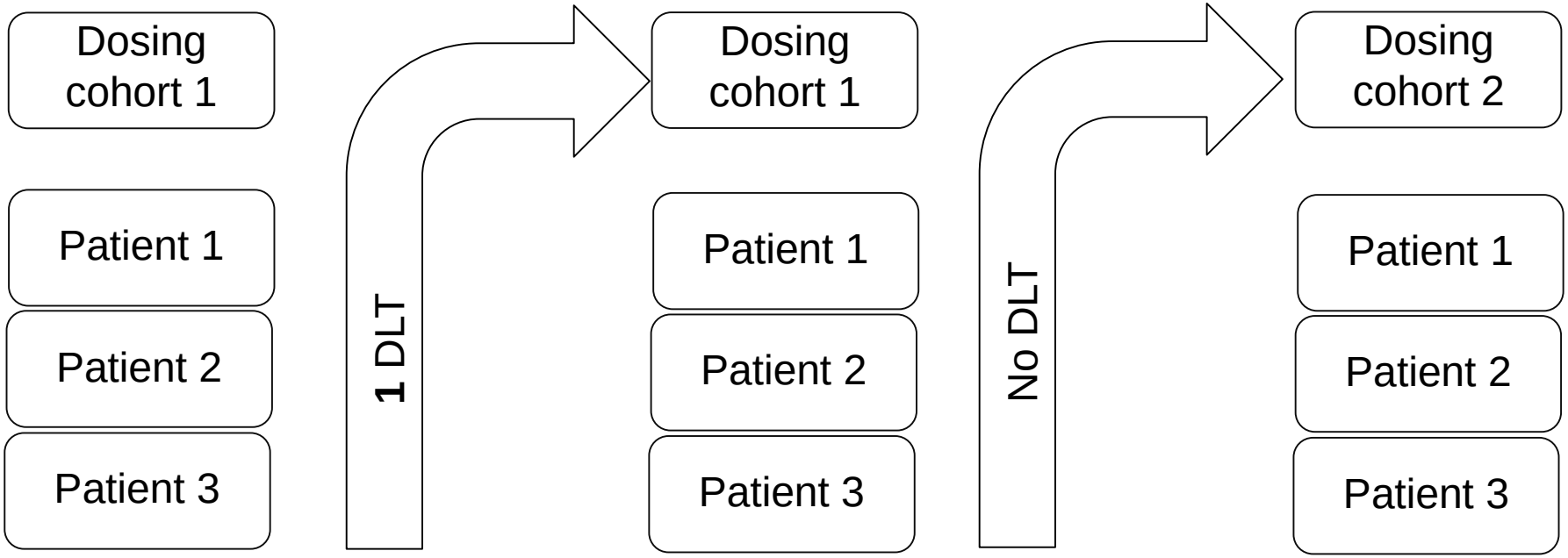
3+3 design – classical dose escalation




DLT= dose-limiting toxicity

# Clinical trial design

3+3 design – classical dose escalation

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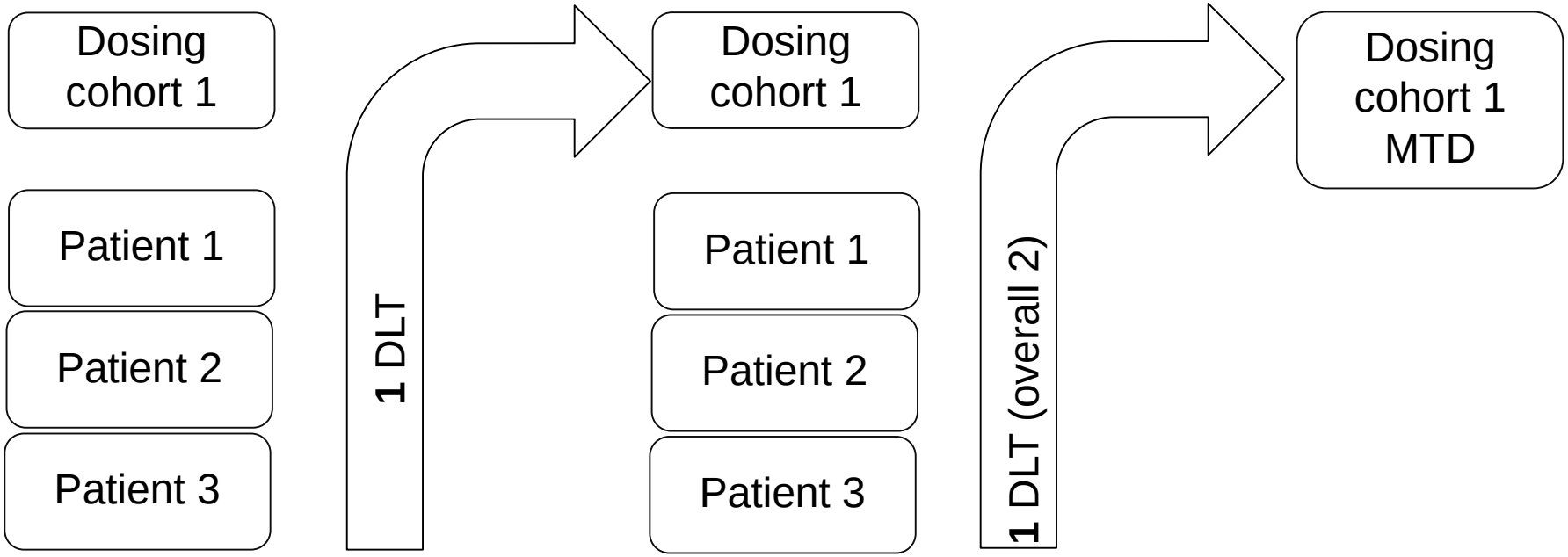


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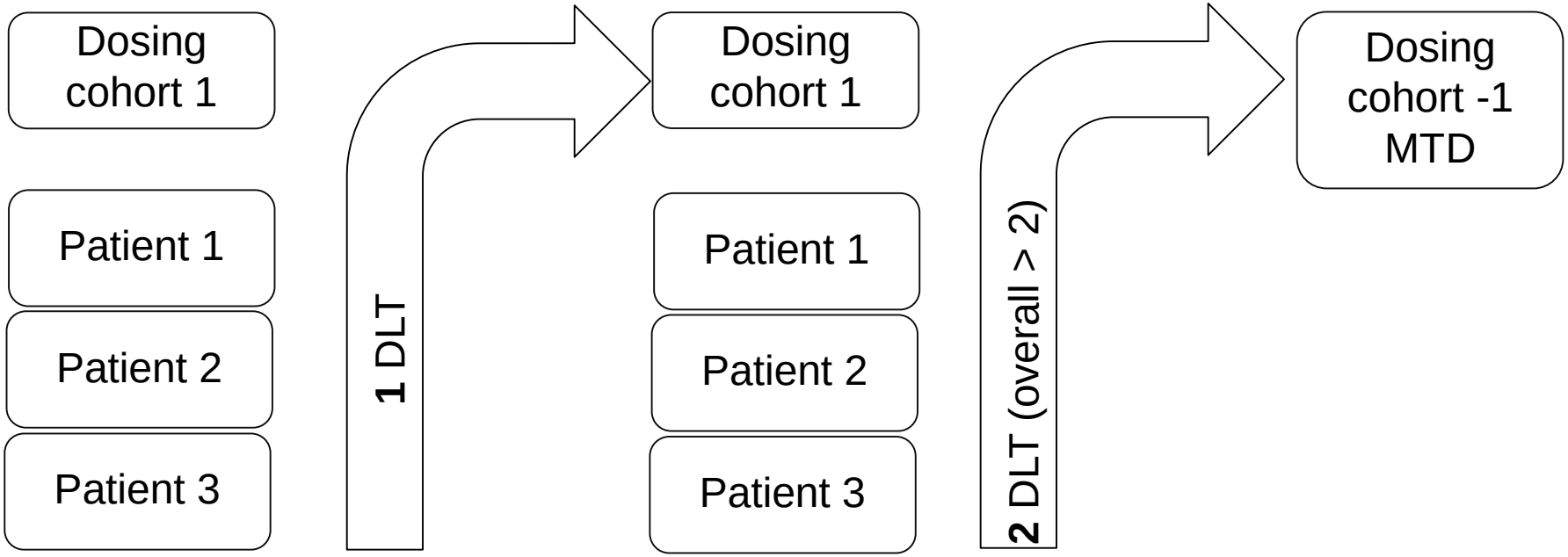



DLT= dose-limiting toxicity

# Clinical trial design

3+3 design – classical dose escalation

With or without placebo
Straight forward, robust, simple

**Limitations:**

- Pre-defined dose levels to be potentially teste
- MTD is not a dose with any particular probability of DLT, but in the range from 20% to 25% DLT.
- Many patients are likely to be treated at low doses.
- ….

# Clinical trial design

**Challenges for dose-finding studies in the area of new molecular agents**

- Late-onset and cumulative toxicities
- Maximum tolerated dose (MTD) vs. maximum effective dose (assessing an exposure–response relationship)

**Alternative phase I dose escalation study designs:**

- Continual Reassessment Method
- Bayesian approach
- Modified Toxicity Probability Interval Design

# Methodology of clinical trials

## Evidence level

| Level | Therapy/Prevention, Aetiology/Harm |
|---|---|
| 1a | Systematic Review (with homogeneity) of RCTs |
| 1b | Individual RCT (with narrow Confidence Interval) |
| 1c | All or none |
| 2a | Systematic review (with homogeneity) of cohort studies |
| 2b | Individual cohort study (incl. Low quality RCT; e.g. < 80% fol.up) |
| 2c | „Outcomes" Research; Ecological studies |
| 3a | Systematic review (with homogeneity) of case-control studies |
| 3b | Individual Case-Control-Study |
| 4 | Case –series (and poor quality cohort and case-control studies |
| 5 | Expert opinion without explicit critical appraisal, or based on physiology, bench research or „first principles" |

# Methodology of clinical trials

The „gold standard“ is a prospective, randomized, controlled, double-blinded clinical trial.

Patient eligible

Informed consent

Intervention/ Data collection

# Methodology of clinical trials

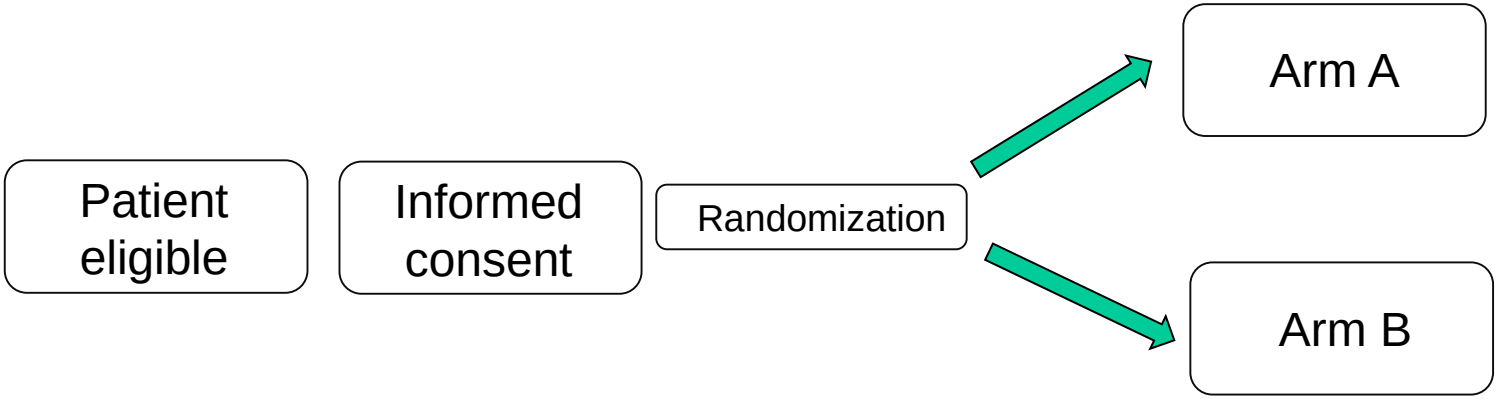
**Prospective**= refers to future events

Data will be collected after the hypotheses has been formulated.

Opposite: retrospective trial

# Methodology of clinical trials

The „gold standard“ is a prospective, randomized, controlled, double-blinded clinical trial.



# Methodology of clinical trials

**Randomized** = Study participants will be randomly allocated to the treatment arms to reduce bias and and to equally distribute participants among all trial arms (reduced selection bias). This should reduce interferenced caused by irrelevant variables (or unknown confounders).

**Stratified random sampling** should be used to ensure equal allocation of confounding variables among the study arms (e.g. age, gender,…).

# Methodology of clinical trials

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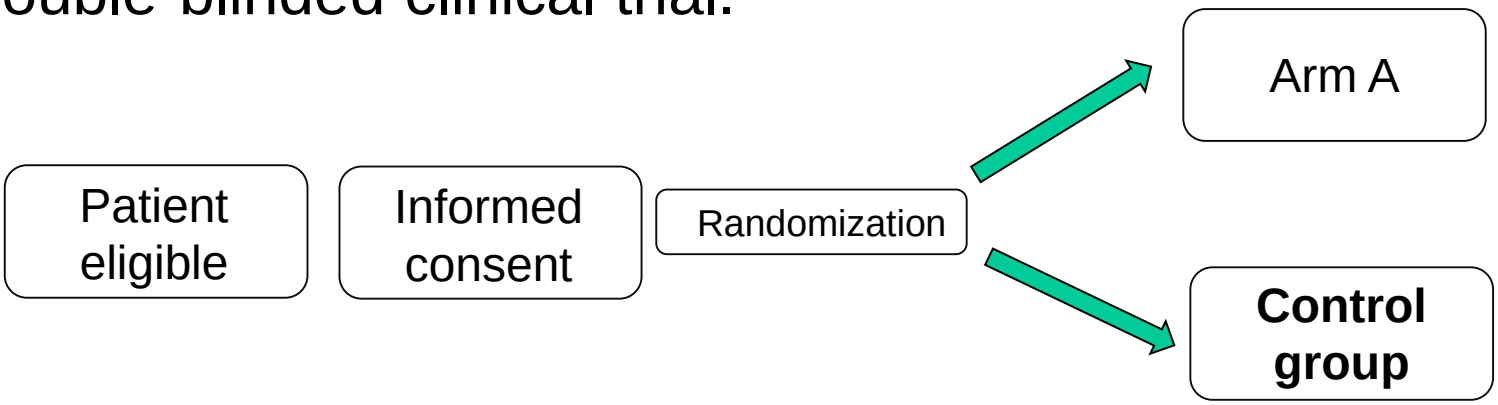


Ideally, the control group recieves the currently best availible treatment. Other options: placebo, no treatment, historical control,… .

# Methodology of clinical trials

The „gold standard“ is a prospective, randomized, controlled, double-blinded clinical trial.


2 Surgeons with an ECG

# Methodology of clinical trials

Reasons for blinding:

- Avoiding/equally distributing Hawthorne-effect: participant changes behaviour due to the study participationandthe awareness of being observed (e.g. compliance).

- Avoiding Rosenthal-effect (pygmalion effect): self-fulfilling prophecy, the investigator expects a benefit and therefore finds it.

# Methodology of clinical trials


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# Clinical trial design

From trial “designed to learn” to real life situation

**Early clinical trials (R&D)**
- Biology / imaging driven
- Integrated TR
- Screening platforms
- Quality Assurance programs
- Sophisticated trials

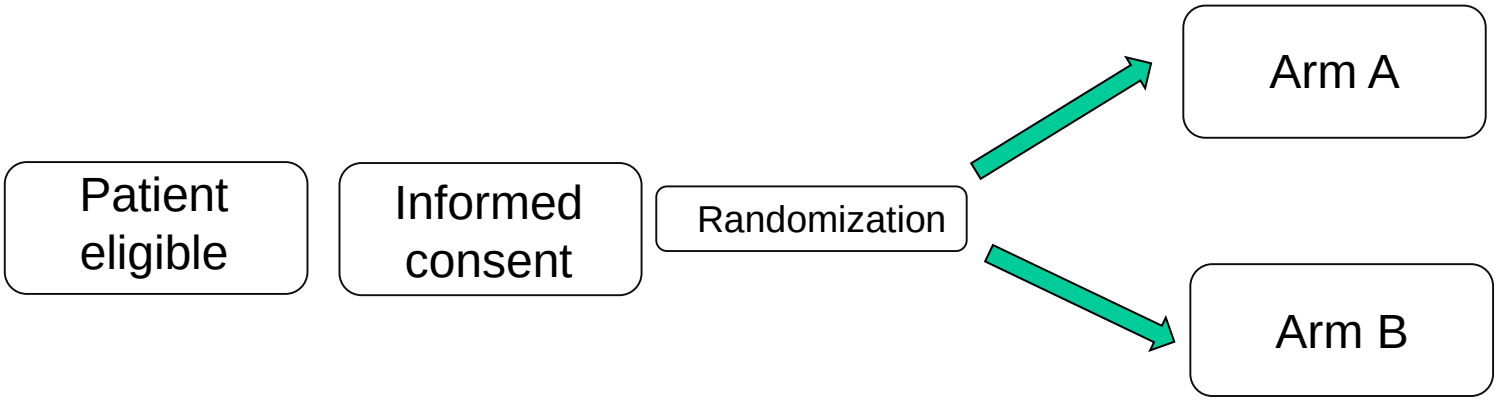
**Pivotal trials**
- Highly targeted
- Large differences

**Population based studies**
- Real world data
- QoL
- Outcomes research
- Health economics
- HTAs
- Pragmatic trials

Burock et al

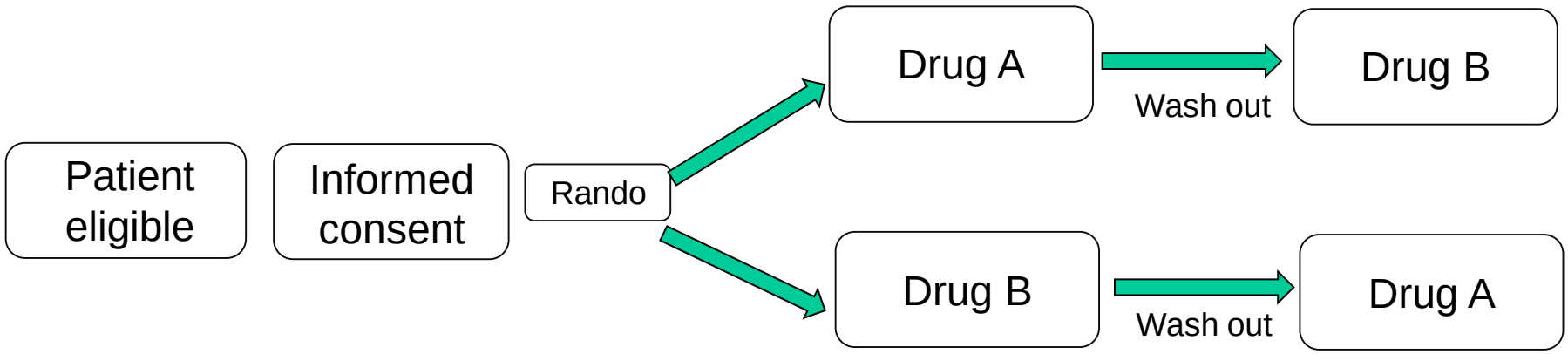
# Clinical trial design

Parallel design



# Clinical trial design

Cross over




Each person serves as own controll

Avoids participants variation

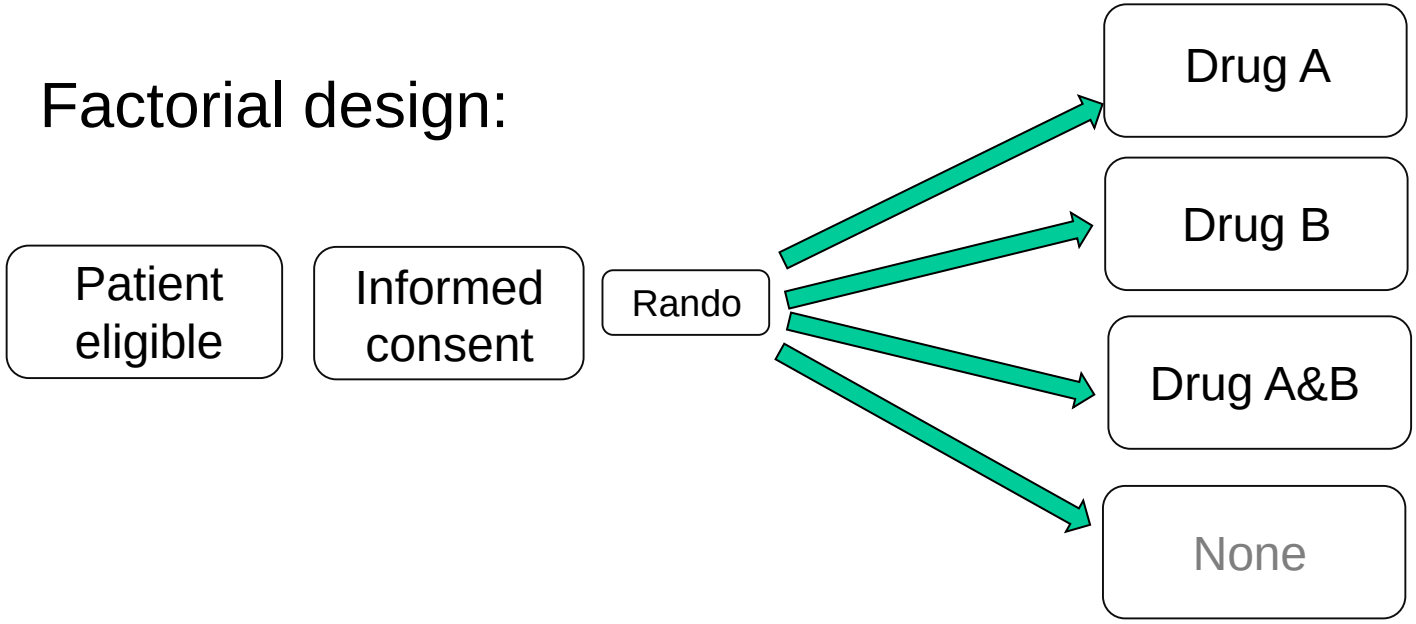
Requires a smaller sample size

CAVE: Carry over effects (wash-out period 5 half lives), late tox

Not suitable for acute disease but for chronic, stable ones

# Clinical trial design

Factorial design:




Testing the effect of 2 or more treatments simultaneously using various combinations.

Requires a smaller sample size if there is no interaction between the interventions.

Allows to study interactions (at least to some extent).

# Clinical trial design


Innovative trial design

# Basket trials

AACR Cancer Progress Report 2017

# Basket trials

**Efficacy of a targeted therapy with a specific mutation in multiple diseases.**

- Randomized
- Early stopping rules different for the various entities
- One trial protocol with sub-protocols and subsequent risk-benefit-analyses.

# Basket trials

**Advantages:**

- Mainly organisational advantages: molecular analyses can be done in a more efficient and consistent way

**Challenges:**

- Who should be the study lead with profund and sufficient knowledge about all diseases studied?
- From a regulatory point of view: many single studies would be preferable… .

# Umbrella trials

AACR Cancer Progress Report 2017

# Umbrella trials

**One disease with different molecular subtypes. Each subtypes recieves a different targeted treatment.**

Randomized, one control group

- The same early stopping rule applies for each subtype
- One trial protocol with sub-protocols and subsequent risk-benefit-analyses.
- One control group

# Umbrella trials

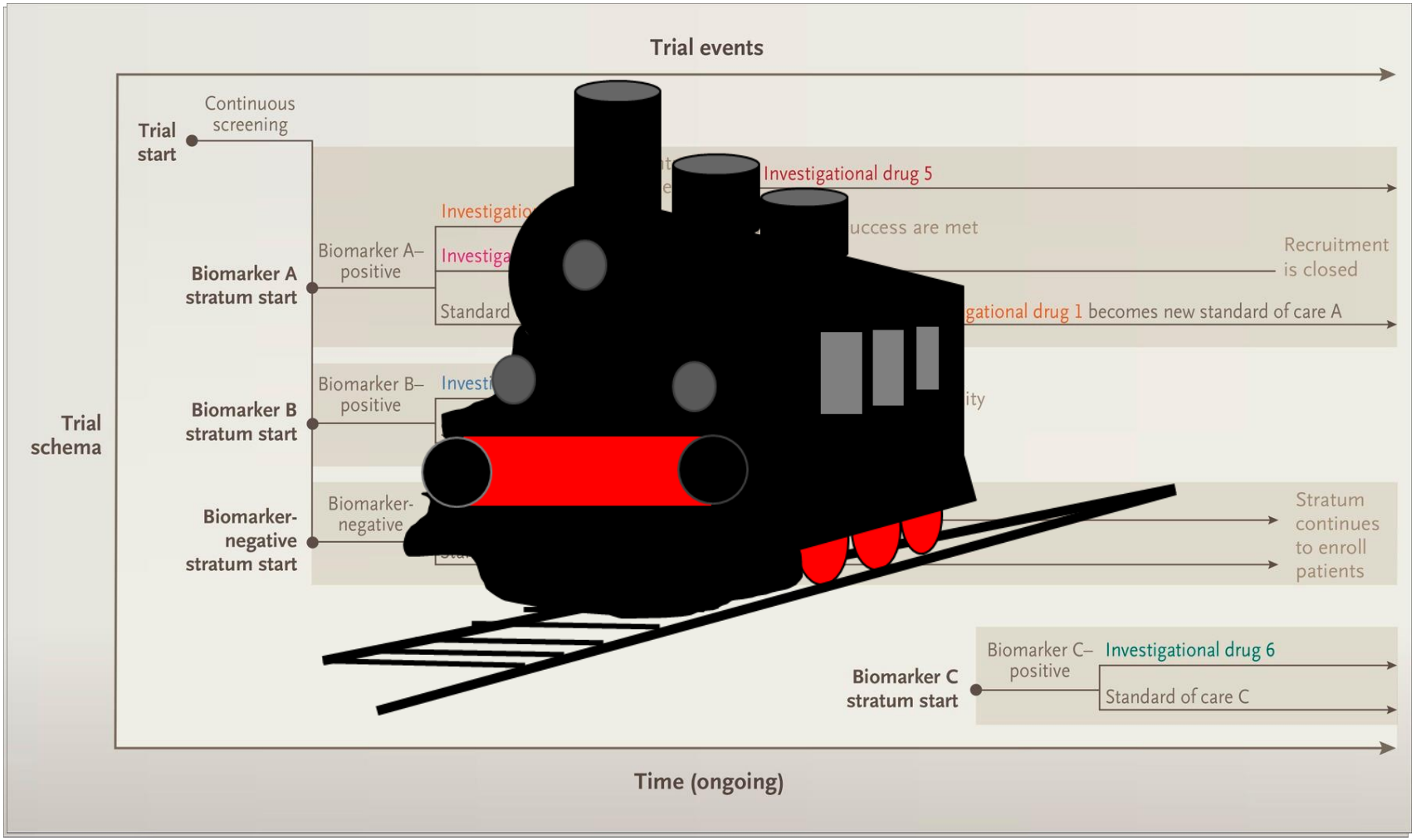
**Advantages:**

- Molecular analyses can be done in a more efficient and consistent way
- Only one control group

**Challenges:**

- Drugs from different companies
- Multiple testing? Adjustment for alpha-error?

# Platform trials



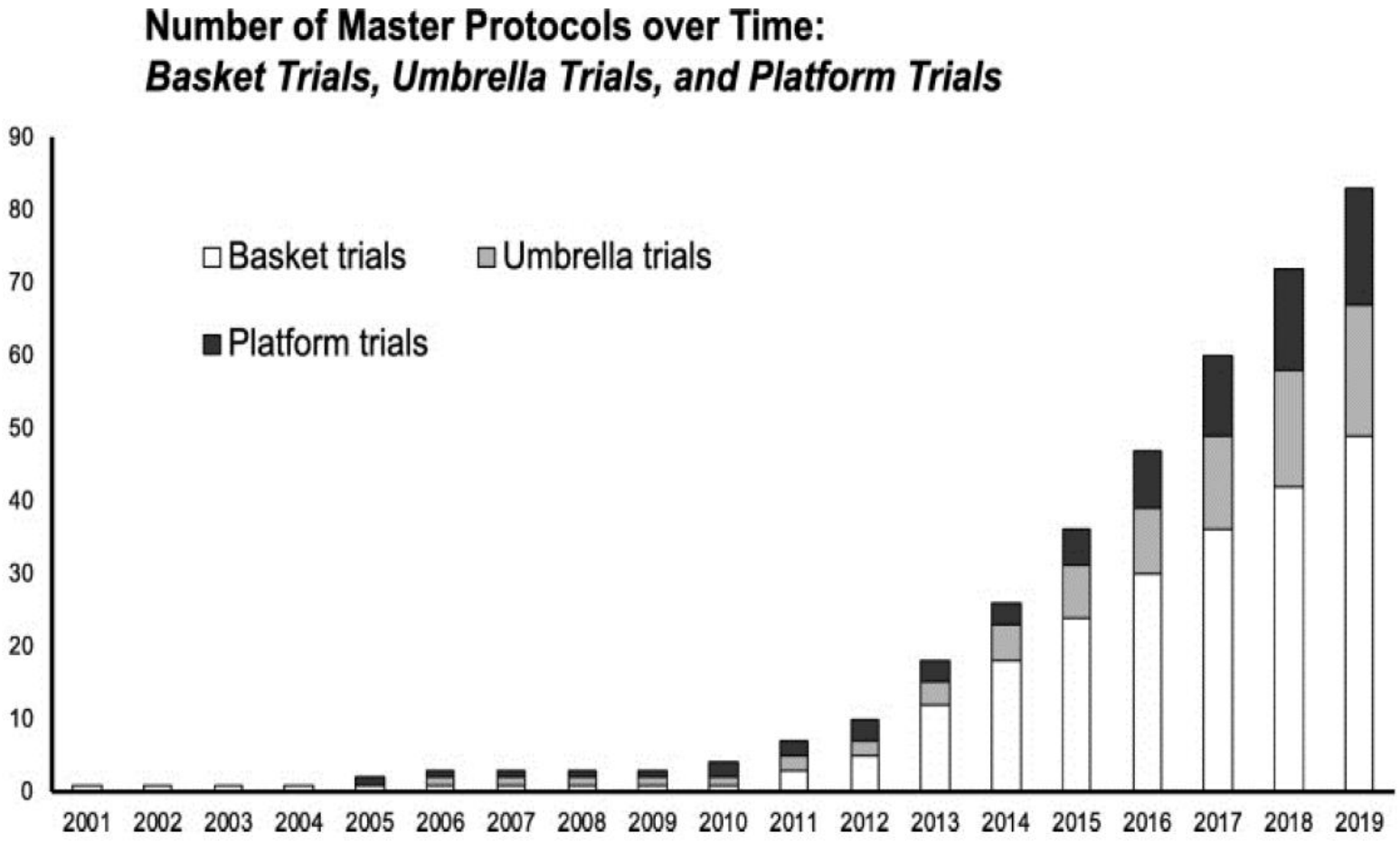

Woodcock et al 2017

# Platform trials

One disease with different molecular subtypes.

Each subtypes recieves a different targeted treatment, therapies are allowed to enter or leave the platform on the basis of a decision algorithm.

# Innovative clinical trial designs




Aus: Park JJ et al 2019

# Others

- Adaptive designs
- Drop the looser
- Pick the winner
- ….


Questions?