Designing Phase I Single Agent Dose-Escalation Studies

Lecture 1: Introduction to Dose-Finding

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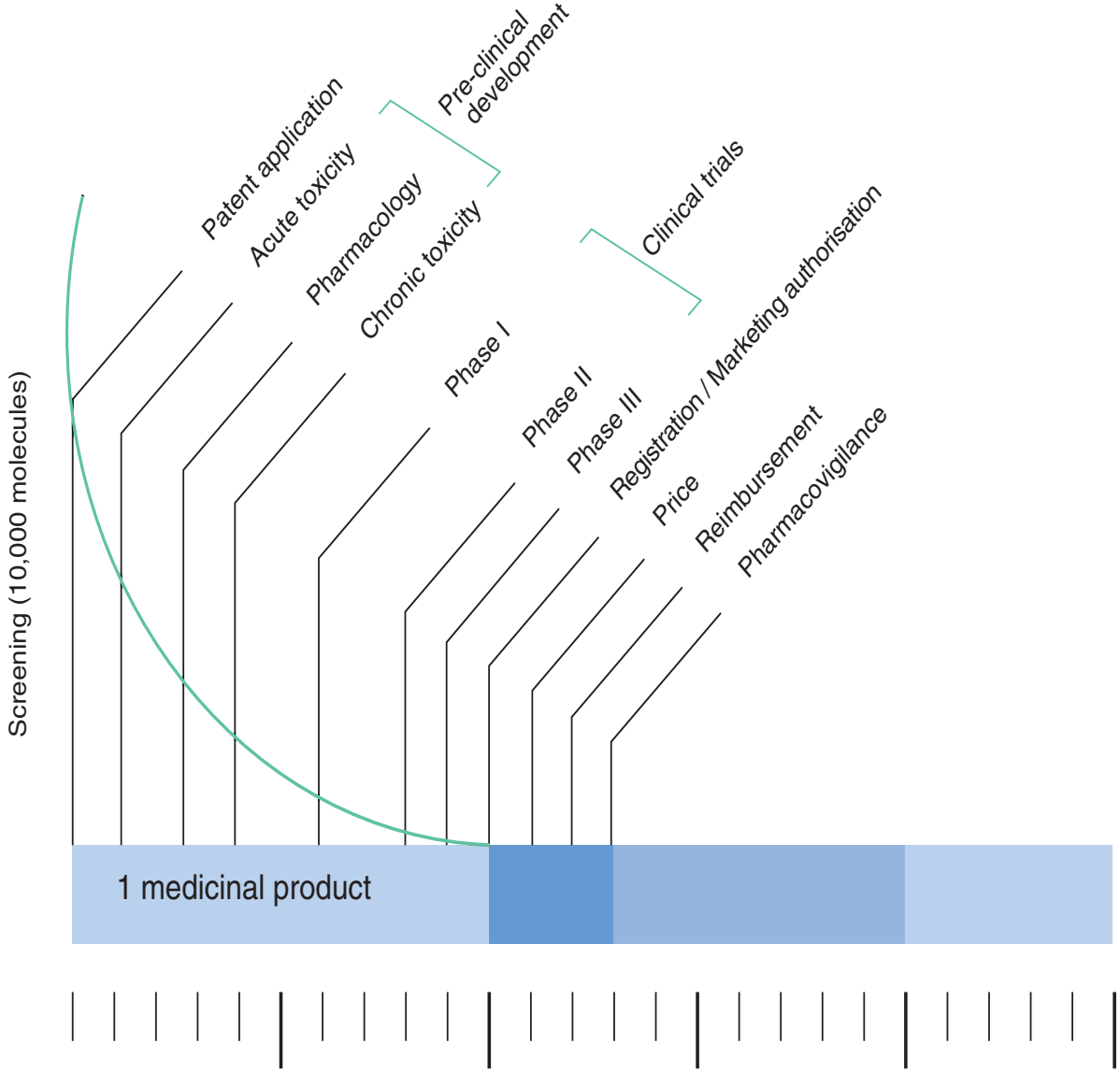
A dose of reality

Ben Goldacre, Guardian 1-09-08:

- **Before 1935** doctors were basically useless
- **1935-1995**: - antibiotics, dialysis, transplants, intensive-care units, heart surgery, every drug you've ever heard of
- **1995-now**: - the low-hanging fruit of medical research has all been harvested, and the industry is rapidly running out of new drugs

The development process

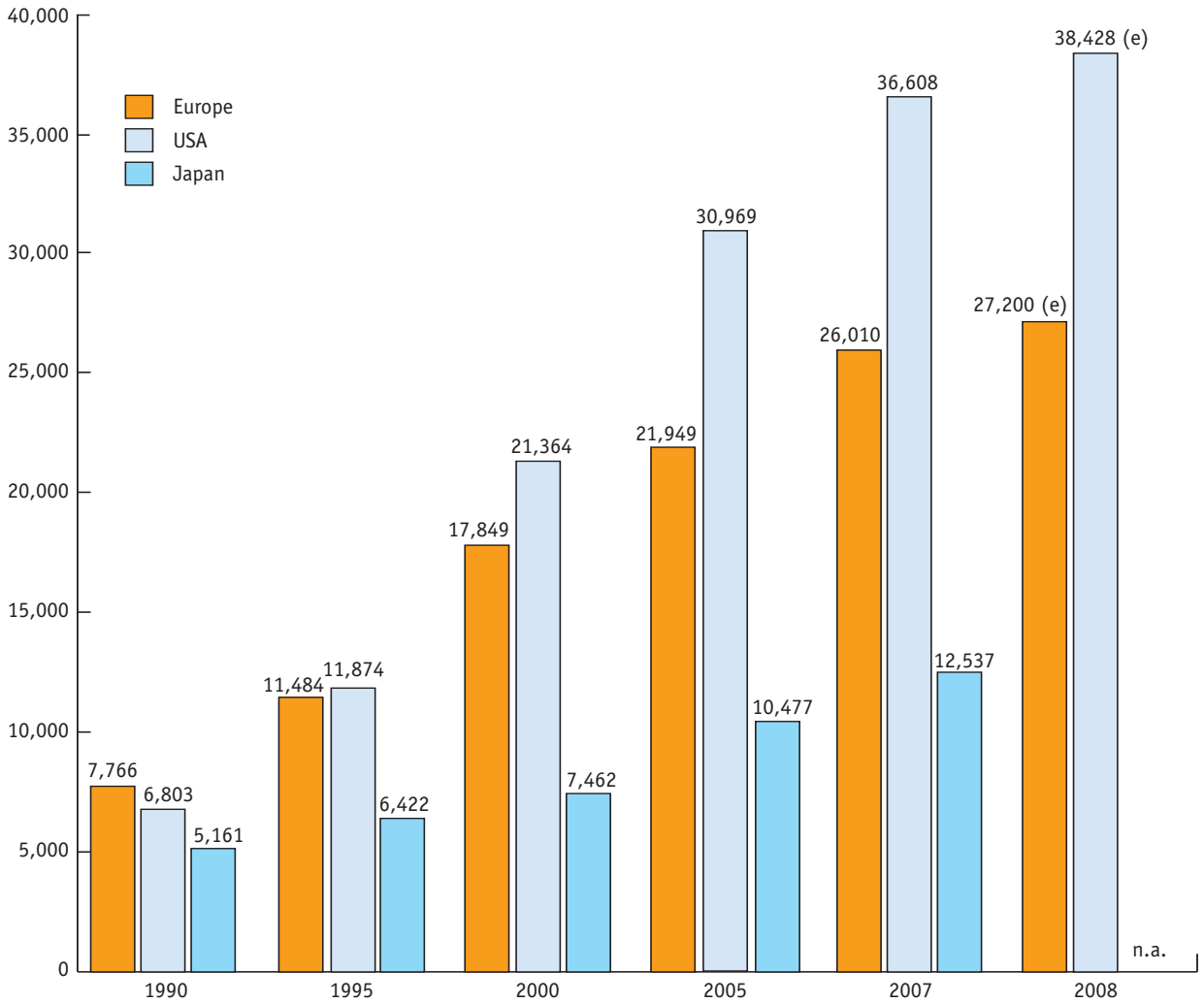


Drug development

Development of a novel medicinal product

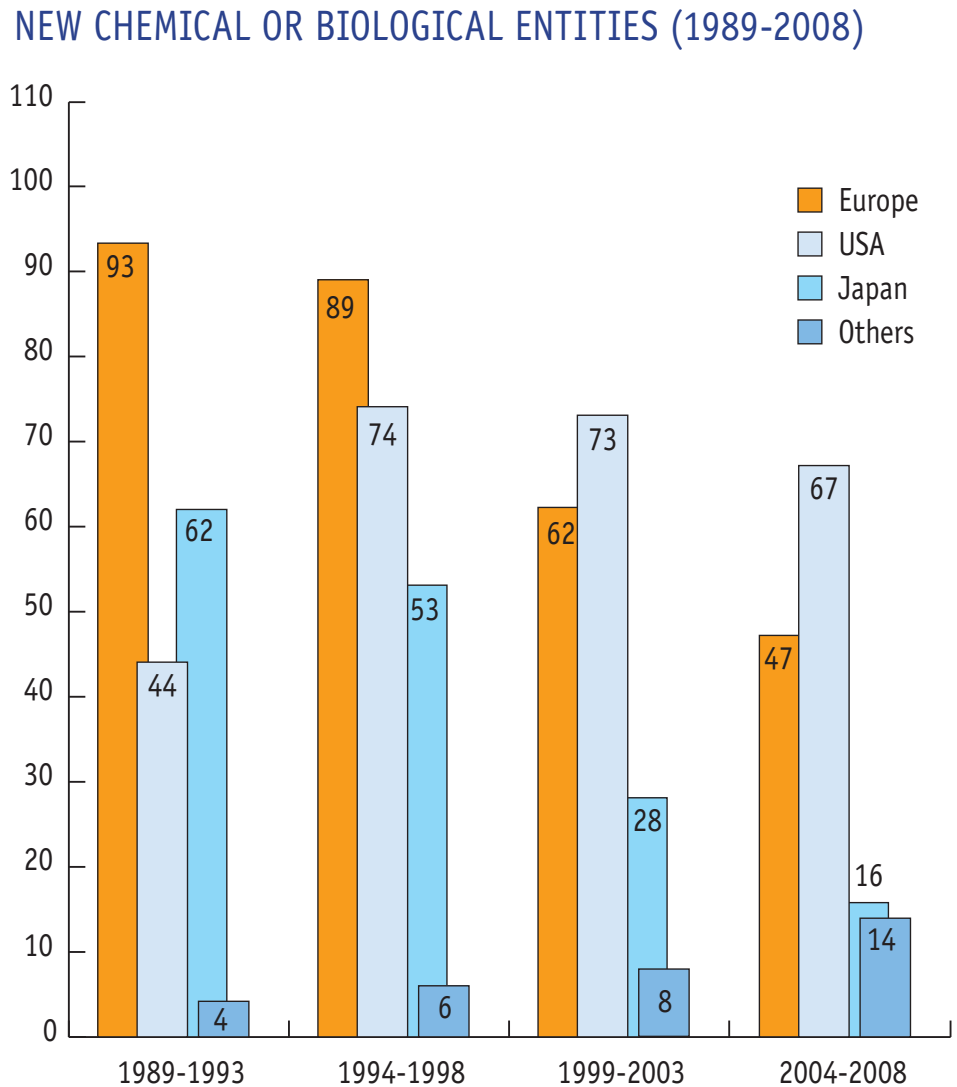
- takes 10-15 years
- costs several hundred million euros on average
  - largest contributors are confirmatory (phase III) trials
  - often involve thousands of patients with follow-up period frequently lasting years

Cost on R&D in Pharmaceutical industry



Source: European Federation of Pharmaceutical Industries and Associations (2009)

New molecular entities



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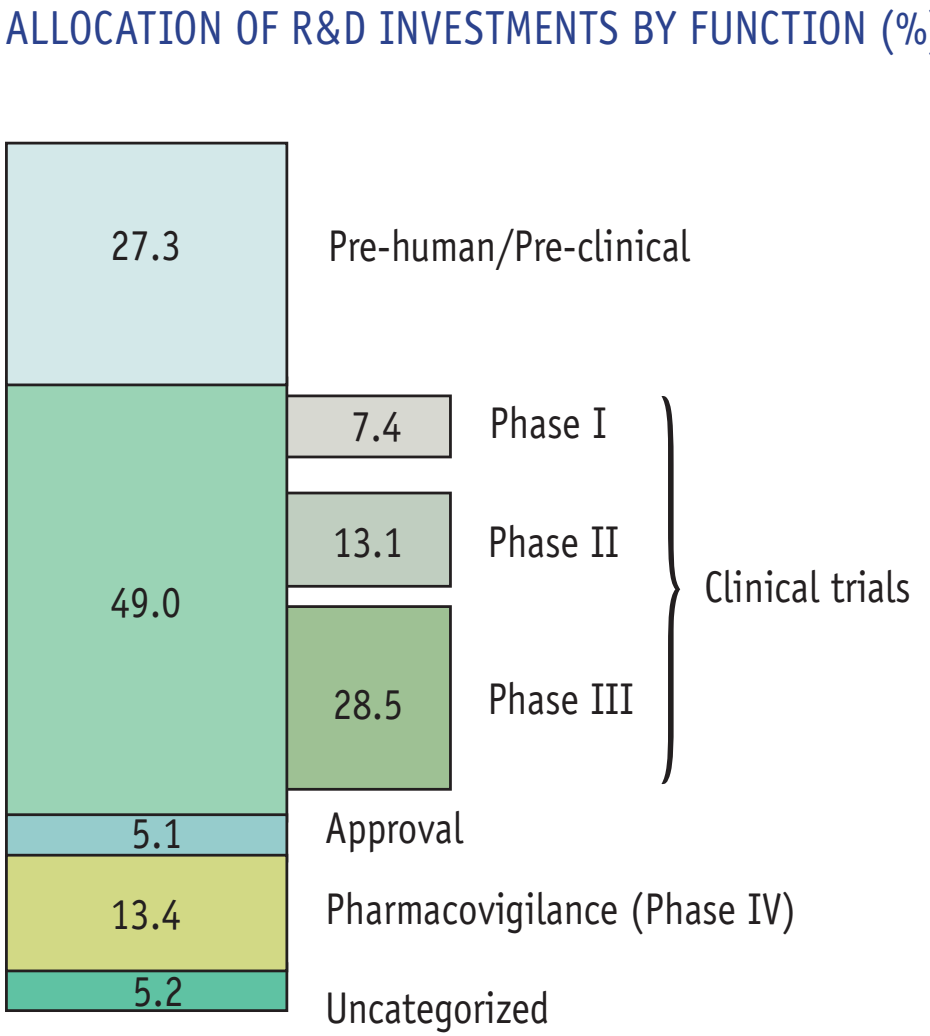
Cost on R & D in Pharmaceutical industry



Source: European Federation of Pharmaceutical Industries and Associations (2009)

Success rates

According to a recent review (Wong, Siah & Lo, Biostatistics, 2019), between 2000 and 2015

- **41.0%** of confirmatory clinical trials overall and
- **64.5%** of confirmatory clinical trials in oncology

have been unsuccessful.

Reasons for failed confirmatory trials

Reasons for failed confirmatory trials are thought to be:

- taking forward treatments that should have been abandoned during early efficacy studies;
- studying the wrong patient population;
- insufficient precision when
  - determining the maximum tolerated dose;
  - assessing safety;
  - determining the optimal dose.

The successes

Between 1980-1999

- 21% of new molecule entities required dose change after registration
- 79% are safety related dose reductions
- Median time to change is 2.0 years (1995-1999)

according to Cross et al (2002).

Consequences

- Avoid going straight into large and expensive Phase III;
- Take more care during Phase I and Phase II trials.

Introduction to Phase I trials

- First experimentation of a new drug in humans
- The emphasis is on **safety**
- Trials are small, typically 20-50 patients
- Patients are added sequentially after side-effects from previous patients have been assessed

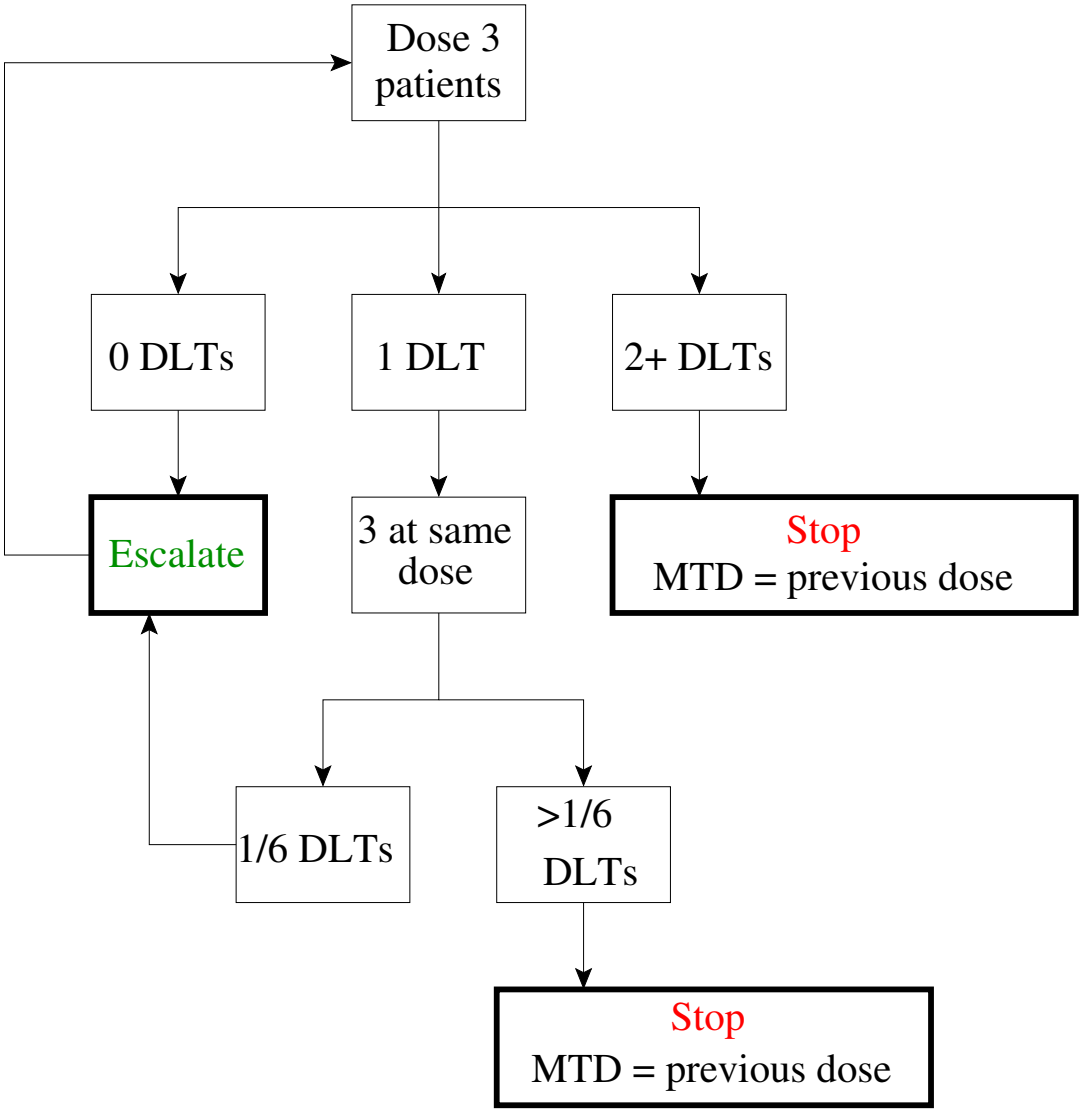
Introduction to Phase I trials

- Subjects
  - **Healthy volunteers** for relatively non-toxic agents
  - **Patients** when drugs are toxic (e.g. in cancer)
- Aim: Find the highest dose with acceptable level of toxicity
  - This is known as the **maximum tolerated dose** (MTD)
  - Based on the assumption that **both benefit** (efficacy) **and risks** (toxicity) of treatment **increase with the dose**
  - Ethically, we would like to treat every patient just below their MTD
  - In practice, individual MTDs are unknown

Key elements

- A **starting dose** that will be given to the first patient
  - Often $\frac{1}{10} LD_{10}$ in mice (one tenth of lethal dose in 10% of mice)
- A toxicity **outcome**
  - Often binary (e.g. a *dose-limiting toxicity* (DLT) in cancer trials)
- A **target toxicity level** (TTL)
  - The desired toxicity at the MTD (e.g. 20-33% is common in cancer)
- A **dose-escalation design**
  - Assigning patients cohort-by-cohort
  - Cohort size: No. of individuals treated at each step
  - Possible dose levels for experimentation
  - Sample size / stopping rules

3+3 design with escalation only



- Dose Limiting Toxicity (DLT)
- Simple rule based approach
- No need for a statistician
- Actual dose not used
- The data to declare an MTD are either 0/3 or 1/6

An opinion about the 3+3 design

Phase I trial design: Is 3+3 the best? — Hansen *et al.* (2014)

> *The evidence from this review suggests that the 3+3 design identifies the recommended phase 2 dose and toxicities with an acceptable level of precision in some circumstances*

> *Novel trial designs demonstrating superiority over the 3+3 method in statistical simulations without corroborating clinical evidence are of theoretical value alone*

What comes first the simulations (chicken) or the practice (egg)?

The truth about the 3+3 design

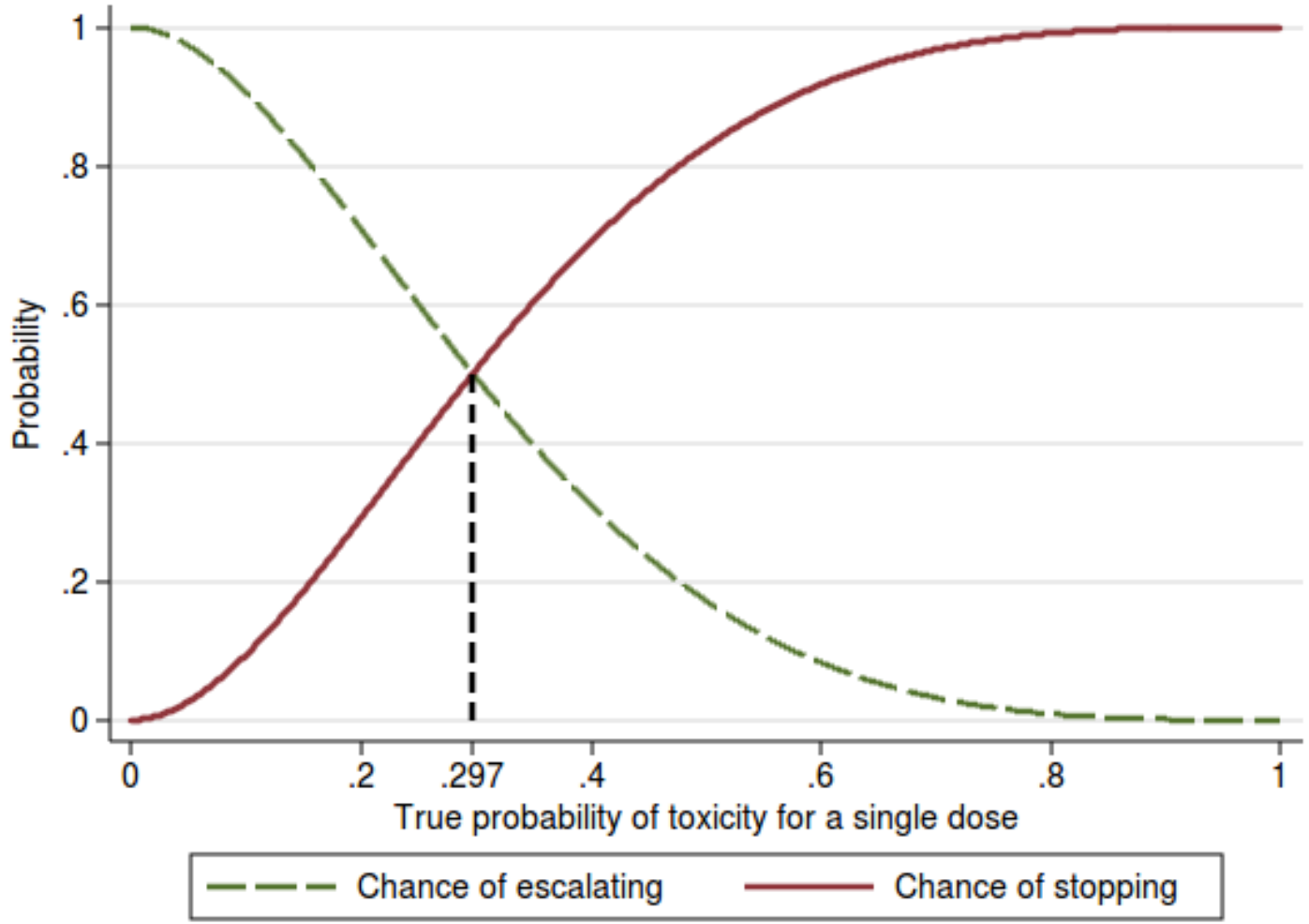
"Given such simple rules there is no need for simulations"

Lin and Shih (2001)

- Example with 4 doses. True toxicities: $(0.04, 0.29, 0.36, 0.74)$
  - The percentage of patients experimented on each dose are $(35\%, 43\%, 17\%, 5\%)$ —averaged over all possible trials
  - The probabilities to recommend each dose as MTD are $(48\%, 31\%, 19\%, 0\%)$, 2% no recommended doses
- The 3+3 design
  - is conservative if the TTL is 33%
  - tends to underestimate the MTD
  - is inflexible and memoryless

The tipping point - 0.297 (Maximum TTL)

For any true toxicity probability for a single dose — the exact chance of escalating or stopping the 3 + 3 design



Why not to use A+B designs (I)

	Rule-based designs	Model-based designs
Target DLT rate	unclear	clearly defined and can be flexibly chosen
Patients on optimal dose	(relatively) few	(relatively) many
Patients on subtherapeutic dose	(relatively) many	(relatively) few
Utilisation of available data	poor	efficient
Extension to complex questions	difficult	straightforward
Deviations from the plan (doses, number of patients)	hard to incorporate	easily accommodated

Why not to use A+B designs (II)

- The choice of a design for Phase I trial have an effect on the probability of success in later phases.

- According to a recent study by Conaway & Petroni (2019), the 3+3 design leads to a noticeably lower success rates in a Phase III trial compared to more statistically sophisticated alternatives.

- On average, the probability of success in Phase III if 3+3 designs was used in Phase I is lower by nearly **10%**

What to use (and how)

In this short course, we will cover

- **alternative designs** to the rule-based dose-escalation designs that leads to better acuracy while safeguarding the patients;
- **how to implement** these designs in the software;
- **how to apply** these designs in practice.