Adaptive trial design for early phase trials

Why not to use 3+3

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Introduction to Phase I trials

- First experimentation of a new drug in humans
- The emphasis is on finding safe doses
- 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

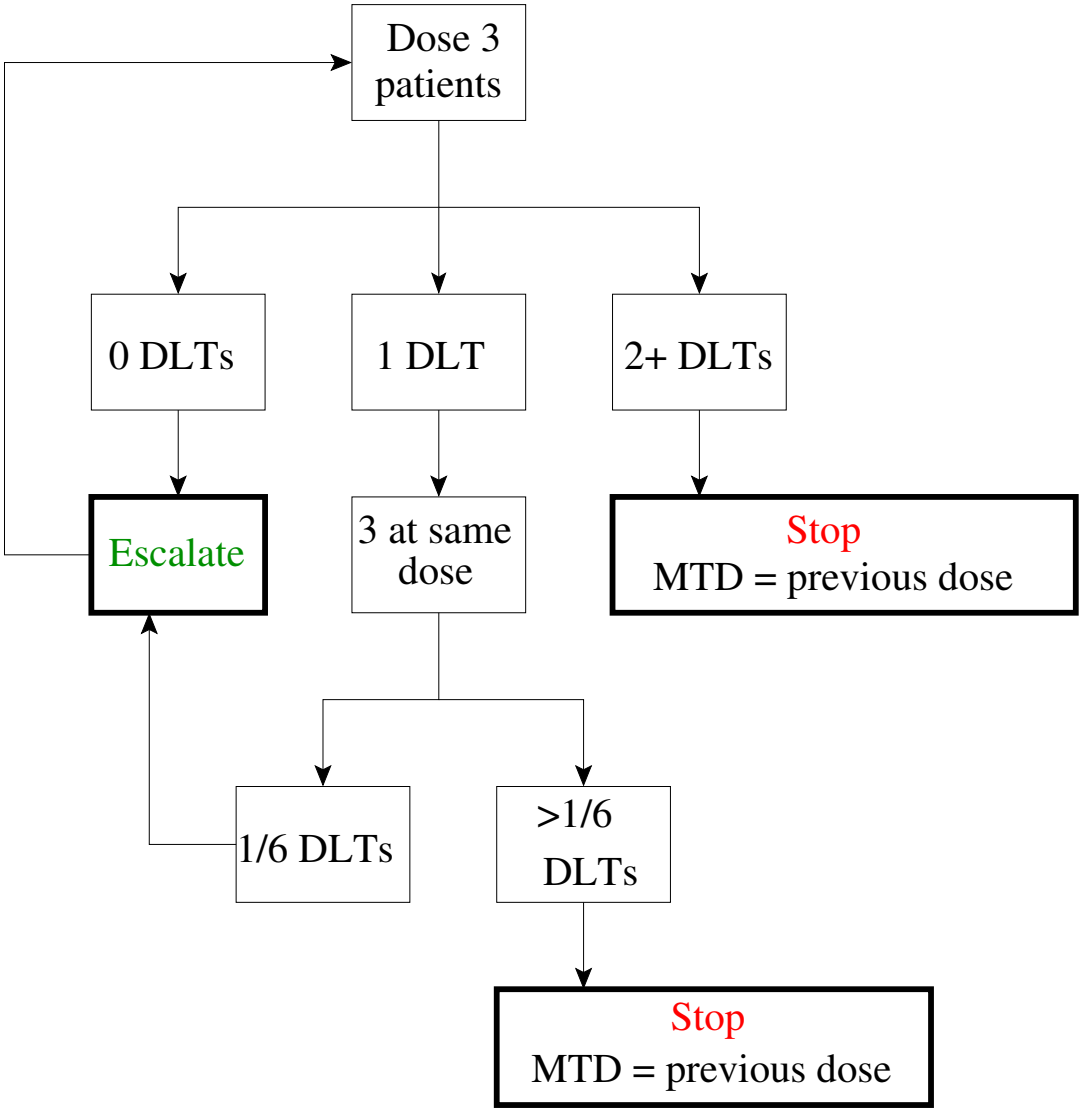
- Subjects
  - Healthy volunteers for relatively non-toxic agents
  - Patients when drugs are toxic (e.g. cytotoxic agents in cancer)
- Aim: Find the highest dose with acceptable toxicity
  - This is known as the *maximum tolerated dose* (MTD)
  - Based on a monotonicity assumption that the benefit (efficacy)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

Key elements

1. A starting dose that will be given to the first patient
   - Often chosen as $\frac{1}{10}LD_{10}$ in mice (one tenth of the lethal dose in 10% of mice)
2. A toxicity outcome
   - Often binary (e.g. occurrence of a *dose-limiting toxicity* (DLT) is used in cancer trials)
3. A *target toxicity level* (TTL)
   - The desired risk of toxicity at the MTD (e.g. cancer trials often propose 30% prevalence of DLT at the MTD)
4. A dose-escalation design
   - Rule or model based
   - Cohort size: # individuals at the same dose level
   - Possible dose levels for experimentation
   - Sample size / stopping rules

3+3 design with escalation only

Storer (1989)



- 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 $1/6$

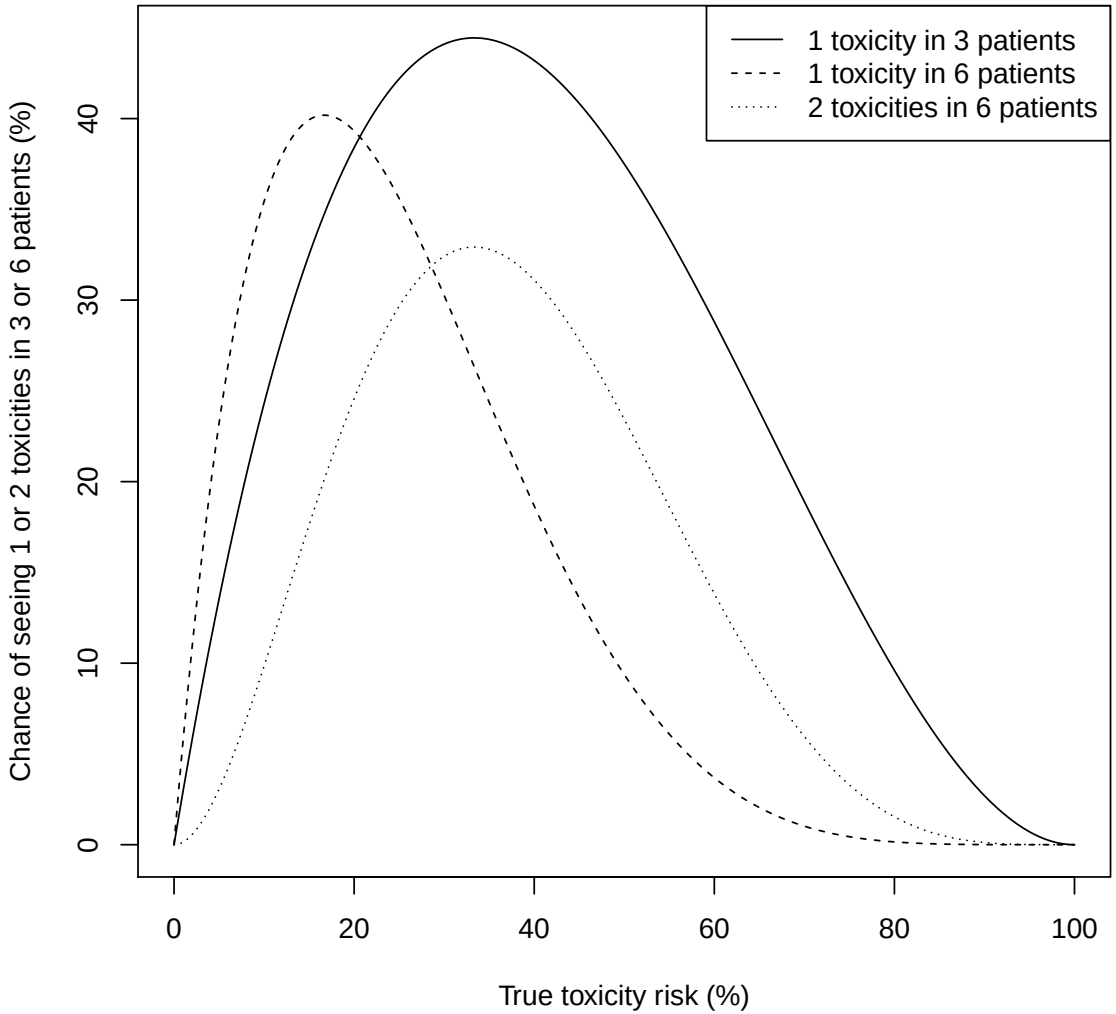
Current opinion about the 3+3 design

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



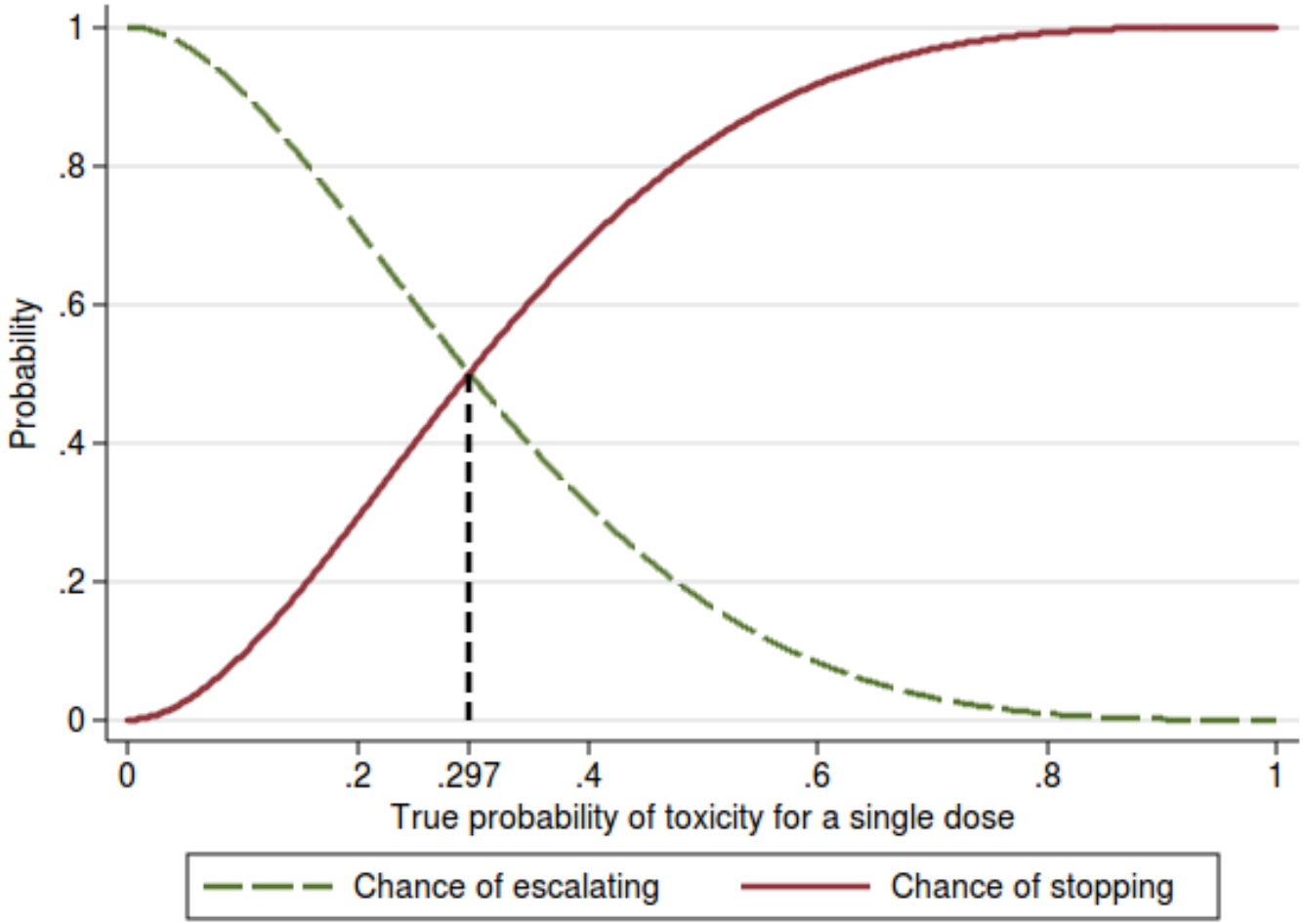
The truth about the 3+3 design

> Given such a simple system of rules there is no need for simulations
>
> *Lin and Shih (2001)*

- Take one example with 4 doses
  - Let the true toxicity probabilities be $(0.04, 0.29, 0.36, 0.74)$
  - The percentage of patients experimented on each dose are $(35\%, 43\%, 17\%, 5\%)$ —averaged over all possible trials
  - The recommended MTD probabilities are $(48\%, 31\%, 19\%, 0\%)$, 2% no recommended doses
- The 3+3 design
  - is conservative if the TTL is 33%
  - can recommend MTDs with minimal toxicity
  - is 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



Final thought about the 3+3

The 3+3 design is about finding the unknown toxicity probabilities with an unknown target toxicity limit.

> *"... there are also unknown unknowns – the ones we don't know we don't know. And if one looks throughout the history of our country and other free countries, it is* **the latter category that tend to be the difficult ones**.*" Donald Rumsfeld*