Adaptive dose escalation in first-in-human studies needs less participants and is as effective as the conventional fixed cohort design.

**Pharmacology-guided rule-based adaptive dose escalation in first-in-human studies**

**PRESENTER:**
Ewoud-Jan van Hoogdalem

**QUESTION:** How can we tailor the design of first-in-human studies to what we want to know about a dose level? Is it safe? Can it be efficacious?

**OBJECTIVE:** Define a pharmacology-guided rule-based adaptive dose escalation design that makes ‘best use’ of study participants.

**METHODS:** Adaptive design starting with sentinel group, continuing with cohort sizes 3 active + 1 placebo, expanding to 6 active + 2 placebo based on exposure or pharmacodynamics.
- Retrospectively tested in 20 published studies + 20 in-house studies.
- Tested on 10,000 simulated trials on different compound profiles (Table 1).

**RESULTS**
- Retrospective testing: Adaptive dose escalation determined the same top dose as the original study in 97.7% of the cases. In 1 case, the adaptive approach led to a 14% lower estimated maximum tolerated dose. Median sample size reduction was 38% (Fig. 3).
- Simulation of trials of a promising compound profile: Adaptive and conventional algorithm led to the same highest safe and efficacious dose. The adaptive approach had a higher probability of a dose recommendation than the conventional approach (94% vs. 82%); combined with a smaller trial size by about 23% (Fig. 4; Table 6).

**CONCLUSION**
Adaptive dose escalation makes ‘better use of participants’ in first-in-human studies compared to the conventional fixed cohort approach; we encourage it as preferred approach.