Workshop # 3 :
Application of Bayesian Statistics in early development studies

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Workshop Objectives

- Introduce the use of Bayesian statistics and adaptive designs in phase I
- Share a Roche example and experience
- Discuss opportunities, benefits and challenges
- Give tips for a practical implementation in your next study

Model-Based Approaches

Background

- The objective of Phase 1 is to deliver the most promising treatments (in terms of safety and potential benefit) to later clinical research phases without undue delay or expenditure, while treating Phase I patients/subjects safely (Whitehead et al 2001).
- Classical phase I dose-finding starts with the test of single doses, followed by a randomized multiple ascending dose study consisting in the chronic disease setting of cohorts with 3-6 HV or patients on active drug and 1-2 HV or patients randomized to placebo.
- In oncology, Bayesian adaptive designs in EIH studies and especially the Continual Reassessment Method (CRM) have been used for more than 2 decades.
- Recent publications indicate strong interest in applying these model-based designs in EIH studies outside of oncology (Perlstein et al, 2009; Chu et al., 2008; Tibaldi et al., 2008)

Definitions

- DLE = dose limiting events that prevents from dosing further or at higher doses.
- MTD = maximum tolerated dose is the dose at which the DLE rate reaches a predefined target maximum (e.g.30%).
- SAD = single ascending dose trial
- EIH = entry into human

Central idea of the Continual Reassessment Method

- Model based relationship between dose and event/toxicity is updated with data observed in each cohort.
- Subjects in the next cohort are treated at the most current estimate of MTD (posterior distribution) within limits of maximum predefined escalation steps.
- Regarded as an ideal candidate design for dose-finding studies where the precision of MTD estimate is of key importance and the dose-event/toxicity relationship is assumed to be well described by a logistic function.

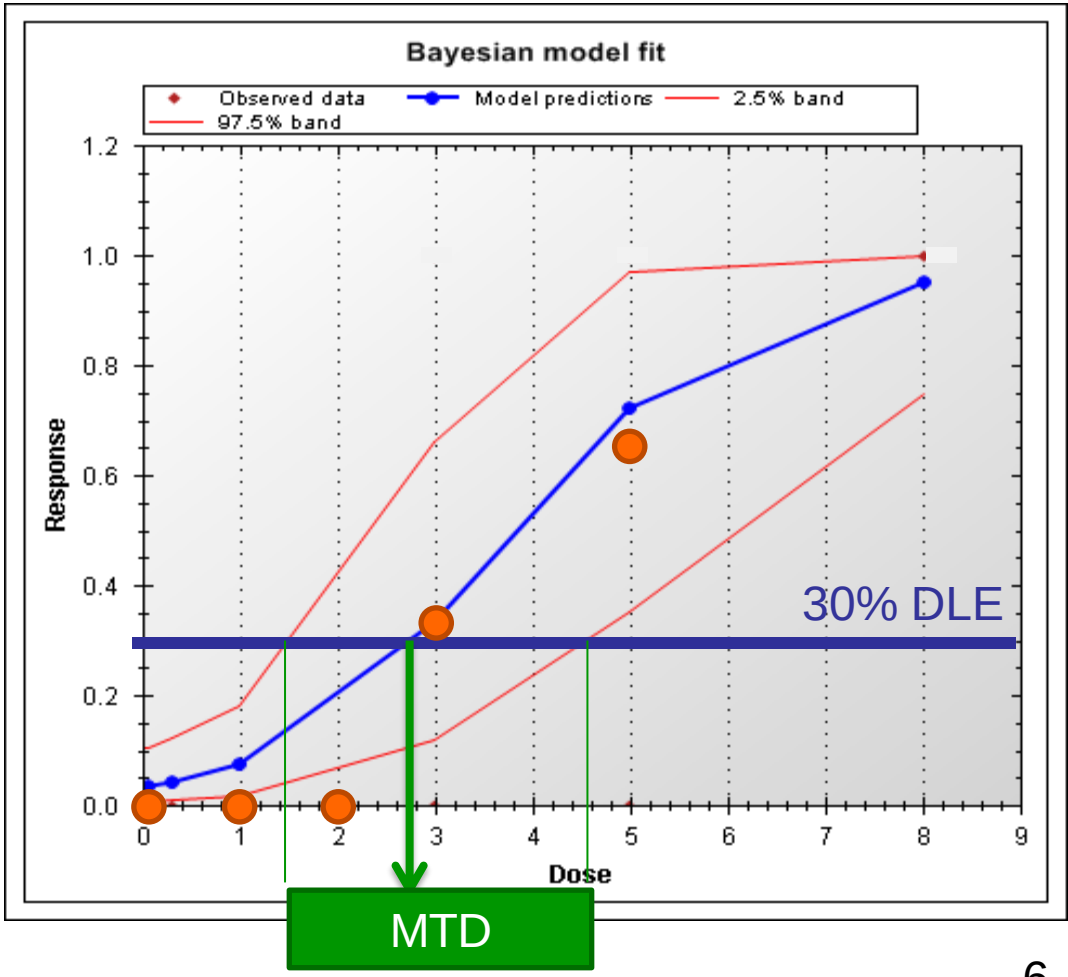
EIH example

Bayesian/Adaptive

- Dose escalation(N=3):
  - No DLE at 0, 1, 2 mg
  - 1/3 DLE at 3mg
  - 2/3 DLE at 5mg
- Next dose = MTD
  - Dose with DLE rate=30%
- Bayesian analysis:
  - Dose-DLE response model
  - Back prediction of MTD:

    2.7mg is the most likely MTD
- Study terminated
  - Precision on MTD is good:

  Here 95%CI: [1.5 , 4.5mg]



Comparison of fixed- and adaptive-design SAD trials

Fixed design

- 6 active + 2 placebo per dosing cohort
- Dose escalation by fixed multiples (2-fold, 3-fold)
- Stop when 50% of patients have DLEs
- MTD = dose prior to stop

Pros = Simple

Cons = biased MTD, sub-optimal dosing

Adaptive design

- Cohorts of various sizes (eg: 3 + 1) possibly expanded to 6 + 2
- Dose escalation depends on DLE:
  - No DLE => fixed multiple
  - DLE => model based to approach MTD with maximum multiple constraint.
  - Expand when DLE rate approaches 30%
  - Stop when precision on MTD is good

Pros = better MTD, optimal dosing

Cons = analysis time, complexity

Roche Case Study

Practical Implementation of Adaptive Design in SAD

April 2013

Application and Implementation of Bayesian

Statistics in early development studies at Roche

- Great focus on the use of innovative trial design
  - To improve productivity of clinical trials in order to optimize cost, cycle time and probability of success.

- Early development is a great opportunity for trial design innovation and there is need to learn how and when to deploy them.

- At Roche all ClinPharm staff has been trained on the methodology
- Simulations were performed to assess benefits of tool vs classical approach
- First non oncology EIH study with innovative design completed
- Expectation is to consider the approach as default in all EIH

Adaptive Design – Dose Escalation Scheme

Dose level 1 **(1+1/2+1)**

Max safe starting dose

Dose level 2 **(3+1)**

Dose level 3 **(3+1)**

.....

Dose level ? **(3+1)**

Dose level ??**(3+1 / or more)**

Dose level ??? **(3+1 / or more)**

.....

Dose level ???? **(3+1 / or more)**

Max tested dose
Exposure cap

Predefined stopping rules met

Sentinel dosing as site specific requirement

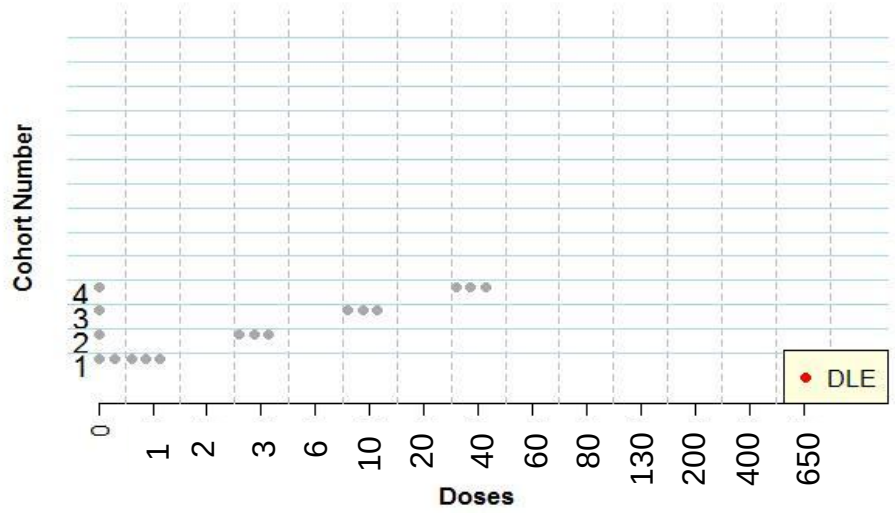
Dose escalation decision based on:

- Obs. 48h safety, vital signs, ECG, labs and 12 h exposure data
- Dose-event/toxicity relationship model-based estimation
  - posterior probability of each dose being the MTD
  - max dose given to next cohort is a dose closest to predicted target toxicity (e.g. pDLE = 30%)
  - dose increase max of ~3-fold

- Model used to guide the dose escalation & dose selection decision in addition to conventional approaches based on safety, tolerability & exposure.
- Not intended as a replacement of clinical judgement & thorough review of safety and PK data
- Protocol submitted Sept 20th, approval received Oct 9th with no question on the innovative study design

Cohort 1-4: 1 mg (3+1) - 40 mg (3+1)

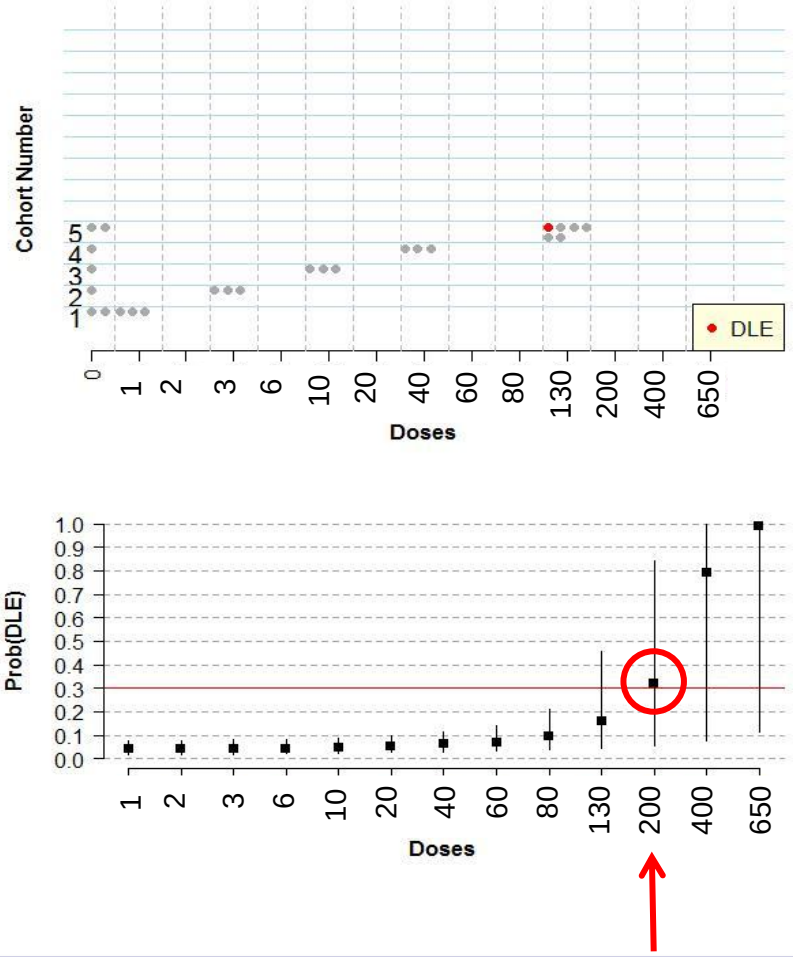
As no DLEs (Dose Limiting Events), decision to increase doses by 3-fold per protocol



Exposure @ next dose (130 mg) was predicted to approach exposure cap; switched to 6+2

Cohort 5: 130 mg (6+2)

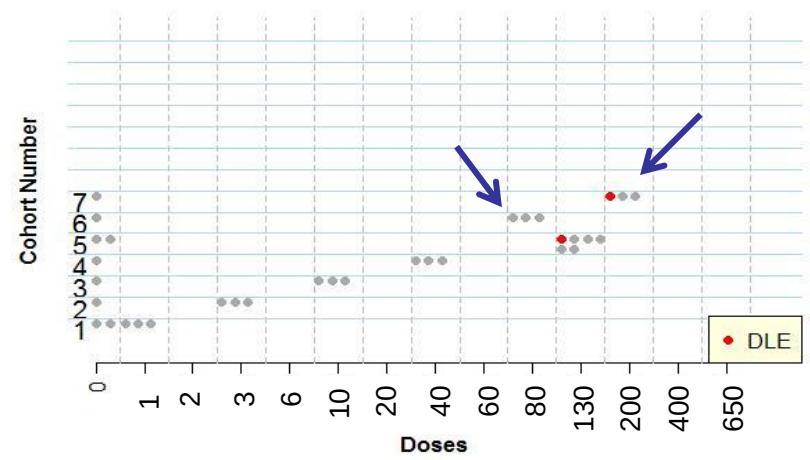
One DLE, model predicts to dose next cohort @ ~200 mg; corresponding to a dose targeting but below the stipulated exposure cap

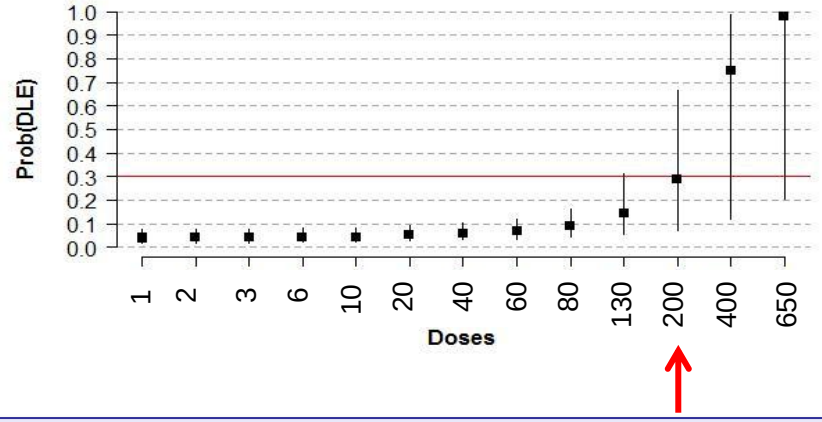


Decision to escalate 3+1 to **200 mg** (close to exposure cap; predicted MTD; not life-threatening and manageable AE) and 3+1 @ **80mg** (to fill the gap betw. 40 mg and 130 mg)

Cohort 6: 80 mg (3+1) and 200 mg (3+1)

One DLE @ 200 mg, model predicts MTD @ ~200 mg



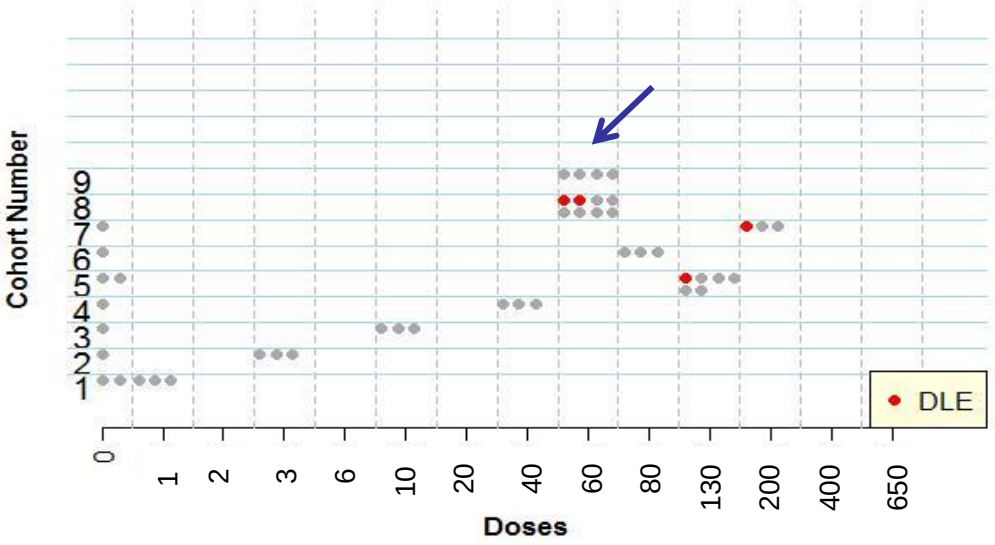


Dose Decision

- Enrich **200 mg** dose group with 6+2 to have precise estimation of MTD
- Dose @ **60 mg** in the Food Effect part

Food Effect Cohort: 60 mg (n=12)

Two subjects with DLEs @ 60 mg, model predicts MTD @ 200 mg

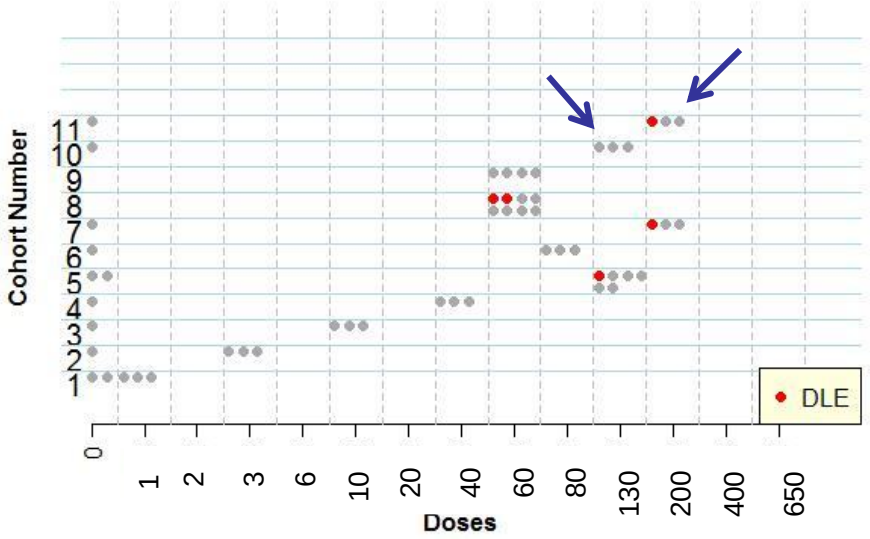


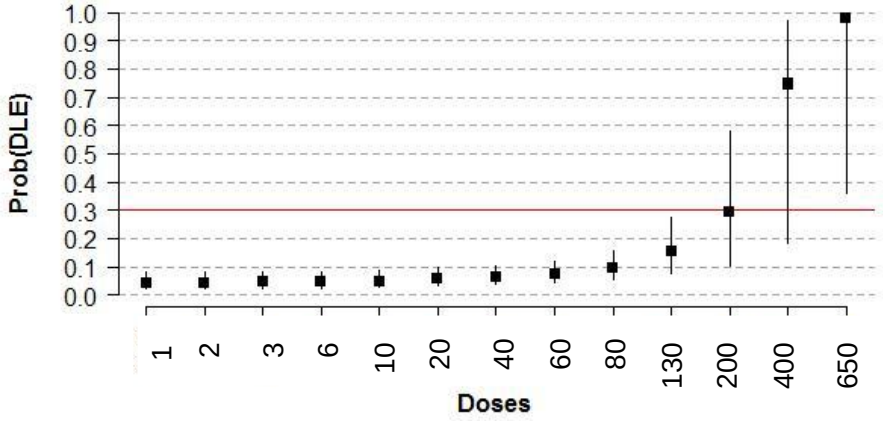
Decision to revisit dose selection for Cohort 8

- Instead of exposing 6+1 @ 200 mg
- 3+1 @ 200 mg and 3+1 @ 130 mg

Cohort 8: 130 mg (3+1) and 200 mg (3+1)

One subject with DLEs @ 200 mg, model predicts MTD @ 200 mg (CV% 21%)





Decision stop study

- MTD defined as 200 mg with satisfying precision

Model-based Bayesian approach to support dose escalation decision and evaluation of MTD in a FIM

Conclusion

- Very helpful in guiding dose escalation and dose selection decision especially once 1st DLE was observed (escalation to highest dose)
  - Enabled to explore doses which potentially may not have been explored using traditional design
- Allowed robust estimating of the MTD (maximum tolerable dose)
  - Without exposing subject at doses above the identified MTD
- Resulted in a more efficient conduct of the trial :
  - number of subjects in the non informative dose groups was reduced
    - n=18 subjects, 4 first dose levels
  - Enriched /optimized allocation of subjects to most informative dose groups
    - n=35 subjects, 4 dose levels
  - Explored 8 dose levels and effect of food with a total of 53 subjects to be compared to 68 in the traditional design

Discussion

Opportunities, benefits and challenges

What is your experience?

- What are in your view the benefits & opportunities ?
- What are experienced and/or anticipated challenges?

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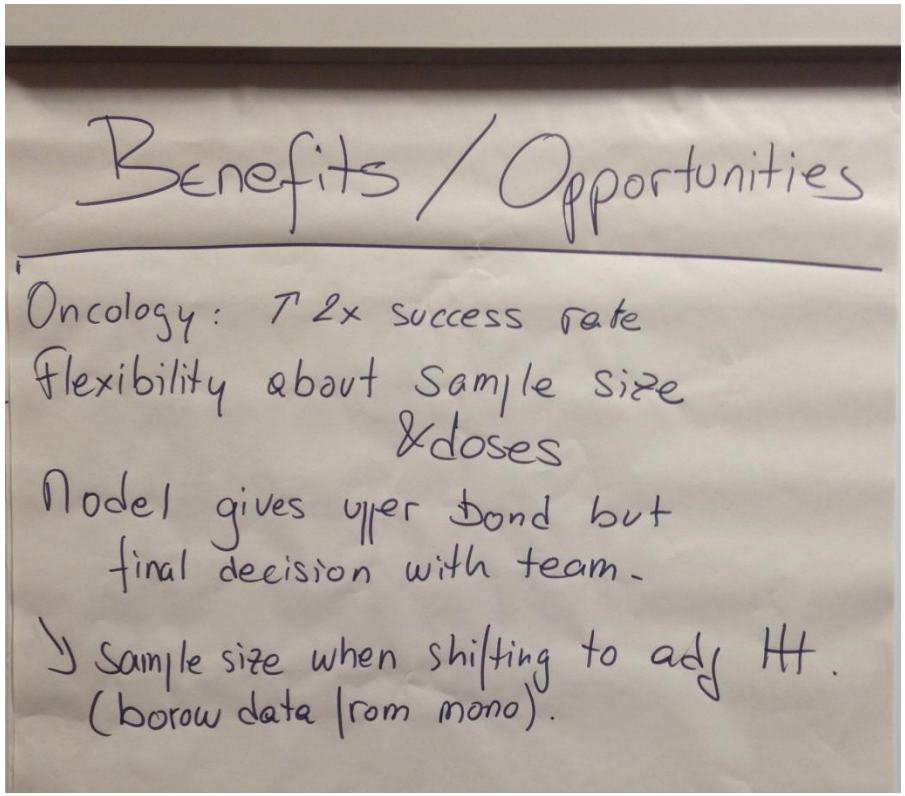
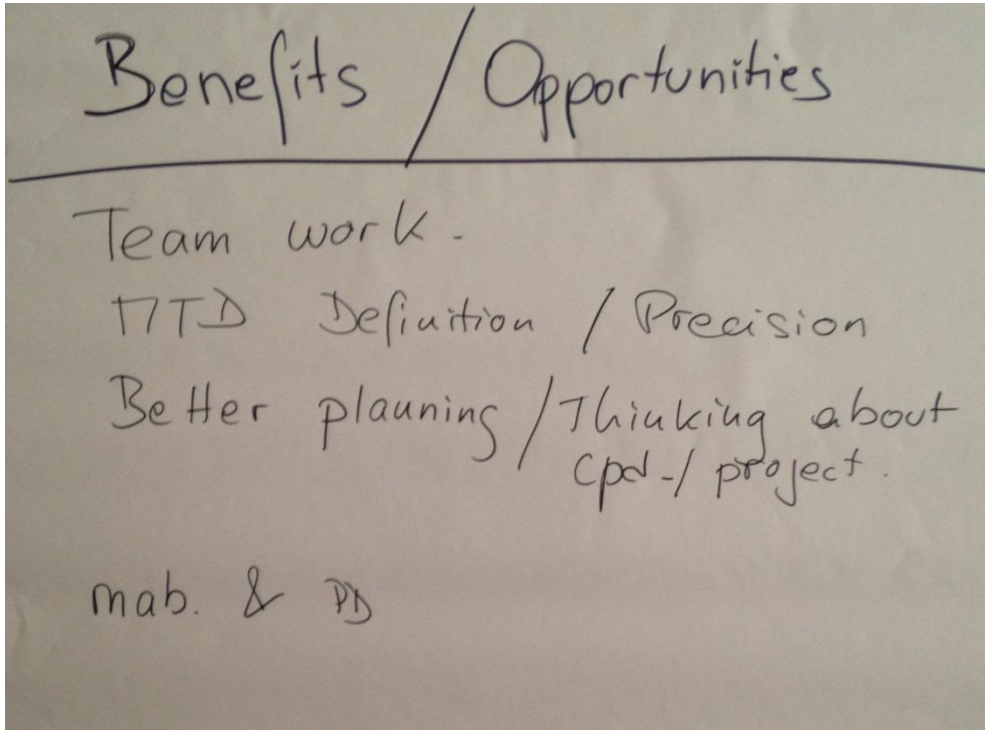
Group 1



Group 2



What is your experience?

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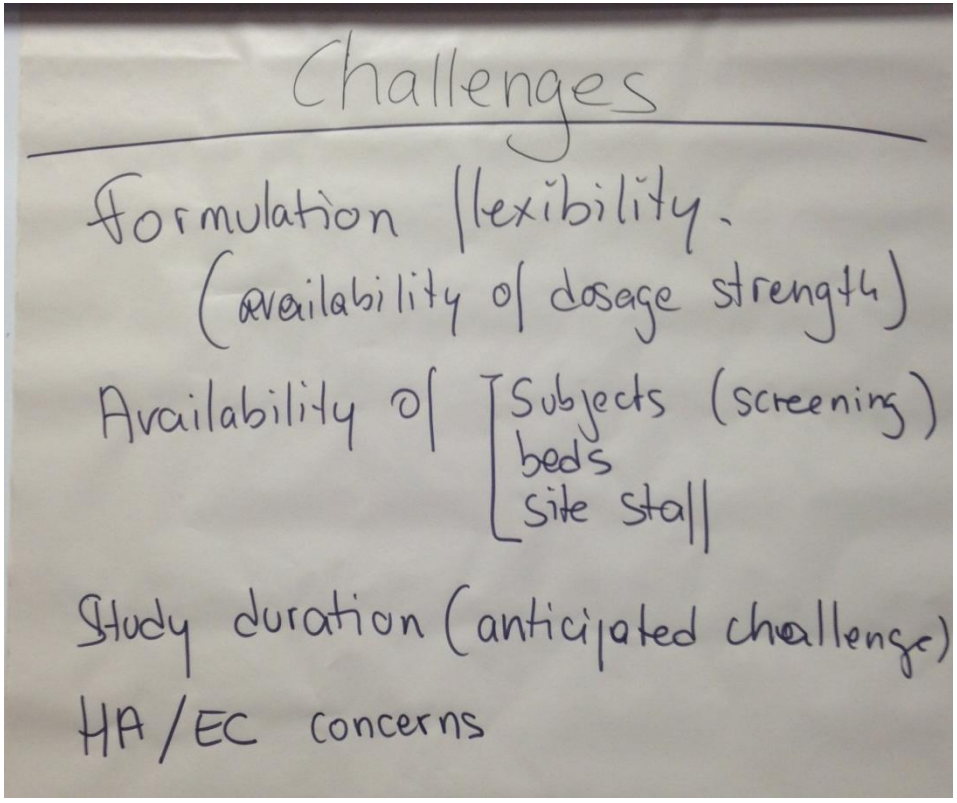

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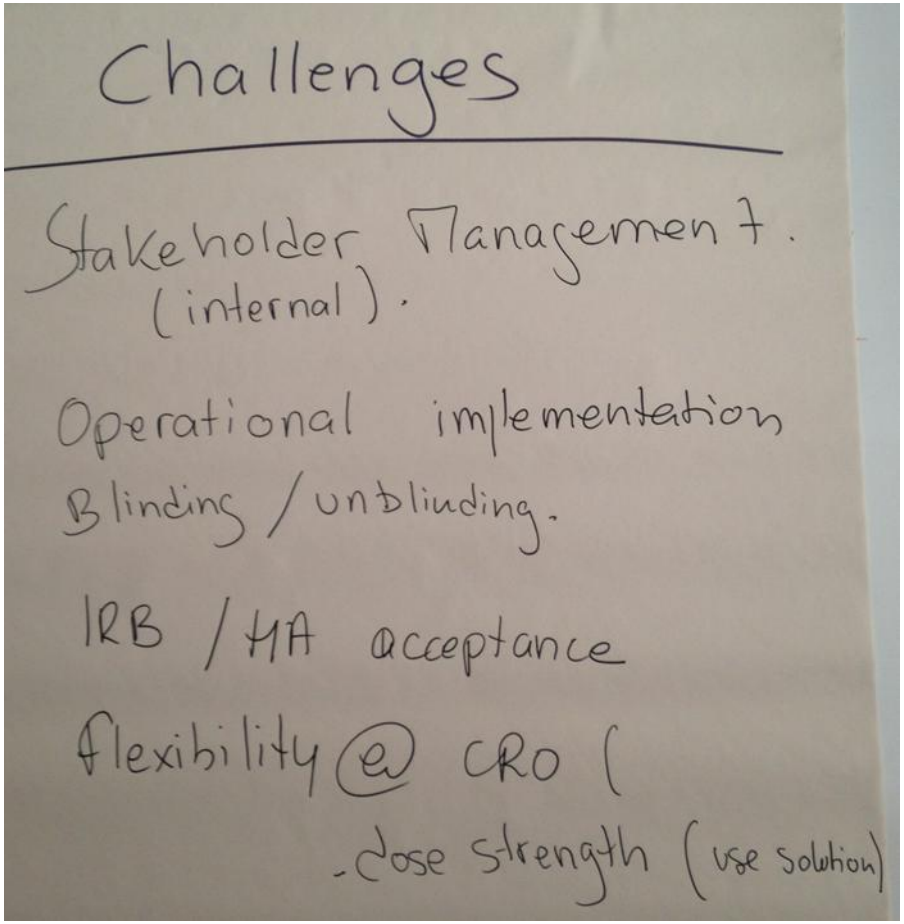
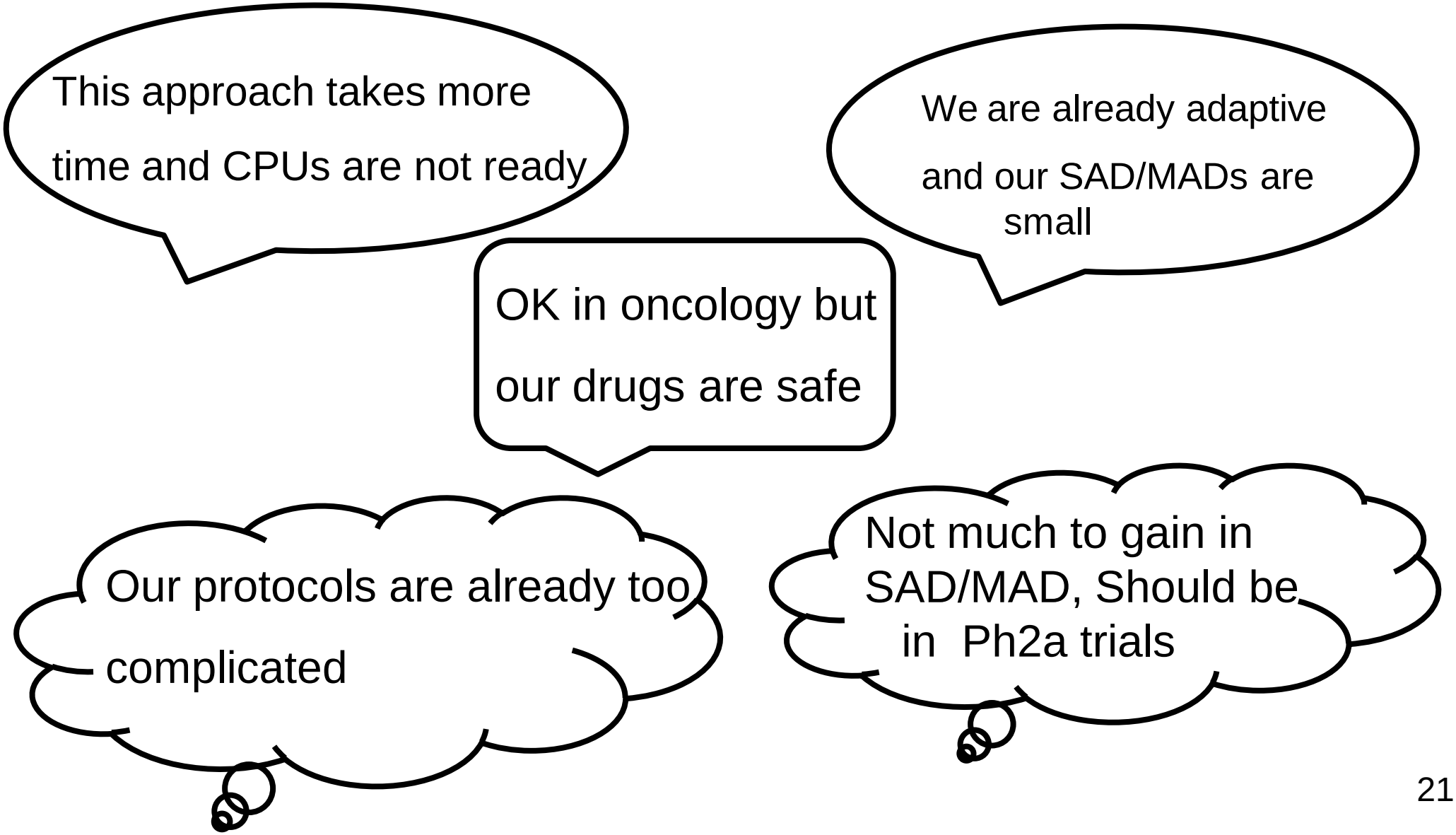


Common believes regarding Challenges and Concerns



Vote in the audience:

Would you consider a model-based method in your next SAD trial ?

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Would you consider a model-based method in your next SAD trial ?

	Yes	No	Maybe
Group 1	**9**	**0**	**4 (concern about Timelines/Indication**
Group 2	**15**	**1 (concern re variability in PK and safety)**	**0**

Adaptive Design Tool Box

Protocol writing
Site feasibility
Analysis

April 2013

Adaptive Design Tool Box

Protocol Writing

- Protocol sections:
  - Dose escalation plan:
    - Discuss enrolment of cohorts, starting dose, dose escalation & termination
  - Statistical methods:
    - Discuss interim analyses strategy
  - Appendix : Trial simulations plan and results
    - Define detailed statistical & adaptive methodology
    - Define 5-10 different trial scenarios on putative dose levels
    - Define performance metrics to be monitored:
      - Accuracy & precision of MTD
      - Accuracy of stopping decisions
      - Trial duration & sample size
      - # subjects being over/under doses
    - Present simulation results

    to assess performance of adaptive method

Adaptive Design Tool Box

Protocol Writing: Dose escalation plan

- No statistics in that section – just define CRM & refer to statistical sections.
- Model-based CRM is only an aid to the decision. Define who makes the decisions and what data are being assessed.
- Must be a clear recipe for sites to follow, e.g.:
  - If no DLE -> 3-fold increases
  - If at least 1 DLE -> run CRM before deciding
- Must contain safety constraints on escalation, e.g.:
  - Max. 3- fold increases
  - If at least 2/3 or 4/6 DLEs -> lower doses only.
- Must contain trial stopping rules:
  - Precision of MTD is good (eg, CV<40%)
  - Max. dose is safe: e.g. Pr(MTD>Top Dose)>80%
  - Min. dose is toxic: e.g. Pr(MTD<min dose)>80%
  - Maximum sample size achieved: e.g. no more than 9 subjects/dose.

Adaptive Design Tool Box

Site feasibility

- Early discussion with the site and PI regarding specificity of the design
  - Do you have experience with Bayesian adaptive designs in SAD ?
  - Are you comfortable/do you have experience with the 3+1 design with switch to 6+2 ?
  - Do you anticipate any concerns with respect to IRB/HA ?
  - Has your IRB already been exposed to such designs ?
    - The protocol specified clear dose escalation rules, stopping rules, an exposure cap/maximal dose
  - Do you anticipate any specific challenges from an operational feasibility perspective related to the adaptive nature of the design e.g. cohort sizes to be determined at the dose escalation meeting ?
- Close collaboration and effective communication is key
  - Need the buy in from all stakeholders: internal and external
- Challenges mostly associated with flexible cohort sizes often not compatible with clinic dates/spare beds…

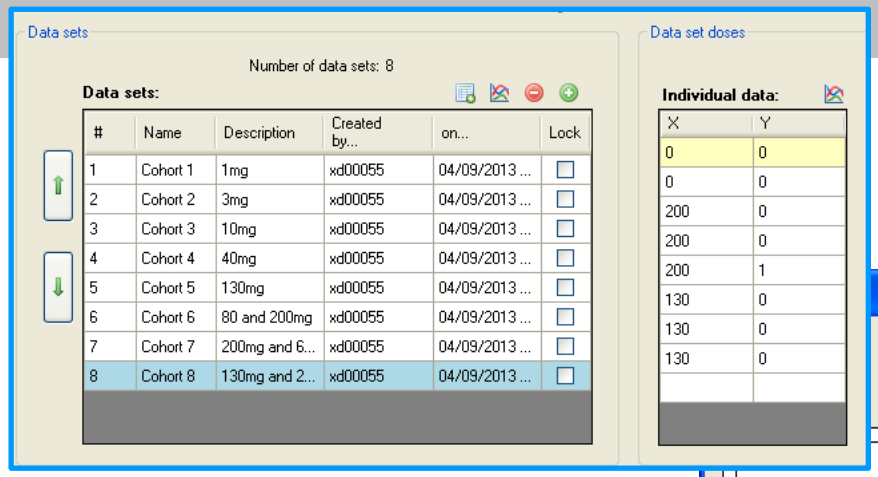
Adaptive Design Tool Box

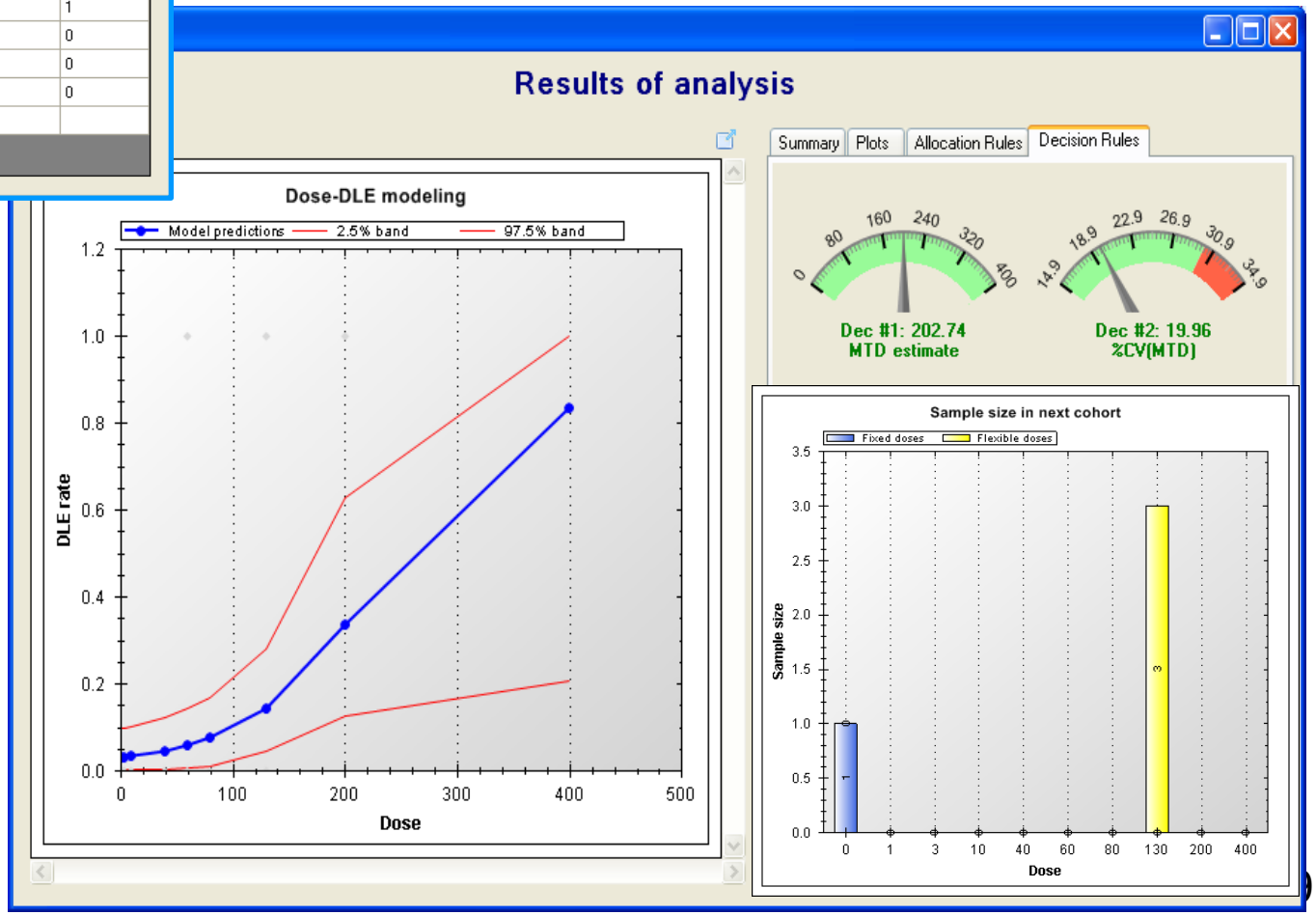
Analysis

- Data flow during study conduct
  - [Blinded] DLE determination by investigator + sponsor review
  - Unblinding plan: Investigator/subject >< Sponsor
  - Little data needed for modeling: List of doses and DLE (Yes/No) for all subjects
- Skills & Software
  - Specialized statistical skills in Bayesian statistics required to design protocols (run simulations) and to analyse data.
  - For standardized trials, learning curve is fast: autonomy after 2 or 3 trials.
  - For more complex trials, specialized consulting is available.
  - Software:
    - Coding in SAS or Winbugs is possible but time-consuming.
    - GUI packages such as Decimaker available for standard studies.

Adaptive Design Tool Box

Decimaker





Final Message

- Application of model based prediction of anticipated MTD in the SAD was
  - Used as a (new/additional) tool to support dose escalation
  - Not intended to be used in isolation
    - Not replacing clinical judgement & thorough review of safety and PK data
  - Very helpful
    - in guiding dose escalation and dose selection decision
    - in estimating MTD (maximum tolerable dose)
    - for efficient subject allocation to most informative doses
- Expectation is to consider approach as default in Roche EIH
- More companies are adopting CRM methods in phase I
  - Practical hurdles and fears are being lifted
  - Learning curve is steep

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Acknowledgements

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- David Guede
- Fabien Linay

Roche

Doing now what patients need next

CLINBAY

Statistical Solutions to Drug Development

Backup slides

Definition of a Dose Limiting Event (DLE)

- A dose limiting event (DLE) is a drug related and clinically significant AE, lab abnormality or change in vital signs that would preclude another drug administration at the same dose level in a given subject .
- Examples of DLE include:
  - drug related severe or serious AE
  - clinically significant and persistent marked laboratory abnormality or a lab abnormality that either by itself or as a result of the change over time or the combination with other lab changes are deemed clinically significant
  - clinically significant and persistent change in vital signs
  - clinically significant and repeated change in ECG parameters
- Maximal Tolerated Dose
  - Dose at which the pDLE=30%

Study Stopping Rules

- MTD estimated
  - CV (MTD) < 30% (good precision)
  - 2 cohorts treated with a dose X, and the next predicted dose is still X
- MTD not estimated
  - Per protocol maximum number of subjects dosed
  - Per protocol maximal dose administered
  - Prob(Prob(DLE at max Dose) < 30%) > 80%
    - equivalent to consider the whole dose range as safe