MODEL-BASED DOSE ADAPTATION OF CAPECITABINE FOR PREVENTION OF SEVERE HAND-AND-FOOT SYNDROME :

in silico comparison with the standard method

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INTRODUCTION

- **5-FU** :
  - inhibitor of cell cycle;
  - one of the most used anticancer drugs for the treatment of solid tumors (colorectal, breast) (since 1957).

- **Capecitabine** (Xeloda®, Roche):
  - prodrug of 5-FU taken orally (a blockbuster since 2002);
  - main toxicity : **hand-and-foot syndrome** (54% patients)

  (redness, peeling, numbness, pain of the skin of palms and soles)

Grade	0	1	2	3
Symptoms	-	Tingling or burning	**Pain**	**Severe pain**
	-	Mild redness, swelling; skin intact	Redness, swelling; skin intact	**Blisters, peeling, loss of function**

DOSE ADAPTATION STRATEGIES

Standard:

If Grade≥2, treatment stopped until Grade ≤1,
then dose is changed accordingly:

Grade	Occurrences			
	1	2	3	4
2	100%	75%	50%	0
3	75%	50%	0	0

DOSE ADAPTATION STRATEGIES

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Alternative:

individual adaptation according to **model-based prediction** of patient-specific toxicity **risk**

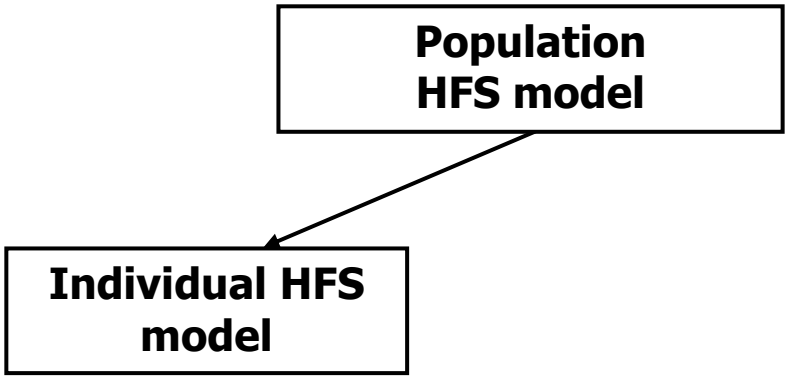
OBJECTIVES OF THIS WORK

- **Develop** an individual model-based dose adaptation method for ordinal observations
- **Evaluate** its feasibility
- **Compare** its performance to that of the standard practice
  ➔ **by randomized *in silico*** clinical trials

INDIVIDUAL DOSE ADAPTATION BASED ON A LONGITUDINAL DOSE-TOXICITY MODEL

Population
HFS model

INDIVIDUAL DOSE ADAPTATION BASED ON A LONGITUDINAL DOSE-TOXICITY MODEL



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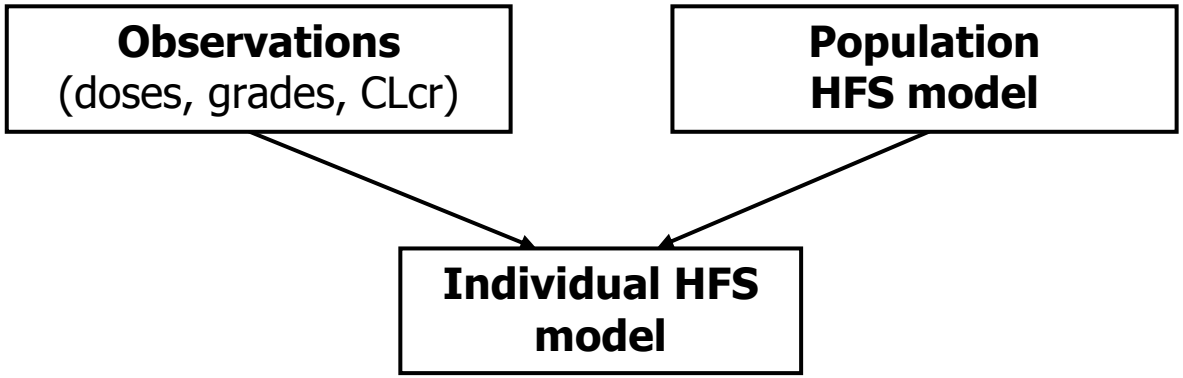

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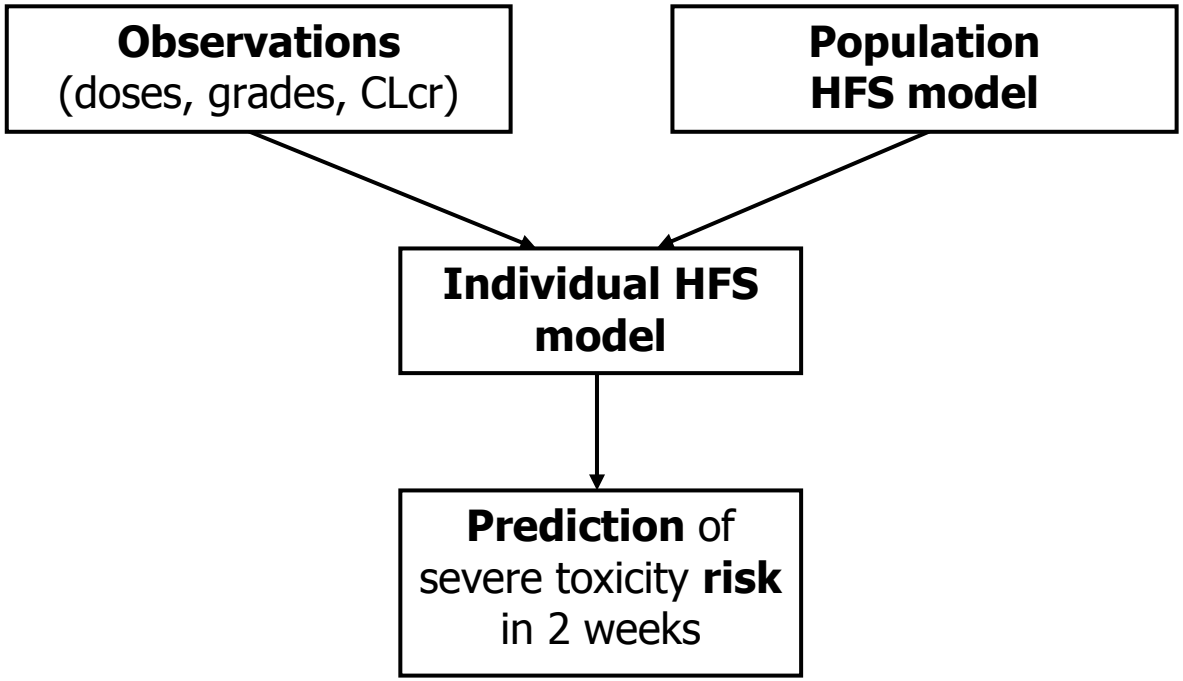

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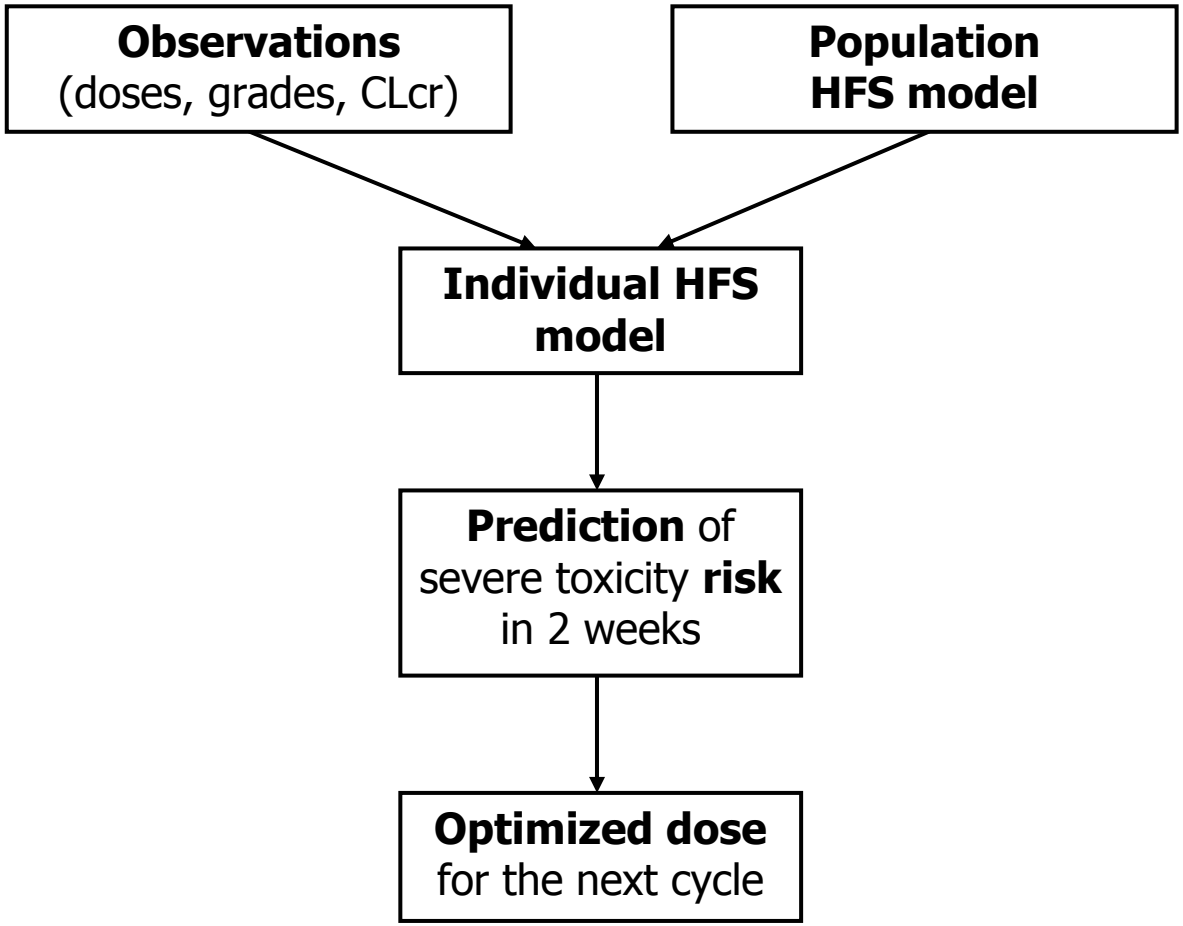
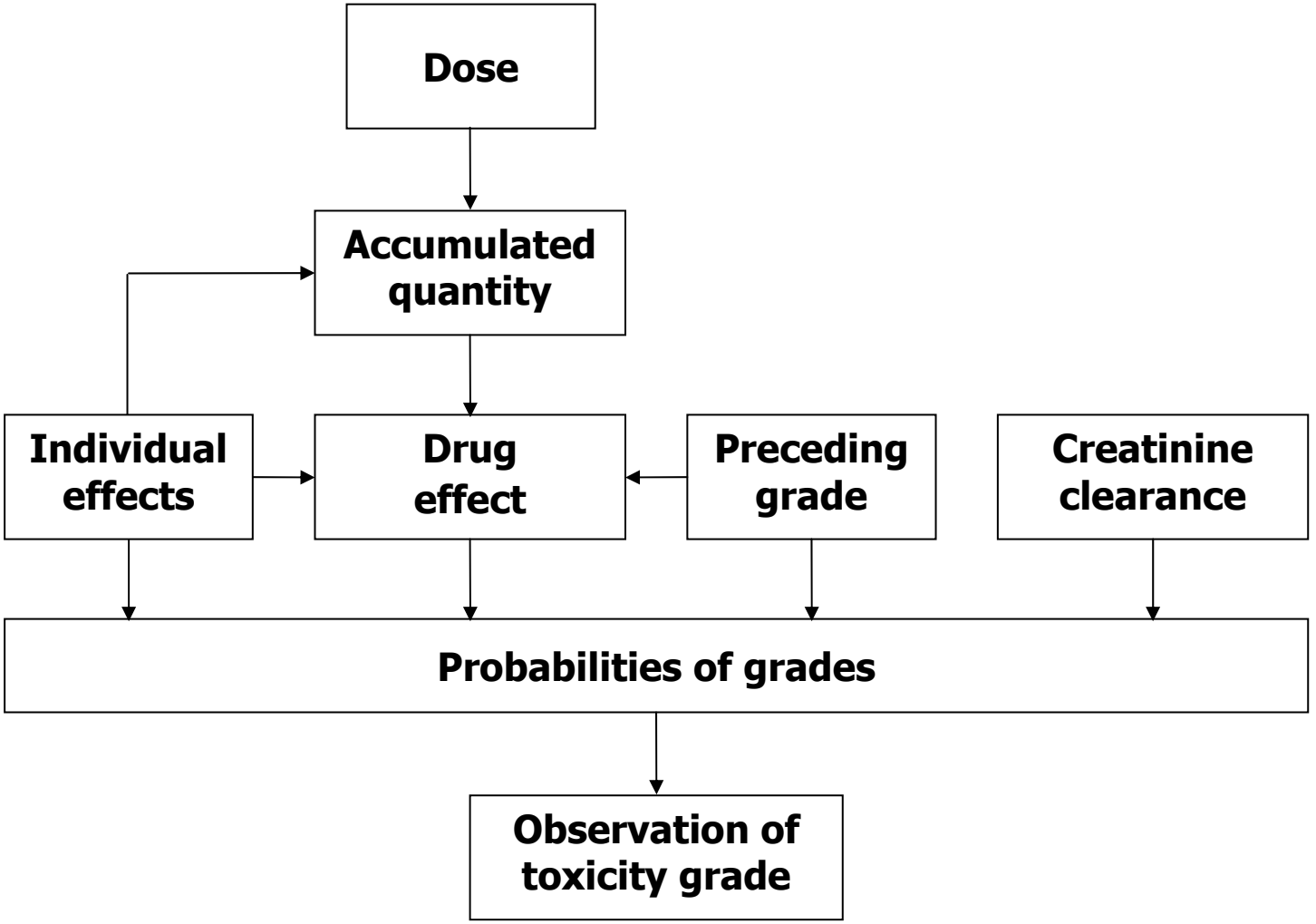


DOSE-TOXICITY MODEL: the principle

(**Hénin** *et al.,* **A dynamic model of hand-and-foot syndrome in patients receiving capecitabine**, advanced publication)



POPULATION DOSE-TOXICITY MODEL

mixed-effects transitional proportional odds model for ordinal data

$$\frac{dQ}{dt} = Dose - K_i \cdot Q, \qquad K_i = K \cdot e^{\eta_{1i}}$$

$$\text{logit}[P(Y_{it} \le 0 \mid Y_{it-1} = G^*)] = B_0^* - \frac{E_{MAX}^* \cdot (Q_{it} \cdot K_i)}{ED_{50} + (Q_{it} \cdot K_i)} + (CLcr_i - 75.5) \cdot \theta_{CLcr} + \eta_{2i}$$

$$\text{logit}[P(Y_{it} \le 1 \mid Y_{it-1} = G^*)] = B_0^* + B_1^* - \frac{E_{MAX}^* \cdot (Q_{it} \cdot K_i)}{ED_{50} + (Q_{it} \cdot K_i)} + (CLcr_i - 75.5) \cdot \theta_{CLcr} + \eta_{2i}$$

$$P(Y_{it} \le C \mid Y_{it-1} = C^*) = \frac{\exp(\text{logit})}{1 + \exp(\text{logit})}$$

$$p_{it0} = P(Y_{it} = 0) = P(Y_{it} \le 0)$$

$$p_{it1} = P(Y_{it} = 1) = P(Y_{it} \le 1) - P(Y_{it} \le 0)$$

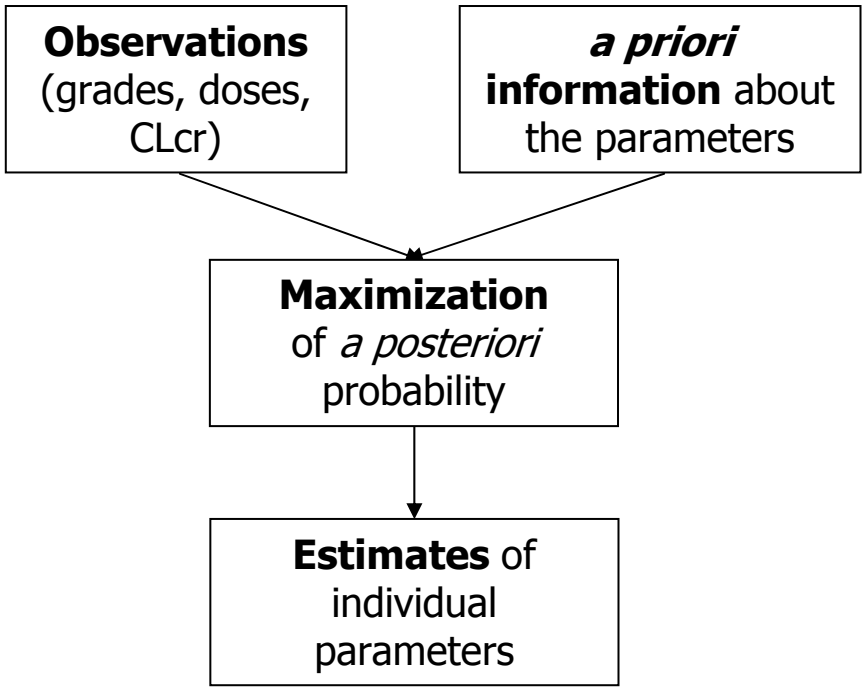
$$p_{it1} = P(Y_{it} = 2) = P(Y_{it} \le 2) - P(Y_{it} \le 1) = 1 - P(Y_{it} \le 1)$$

a priori **information:** $\Theta = (B_0^0, B_0^1, B_0^2, B_1^0, B_1^1, B_1^2, E_{MAX}^0, E_{MAX}^1, E_{MAX}^2, ED_{50}, K, \theta_{CLcr})$

$$\begin{pmatrix} \eta_1 \\ \eta_2 \end{pmatrix} \sim N(0, \Omega), \qquad \Omega = \begin{bmatrix} \omega_1^2 & \omega_{12} \\ \omega_{12} & \omega_2^2 \end{bmatrix}$$

ESTIMATION OF INDIVIDUAL PARAMETERS

Bayesian estimation approach ***Maximum A Posteriori*** (MAP) is used for estimation of individual parameters on the basis of previous observations



ESTIMATION OF INDIVIDUAL PARAMETERS

Implementation of the **MAP method**:

$$\hat{\eta}_{iMAP}(H_{it}) = Arg\left[\max_{\eta_i} \frac{p(\eta_i)\cdot p(H_{it}\left|D_{it}, H_{it-1}, CLcr_i, \Theta, \eta_i\right.)}{p(H_{it})}\right]$$

Likelihood (of **ordinal** observations):

$$p(H_{it}\left|D_{it}, H_{it-1}, CLcr_i, \Theta, \eta_i\right.) = \prod_{j=1}^{t}\prod_{g=0}^{2} p_{ijg}^{y_{ijg}}$$

$$y_{itg} = \begin{cases} 1, \text{ if } Y_{it} = G, \\ 0, \text{ otherwise;} \end{cases} \quad \text{where } G = \{0, 1, \geq 2\}$$

Maximization by Simplex (additional subroutine)

DOSE DETERMINATION RULE

TARGET:

Risk of severe toxicity in 2 weeks = 1%

DOSE:

Daily dose corresponding to this target,
constrained: 50% to 100% of the nominal dose

IN SILICO PROOF-OF-CONCEPT CLINICAL TRIAL

- 3 parallel randomized **arms** according to **adaptation** method:
  - Standard
  - Individual
  - Individual+
- **10,000** virtual patients per arm.
- **Standard dosing regimen**: 2500 mg/m²/day for 2 weeks, 1 week rest.
- Max **30 weeks** (10 cycles of 3 weeks).
- **Interruption** of treatment in case of severe toxicity, until recovery to grade $\leq$1. Next doses are reduced according to the corresponding protocol.
- Definitive **discontinuation**:
  - after 7 consecutive weeks without any dose,
  - after the 4th episode of severe toxicity.

DOSE ADAPTATION PROTOCOLS

Protocol	Start of dose adaptation	Treatment interruption conditions	Dose	Dose limits
Standard	After the 2nd occurrence of severe toxicity	Grade ⩾2 toxicity	-25% after 2nd occurrence of severe toxicity -50% after the 3rd 0% after the 4th	[50%, 100%]

DOSE ADAPTATION PROTOCOLS

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Standard	After the 2nd occurrence of severe toxicity	Grade ⩾2 toxicity	-25% after 2nd occurrence of severe toxicity -50% after the 3rd 0% after the 4th	[50%, 100%]
Individual	After the 1st occurrence of at least grade 1 toxicity, when the risk of severe toxicity exceeds 1%	Grade ⩾2 toxicity Allowed dose is lower than 50% of the nominal dose	Corresponding to predicted risk of severe toxicity in 2 weeks equal to 1%	

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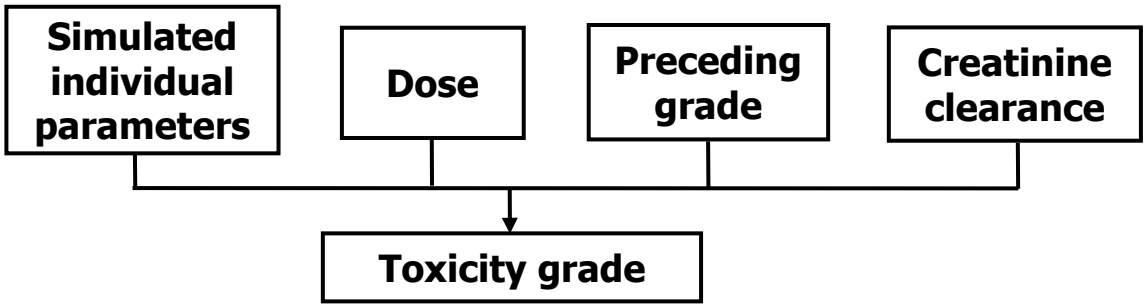
Individual	After the 1st occurrence of at least grade 1 toxicity, when the risk of severe toxicity exceeds 1%	Grade ⩾2 toxicity Allowed dose is lower than 50% of the nominal dose	Corresponding to predicted risk of severe toxicity in 2 weeks equal to 1%	
Individual+				[50%, 150%] for patients without any toxicity (start at the 4th cycle); [50%, 100%] for the rest

IMPLEMENTATION IN TS2™ (Pharsight®)



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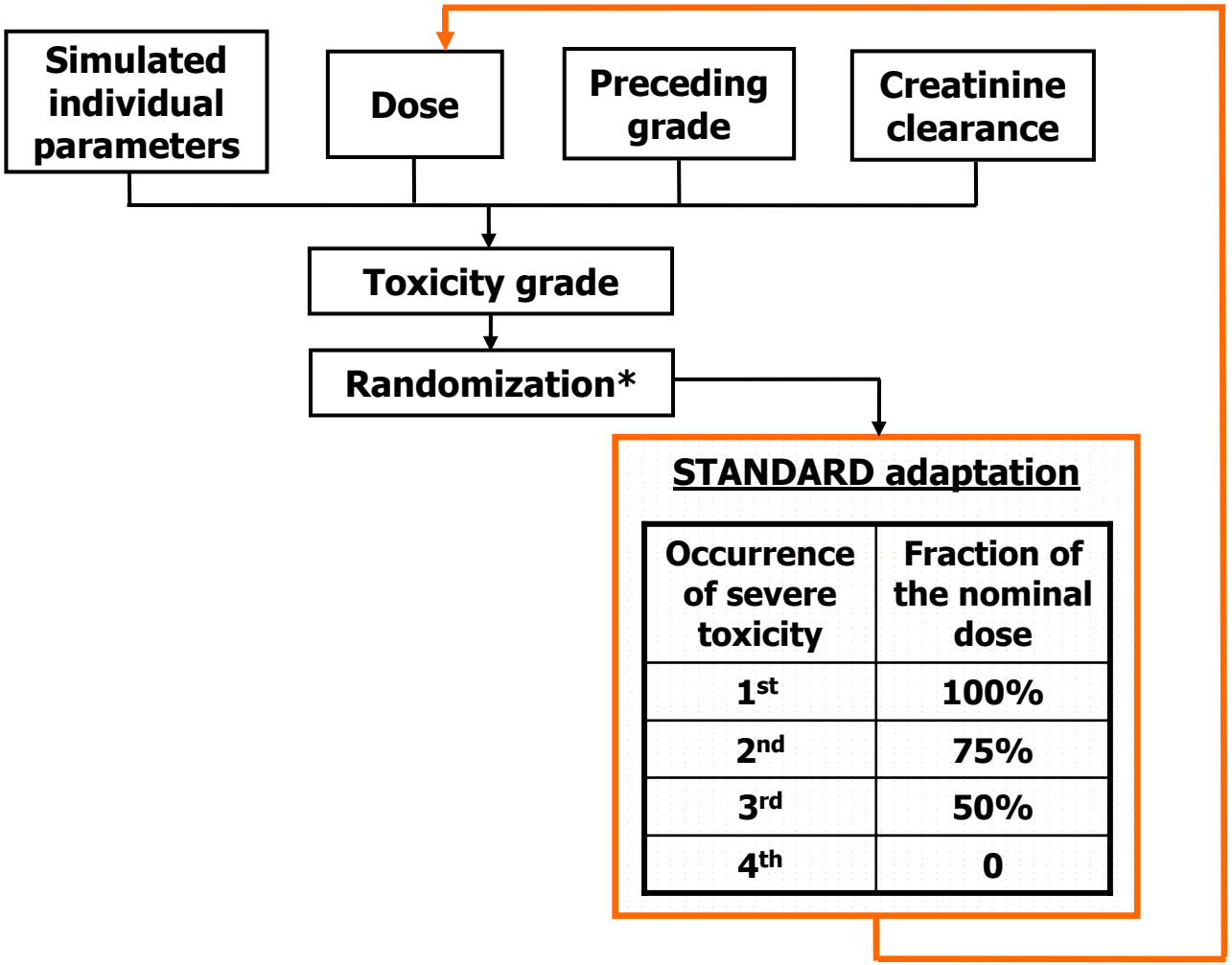
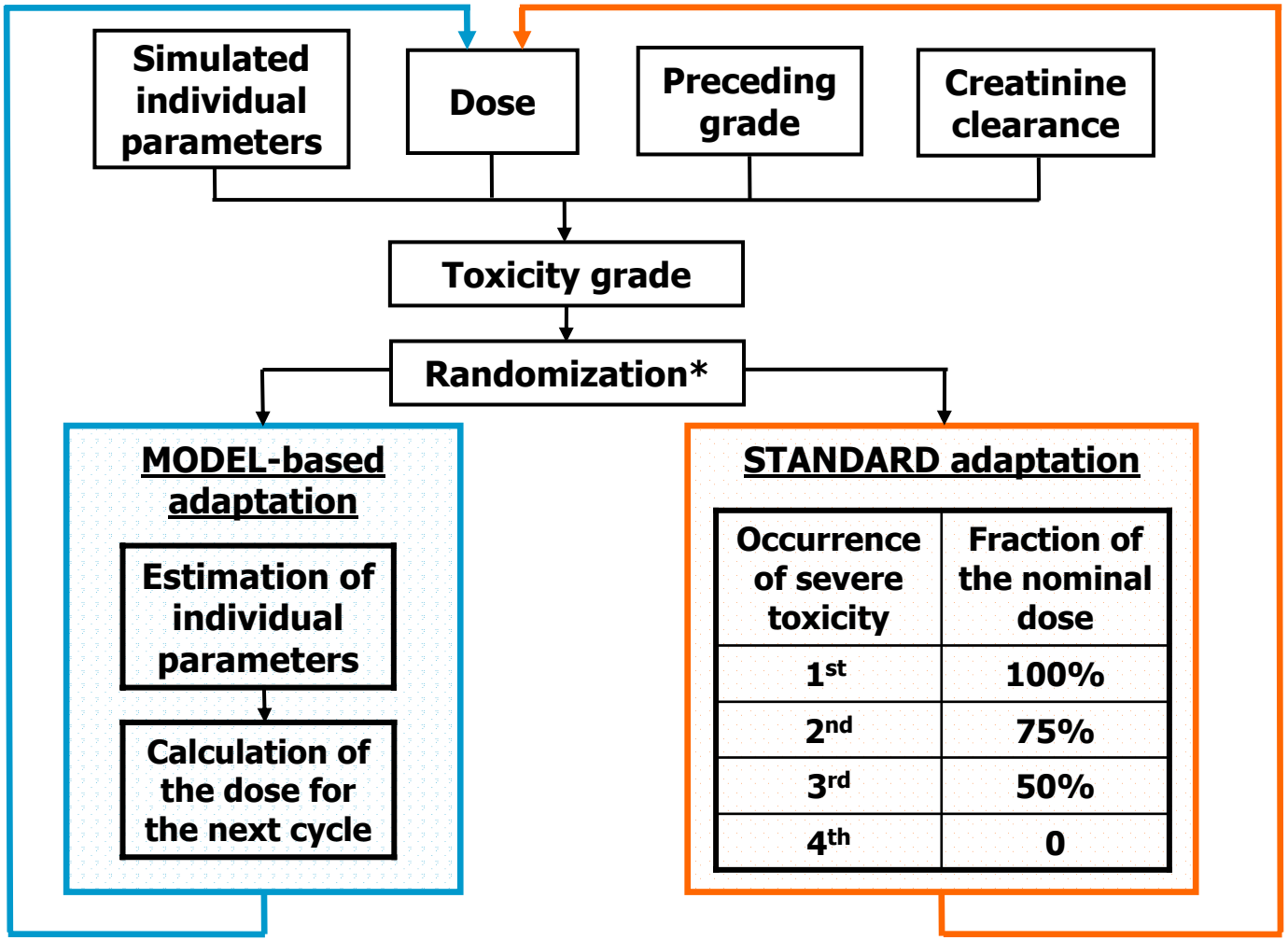


Occurrence of severe toxicity	Fraction of the nominal dose
1st	100%
2nd	75%
3rd	50%
4th	0

*: at the beginning of treatment

IMPLEMENTATION IN TS2™ (Pharsight®)



*: at the beginning of treatment

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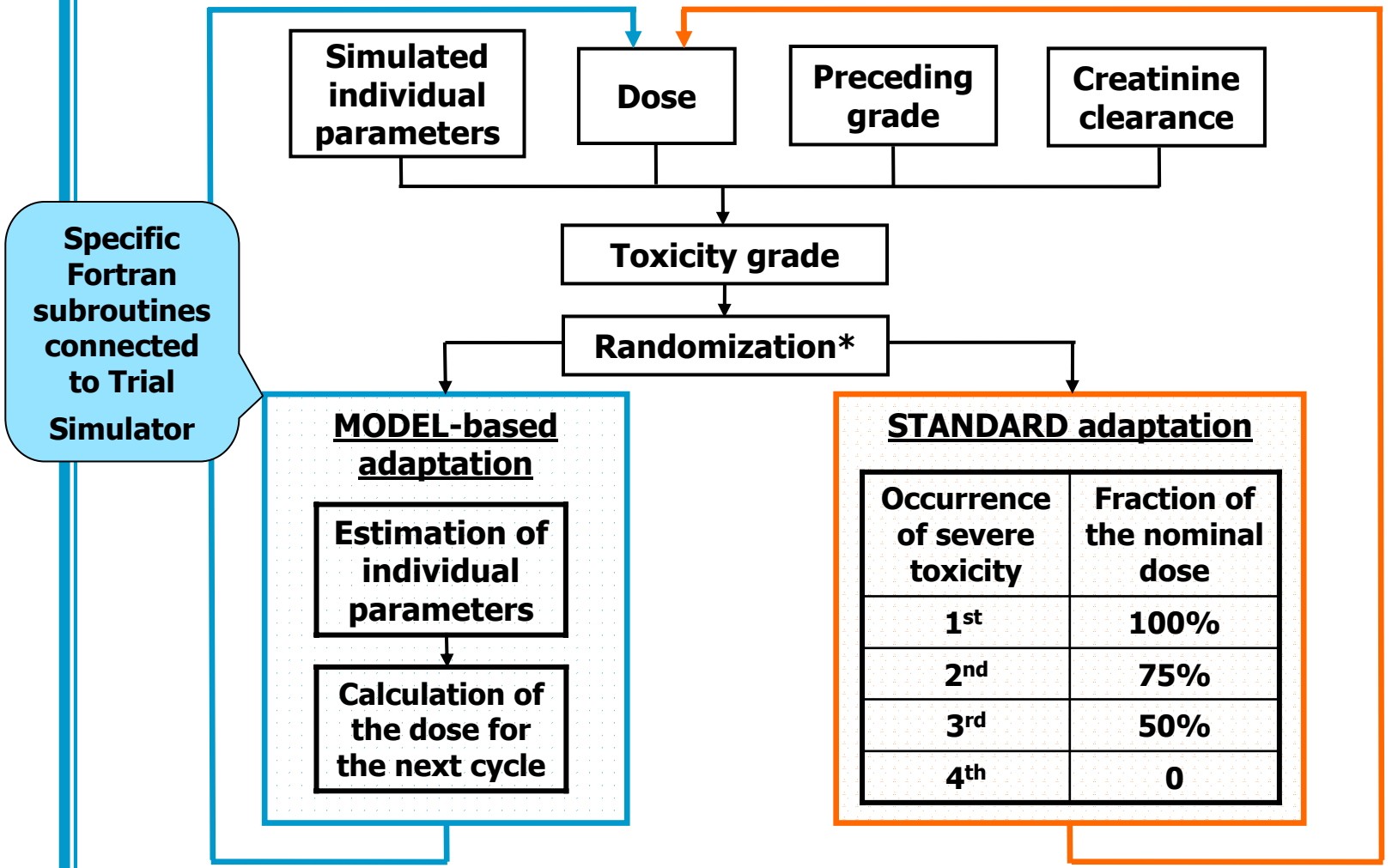
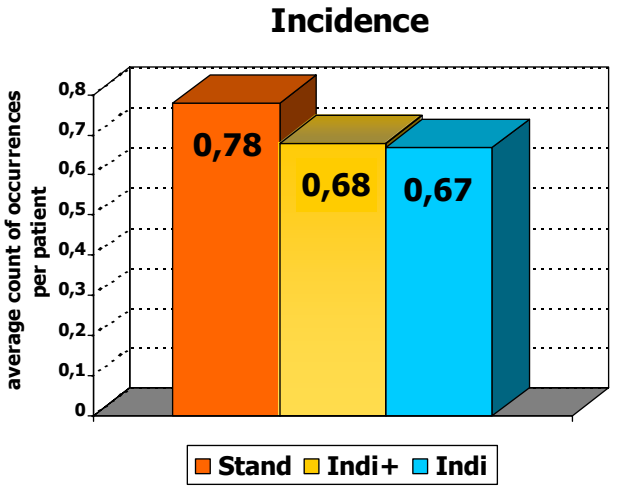
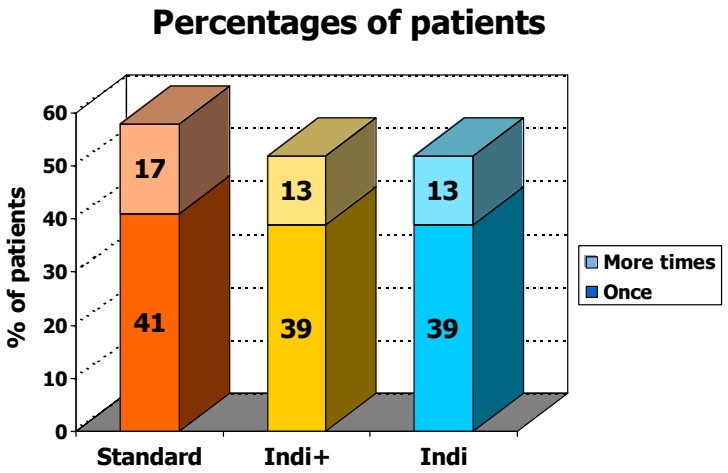


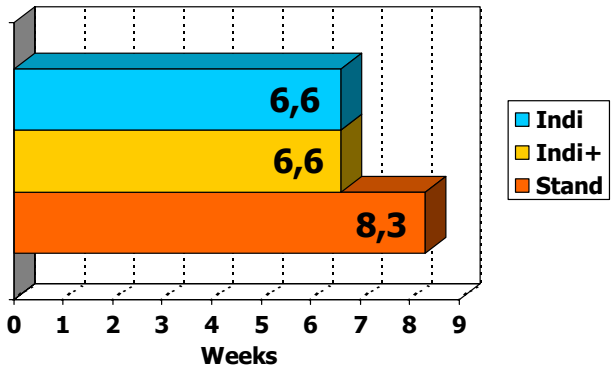
*: at the beginning of treatment

RESULTS:
Performance of adaptation protocols

REDUCTION OF SEVERE TOXICITY







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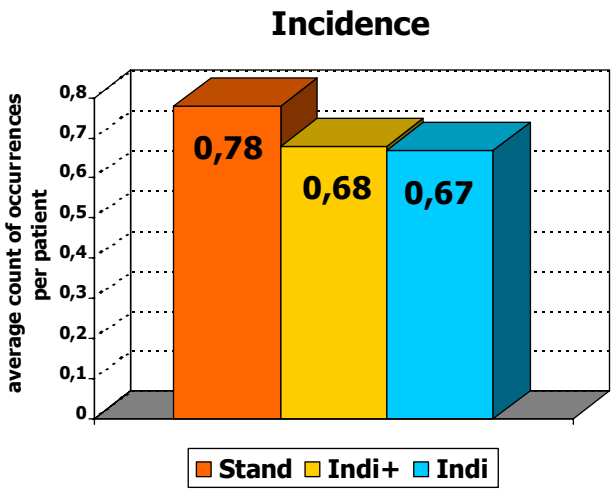

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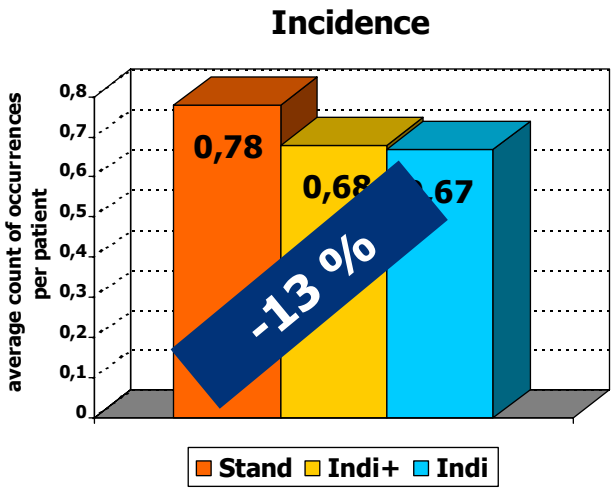

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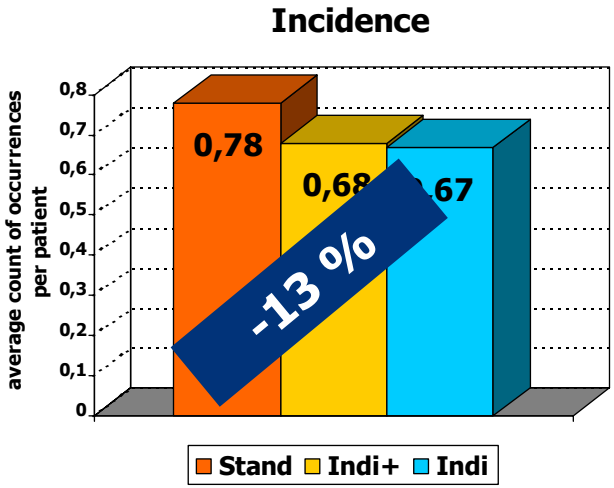

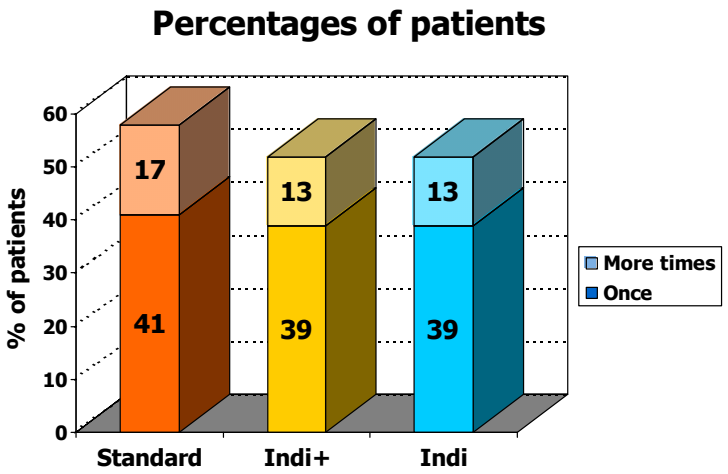

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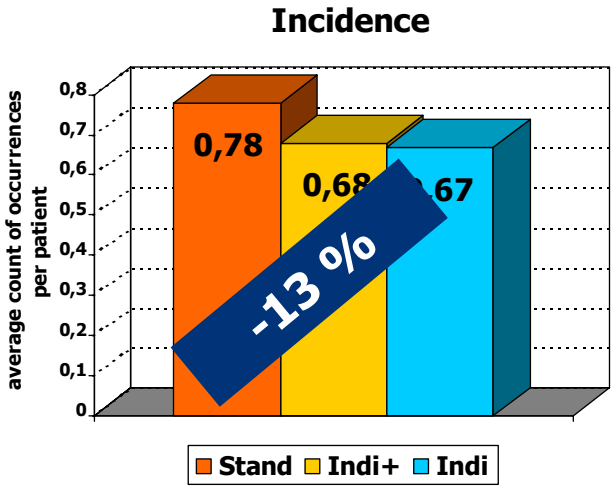

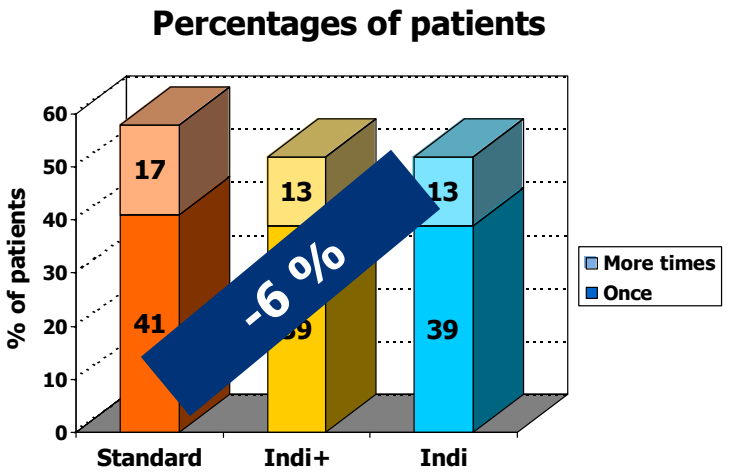

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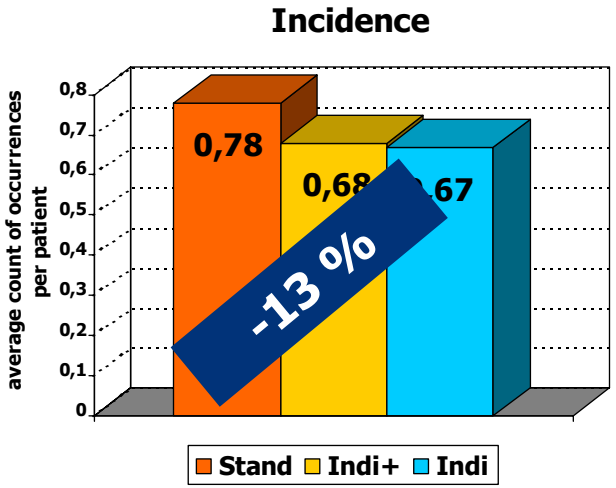

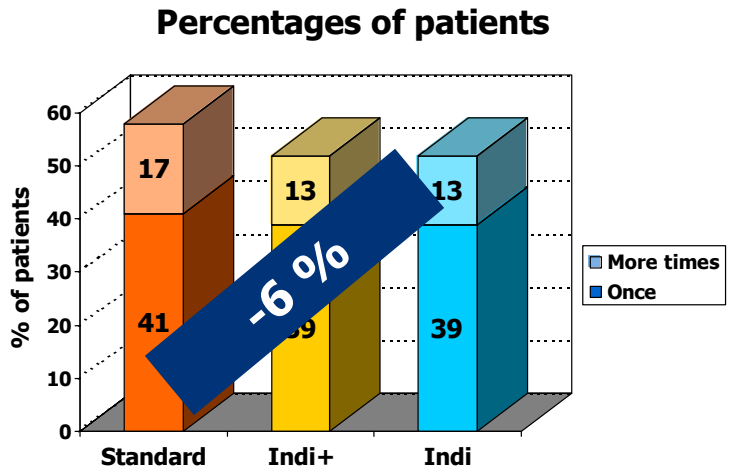

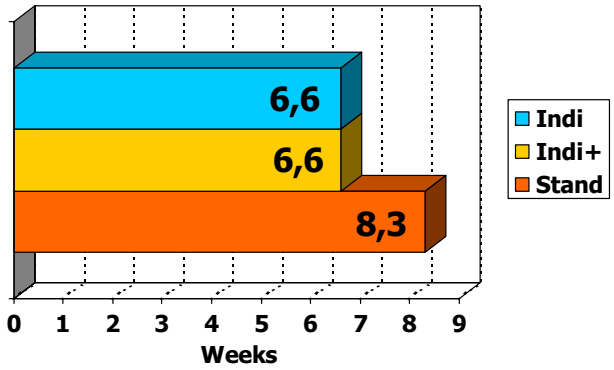

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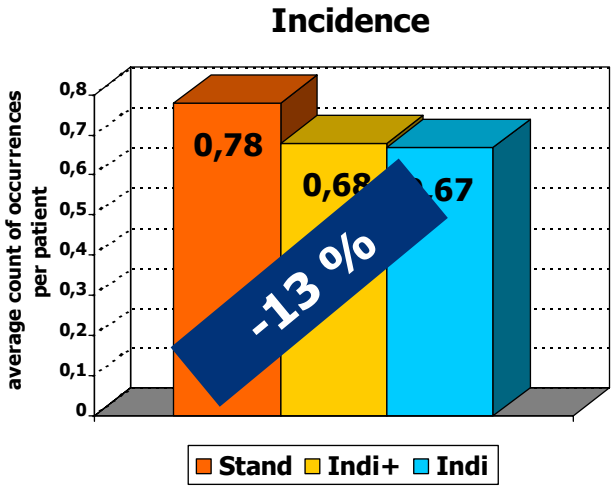
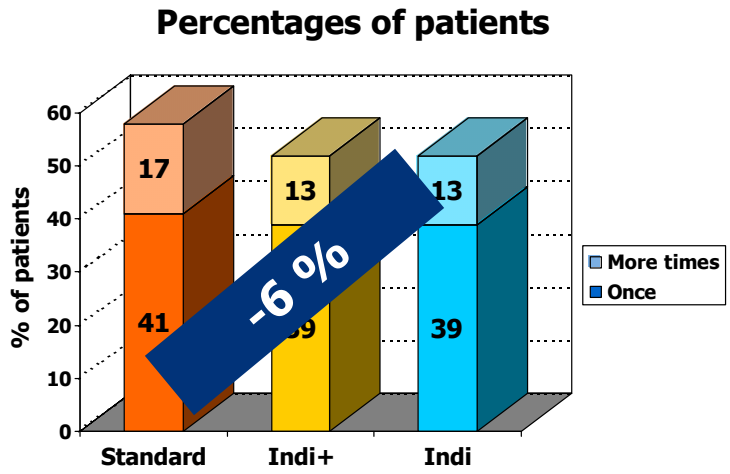
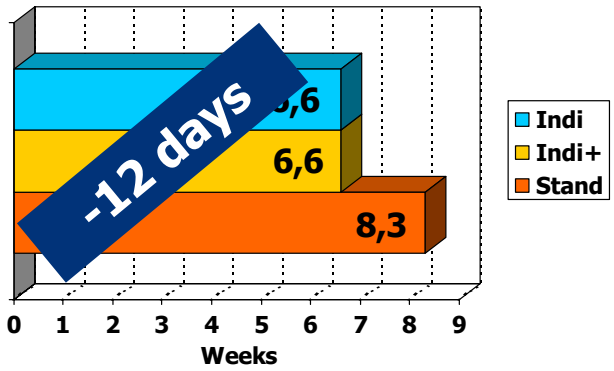
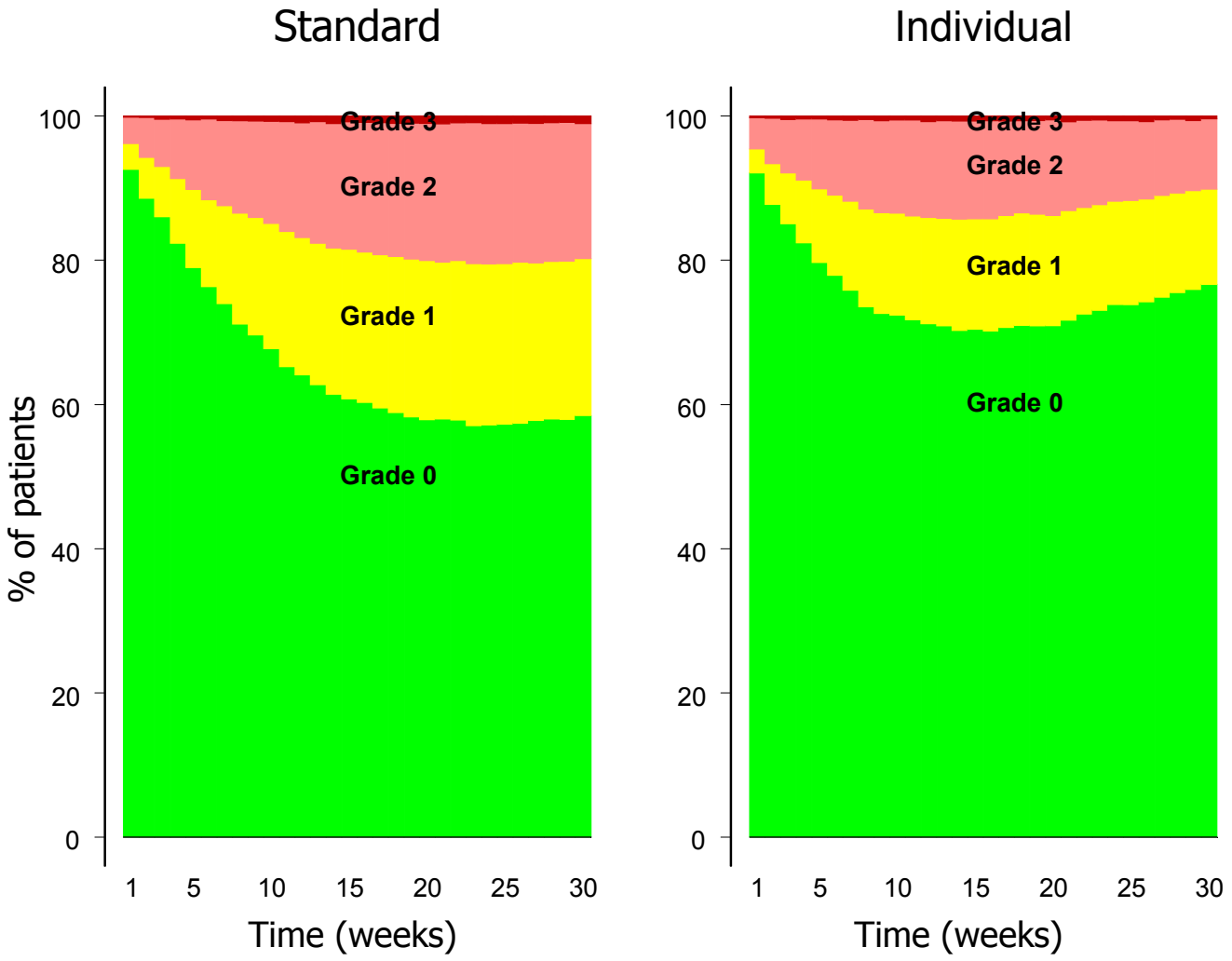




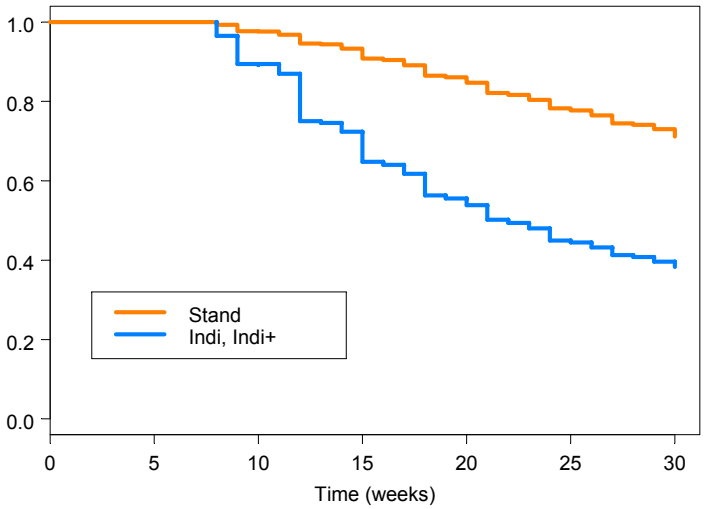


Evolution of the HFS during the 30 weeks of the trial

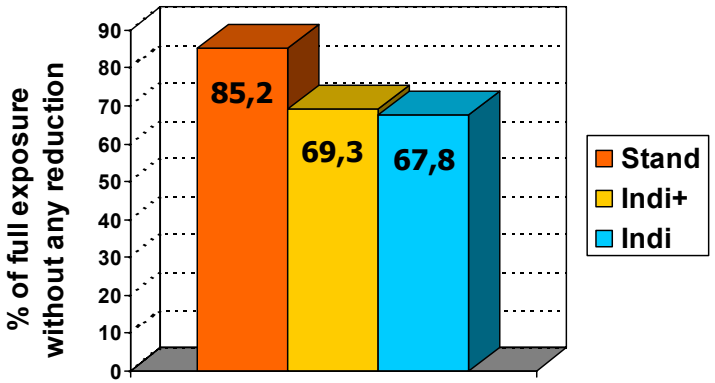


REDUCTION OF TREATMENT

Treatment duration



Drug exposure



STATISTICAL POWER ANALYSIS

100 replications of trials with

- 300 patients per arm
- 400 patients per arm
- 600 patients per arm

Wilcoxon test used to estimate the significance of reduction in **severe toxicity duration**

CONCLUSION:

600 patients per arm are needed to achieve at least a 90% statistical power for a significant (α=0.05) reduction of severe HFS duration.

Results of **Individual+**

- 29% of patients concerned
- No significant increase in toxicity
- Drug exposure of these patients:
  - **Indi** mean: 98.9% of nominal exposure
  - **Indi+** mean: 104.5% of nominal exposure

  → Relative increase: 5.7%

CONCLUSIONS
Benefits

- **Individualized** dose adaptation on the basis of **ordinal** observations showed to be **feasible** and **beneficial**.

- The benefits could be :
  - **↘ 13%** for **incidence**
  - **↘ 12 days** for **duration**
  - **early detection** of **intolerant** patients
  - safe **intensification** of treatment (up to **+50%**) if no previous toxicity

CONCLUSIONS

Limitation

Utility of dose adaptation in this particular case is hindered by a certain **inertia** of toxicity assumed by the model

(true cumulative nature of the drug
or bias of the data and/or model)

CONCLUSIONS

Perspectives

- Application of this methodology for **more reactive drug-toxicity systems** should provide a higher benefit.
- Extension to **multiple toxicities**.
- Incorporation of tumor and survival models for evaluation of the impact on **anti-cancer efficacy** and eventually dose adaptation by **targeting both therapeutic objectives**: maximum effect and minimum toxicity.
- Development of a **web-based application** for dose adaptation for use in clinical routine.

ACKNOWLEDGEMENTS (1/2)

TherapeutiC Targeting in Oncology team in Lyon Sud

Academic (EA3738)

- **Senior/Junior Methodologists (PhD)**
- **Doctorants, masters** (Engineers, Clinicians, Pharmacists)

Clinical - Academic

- **Clinicians (MD, PhD) Pharmacists (PharmD, PhD)**
- **ARC / IATOS**

ACKNOWLEDGEMENTS (2/2)

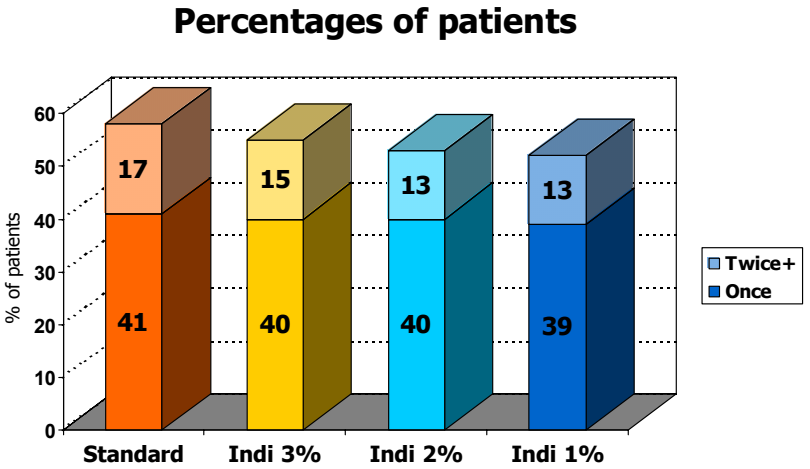
- NOVARTIS for financing my Ph.D. studies
- Roche for providing the capecitabine toxicity data of two Phase III trials

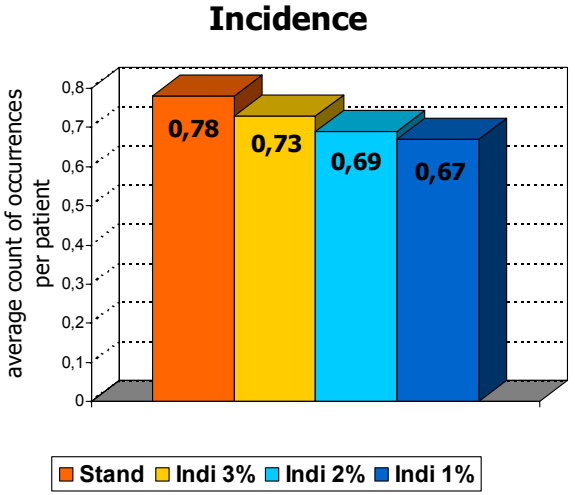
THANK YOU

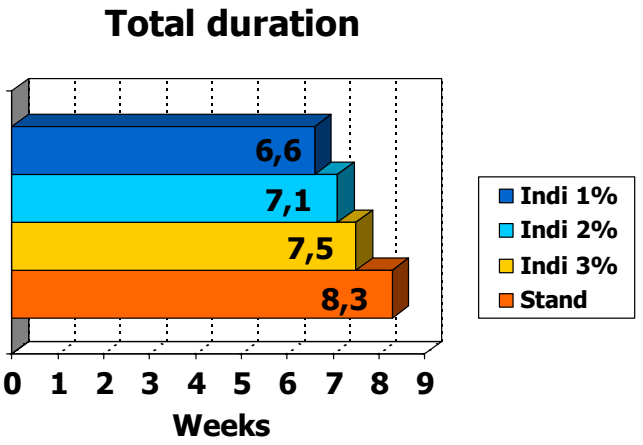
BACKUP SLIDES

SUPPLEMENTAL PROTOCOLS

REDUCTION OF SEVERE TOXICITY

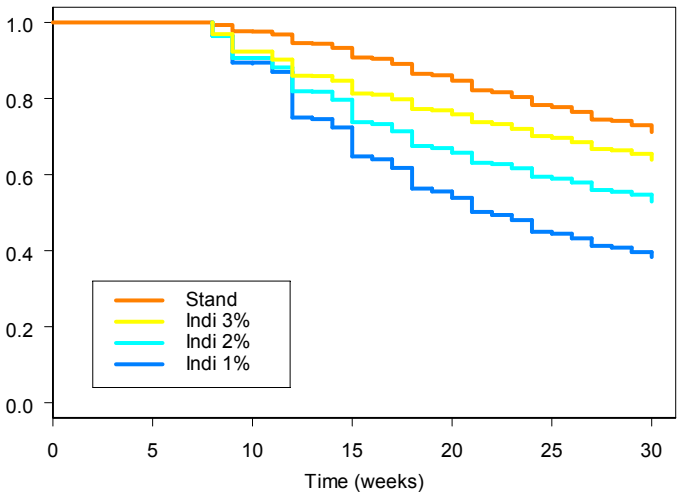




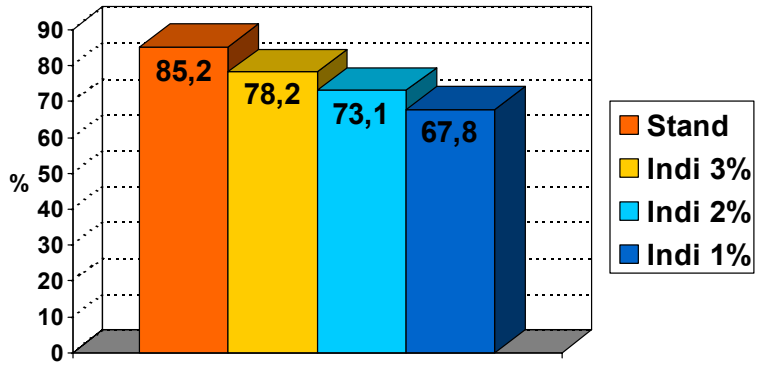


REDUCTION OF TREATMENT

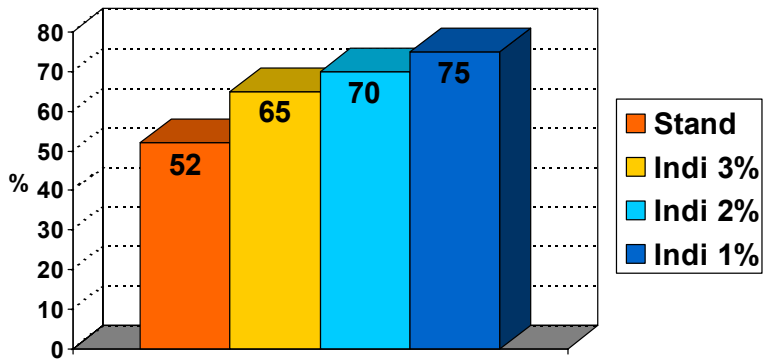
Treatment duration



Drug exposure



Part of patients with reduced doses



Individual B protocol

SPECIAL FEATURE:

no treatment interruption in prevention (grade<2):
50% of the dose even if predicted risk > 1%

RESULTS: ↗ drug exposure BUT ↗ severe toxicities

- Treatment duration: 28.1 weeks (Indi: 21.7 weeks)
- Drug exposure: 72% (Indi: 68%)
- Severe toxicity incidence: 0.74 (Indi: 0.68)
- Part of patients with severe toxicity: 55% (52%)
- Duration of severe toxicity: 7.5 weeks (Indi: 6.6 weeks)

Pop protocol

SPECIAL FEATURE:

Dose calculation is based on predictions given by average **population** model.

RESULTS: ↗ drug exposure BUT ↗ severe toxicities

- Treatment duration: 23.4 weeks (Indi: 21.7 weeks)
- Drug exposure: 72% (Indi: 68%)
- Severe toxicity incidence: 0.69 (Indi: 0.68)
- Part of patients with severe toxicity: 53% (52%)
- Duration of severe toxicity: 7.1 weeks (Indi: 6.6 weeks)

Exact protocol

SPECIAL FEATURE:

Dose calculation is based on predictions given by **true** individual model (with ETAs used for simulation).

RESULTS: light ↗ drug exposure AND ≈ toxicity

- Treatment duration: 22.9 weeks (Indi: 21.7 weeks)
- Drug exposure: 71% (Indi: 68%)
- Severe toxicity incidence: 0.68 (Indi: 0.68)
- Part of patients with severe toxicity: 52% (52%)
- Duration of severe toxicity: 6.6 weeks (Indi: 6.6 weeks)

ESTIMATION METHODS

MODE

- **Local** maximization:
  - simplex (Fortran)
  - quasi-Newton (NONMEM)
- **Global** maximization:
  - Recursive Random Search (RRS) (Fortran)

MEAN, MEDIAN

- **Bayesian** estimation by MCMC (WinBUGS)

COMPARISON OF OPTIMIZATION METHODS

	Simplex	*% of SD(true) (Simplex)*	NONMEM	Recursive Random Search
Bias.eta1	0.120	*12.6%*	0.102	0.120
Bias.eta2	0.086	*5.8%*	0.098	0.085
MAE.eta1	0.592	*62.3%*	0.608	0.592
MAE.eta2	0.595	*40.5%*	0.607	0.595
Cor.eta1	0.524		0.488	0.524
Cor.eta2	0.821		0.814	0.821
Time	5″		21″	5′ 40″

Results of 1000 patients with 29 observations and at least one non-zero grade among them

$$Bias = \frac{1}{N}\sum_{i=1}^{N}(\hat{\eta} - \eta) = \frac{1}{N}\sum_{i=1}^{N}\hat{\eta} - \eta \qquad MAE = \frac{1}{N}\sum_{i=1}^{N}|\hat{\eta} - \eta|$$

COMPARISON OF ESTIMATORS

	Mean (WinBUGS)	**Median** (WinBUGS)	**Mode** (Simplex)
Bias.eta1	-0.029	0.015	0.101
Bias.eta2	-0.014	-0.016	0.076
MAE.eta1	0.587	0.584	0.586
MAE.eta2	0.597	0.599	0.605
Cor.eta1	0.491	0.493	0.507
Cor.eta2	0.810	0.810	0.808
Time	7h 52’	7h 52’	4”

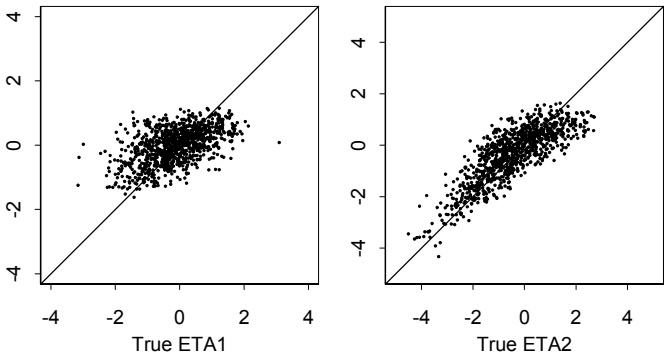
Results of 839 patients with 29 observations and at least one non-zero grade among them

$$Bias = \frac{1}{N}\sum_{i=1}^{N}(\hat{\eta} - \eta) = \frac{1}{N}\sum_{i=1}^{N}\hat{\eta} - \eta$$

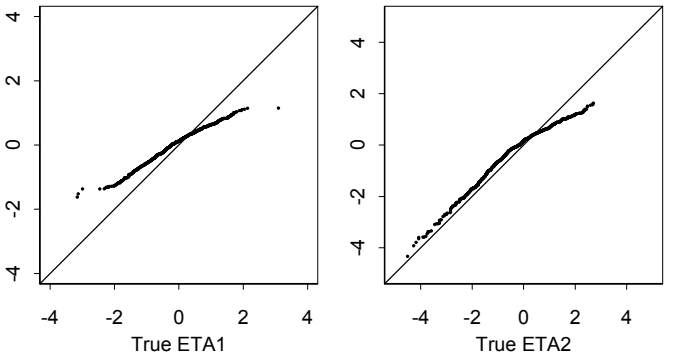
$$MAE = \frac{1}{N}\sum_{i=1}^{N}\left|\hat{\eta} - \eta\right|$$

COMPARISON OF ESTIMATION QUALITY

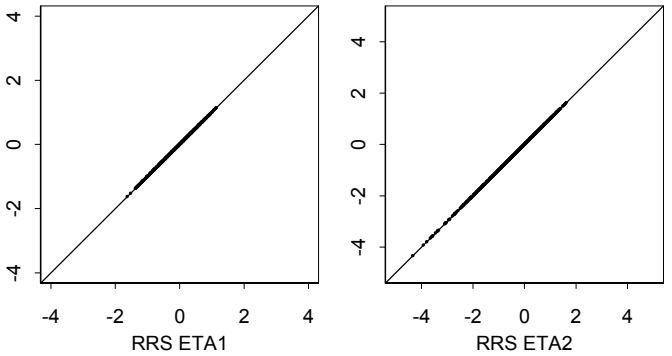
Simplex estimates vs. True values



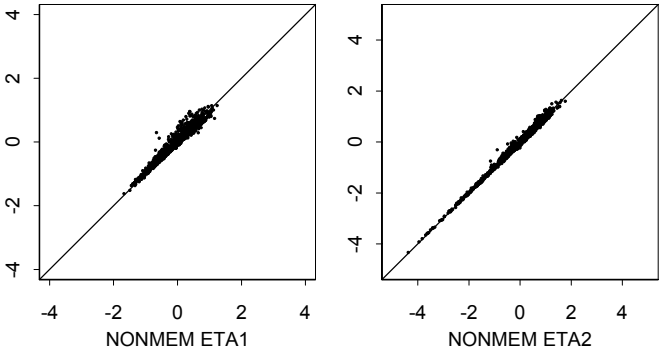
QQ-plot: Simplex estimates vs. True values



Simplex estimates vs. RRS estimates



Simplex estimates vs. NONMEM estimates



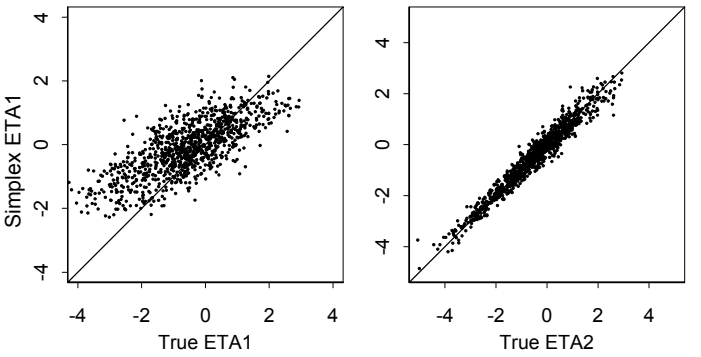
Estimation quality having more observations

	29 obs.	100 obs.	200 obs.
Bias.e1	-0.116	-0.129	-0.097
Bias.e2	-0.088	-0.040	-0.005
MAE.e1	0.626	0.439	0.376
MAE.e2	0.620	0.370	0.301
cor.e1	0.464	0.767	0.835
cor.e2	0.800	0.934	0.958

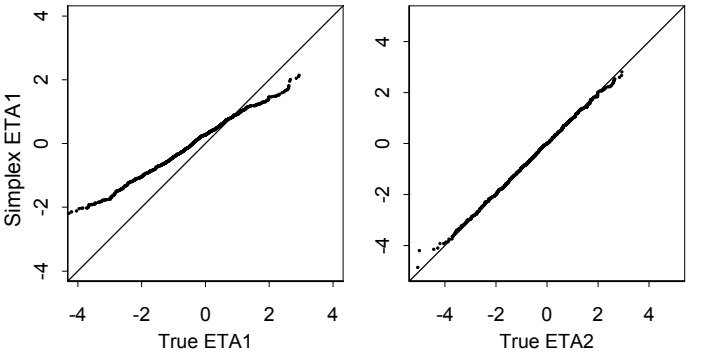
Simplex mode estimates,
the same 1000 subjects with at least one severe toxicity,

Standard dose adaptation

Simplex estimates vs. True values, 200 obs.



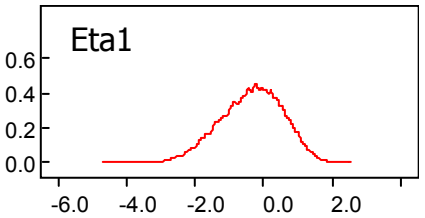
QQ-plot: Simplex estimates vs. True values, 200 obs.



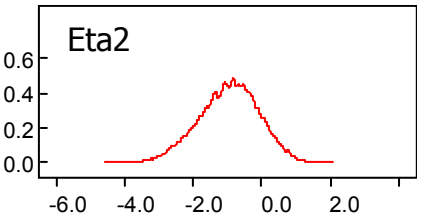
Confidence intervals of the estimates given by Bayesian estimation (WinBUGS)

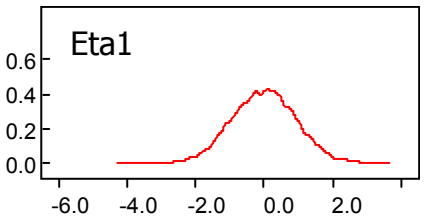
- Nominal dose = 4226
- CLcr = 73
- HFS grades: 0,0,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,0,0,0,0,1,1,1,1,1,1
- True ETA = (-0.34, -0.00)
- MAP estimate = (-0.18, -0.76)

	2.5%	mean	median	97.5%	SD	Prior SD
Eta1	-2.23	-0.35	-0.29	1.25	0.91	0.95
Eta2	-2.74	-0.96	-0.91	0.65	0.87	1.5

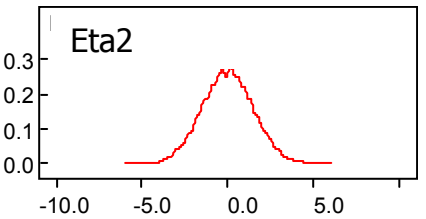


POSTERIOR DISTRIBUTIONS





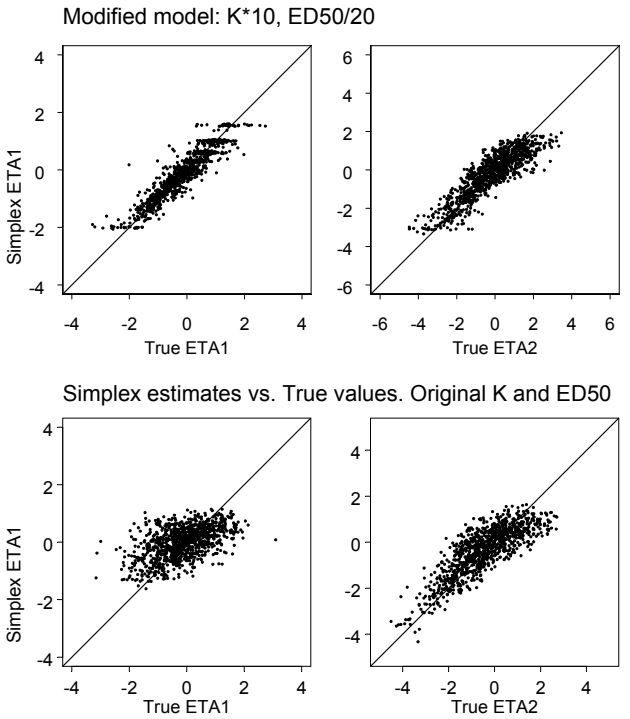
PRIOR DISTRIBUTIONS



Estimation quality for a model with a more reactive dose-toxicity relation

	Model with ED50*0.05 K*10	Original model
Bias.eta1	0.005	0.120
Bias.eta2	-0.041	0.086
MAE.eta1	0.234	0.592
MAE.eta2	0.531	0.595
cor.eta1	0.933	0.524
cor.eta2	0.877	0.821

Simplex, 29 observations, 1000 subjects



I. Uncertainty of the proposed dose

(Sensitivity of the proposed dose to the values of ETAs)

II. Inertia of the risk

(lack of impact on the risk of a 1 cycle drug amount)

Example of treatment

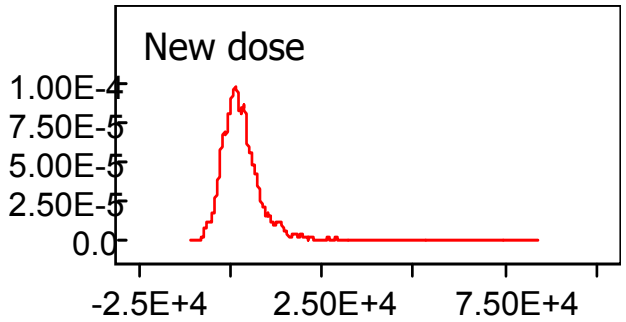
Cycle	Dose	Grades of HFS
1	4784	0,0,0
2	4784	0,0,0
3	4784	0,0,0
4	4784	0,1,1
5	**?**	

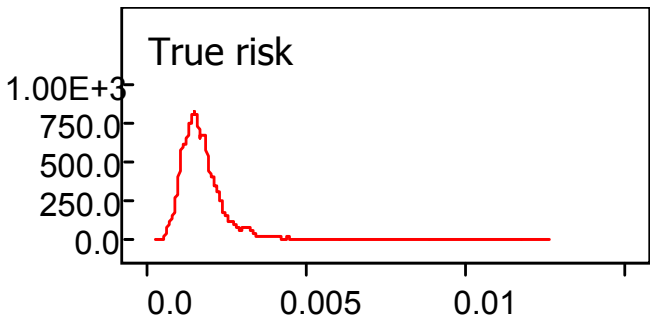
Doses and **risks** according to taken ETA **estimates**

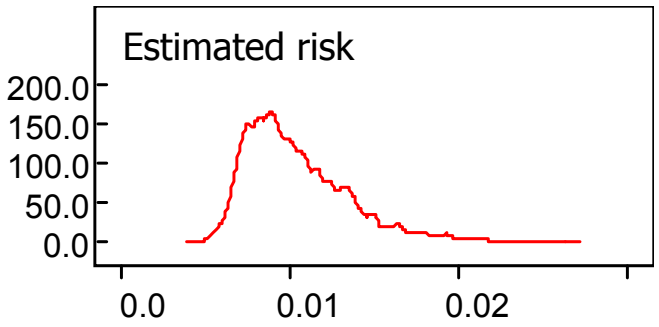
	ETAs	Dose	True risk	Estimated risk
Exact	(0.00, 1.56)	**100**% (33166 ≈ 693%)	0.002	-
Mode (MAP)	(-0.16, -0.51)	**0** (1194 ≈ 25%)	0.0014	0.0096
Mean	(-0.07, -0.33)	**69%** (3303)	0.002	0.011
Median	(-0.06, -0.32)	**0** (2294 ≈ 48%)	0.0014	0.01
Pop	(0, 0)	**88**% (4186)	0.002	0.0089

Distributions (WinBUGS)

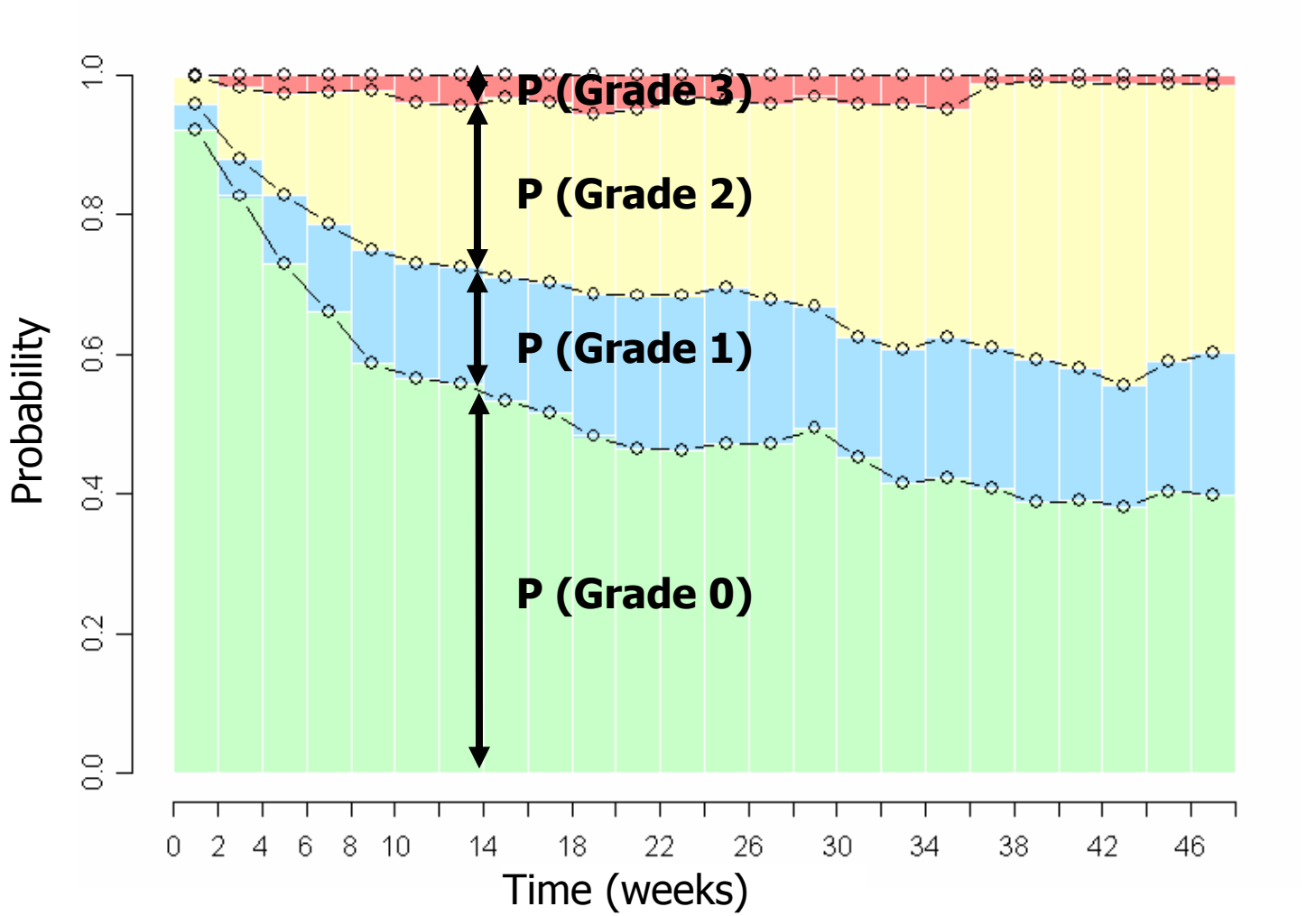
	Mean	SD	2.5%	Median	97.5%
Eta1	**-0.074**	**0.82**	**-1.72**	**-0.063**	**1.499**
Eta2	**-0.330**	**1.00**	**-2.27**	**-0.317**	**1.748**
New dose	**3303 (69%)**	**6096**	**-5125**	**2294 (48%)**	**19080**
True risk [w+1]	**0.002**	**0.0008**	**0.0008**	**0.002**	**0.004**
Estim.risk [w+1]	**0.011**	**0.003**	**0.006**	**0.01**	**0.019**







EVOLUTION OF THE HAND-AND-FOOT SYNDROME:
600 patients, 2500 mg/m²/day, 1 year

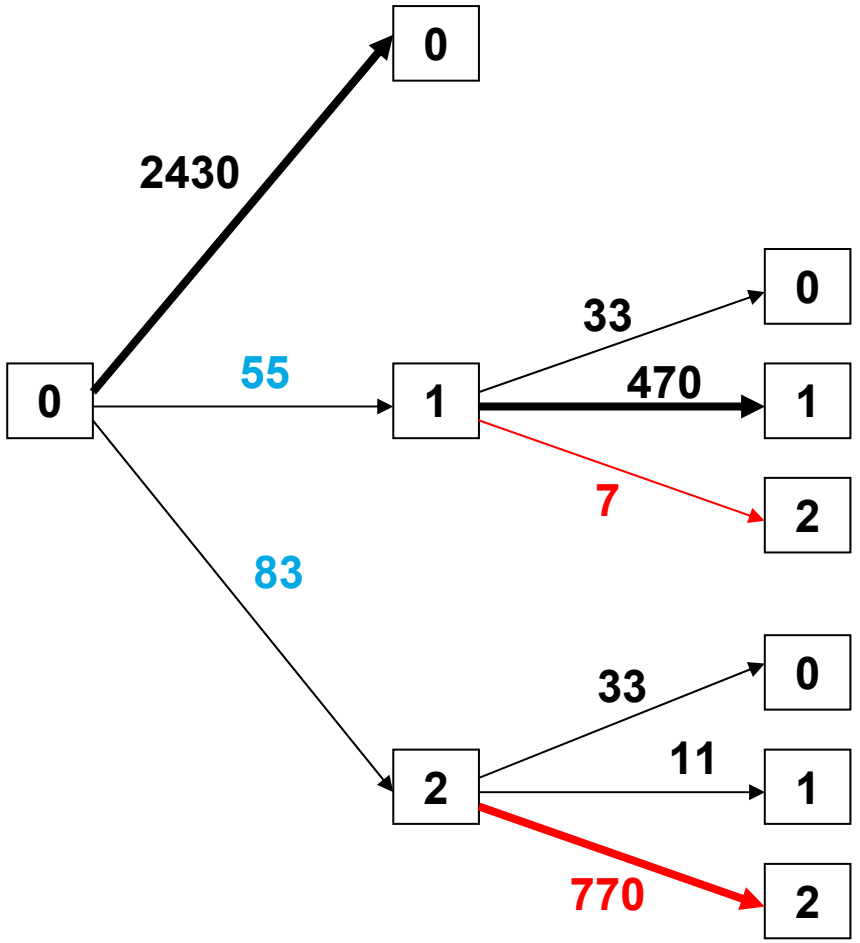


Source: Hénin *et al.,* A predictive model of Hand-and-Foot Syndrome dynamic in patients receiving capecitabine, manuscript

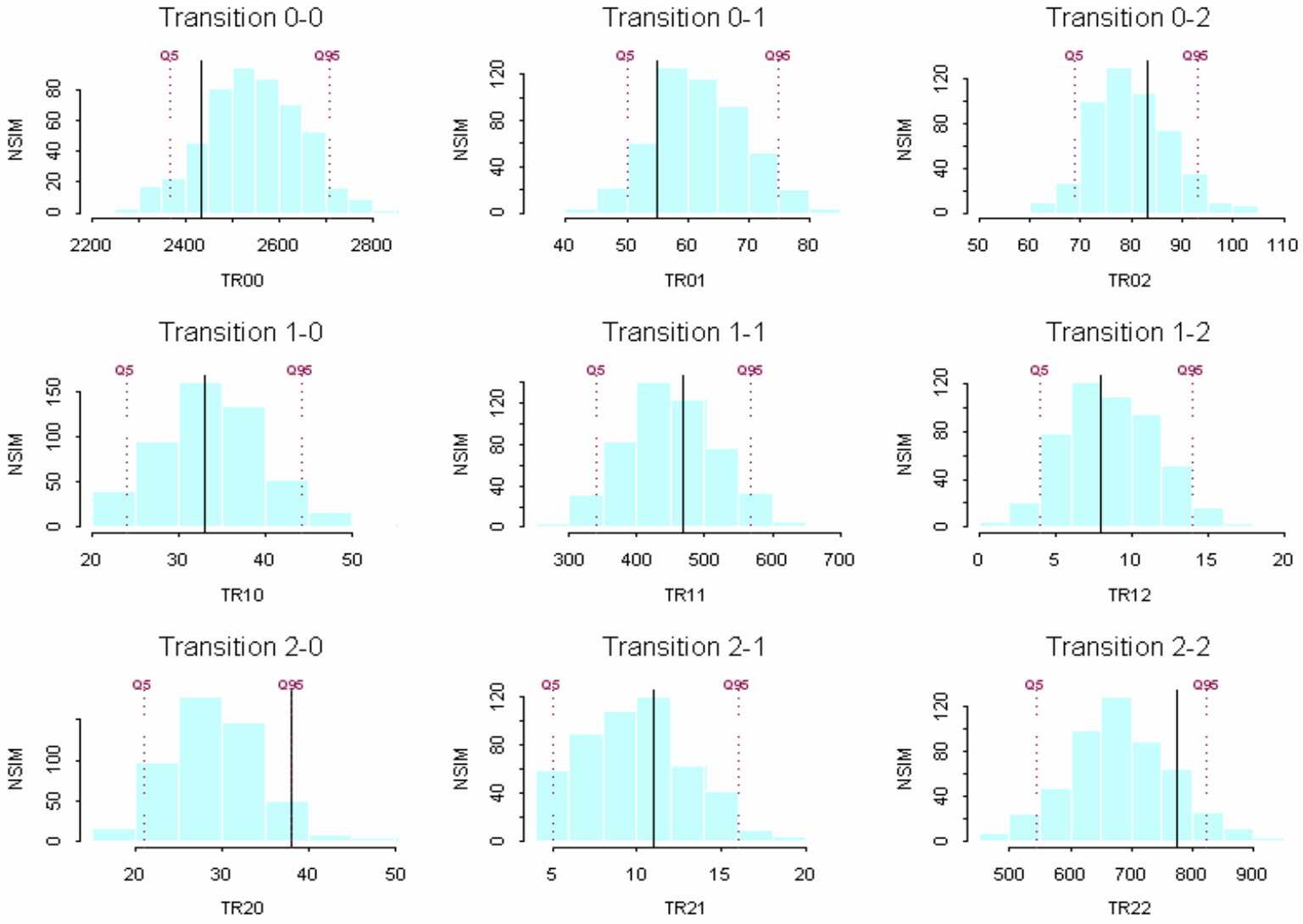
BIAS IN THE DATA?

Transitions between grades in a week

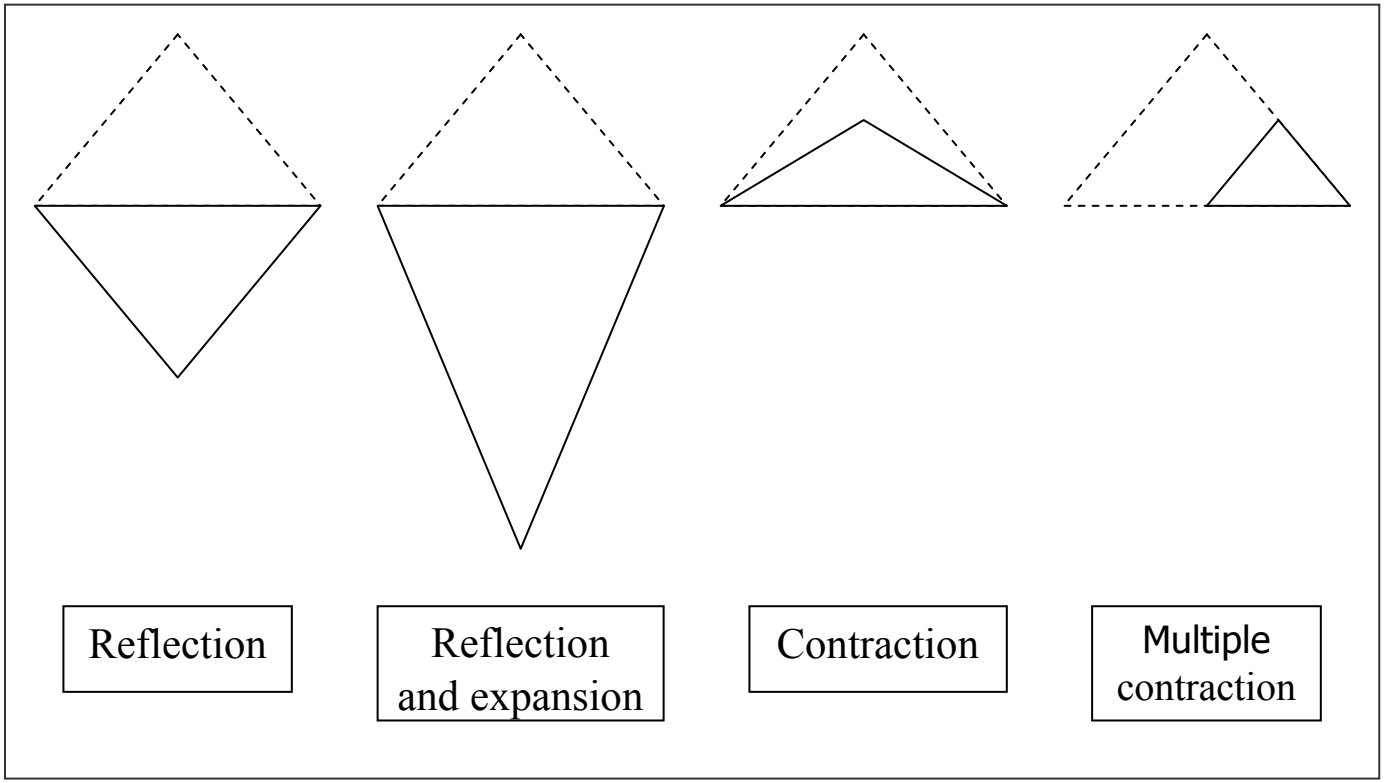
(600 patients)



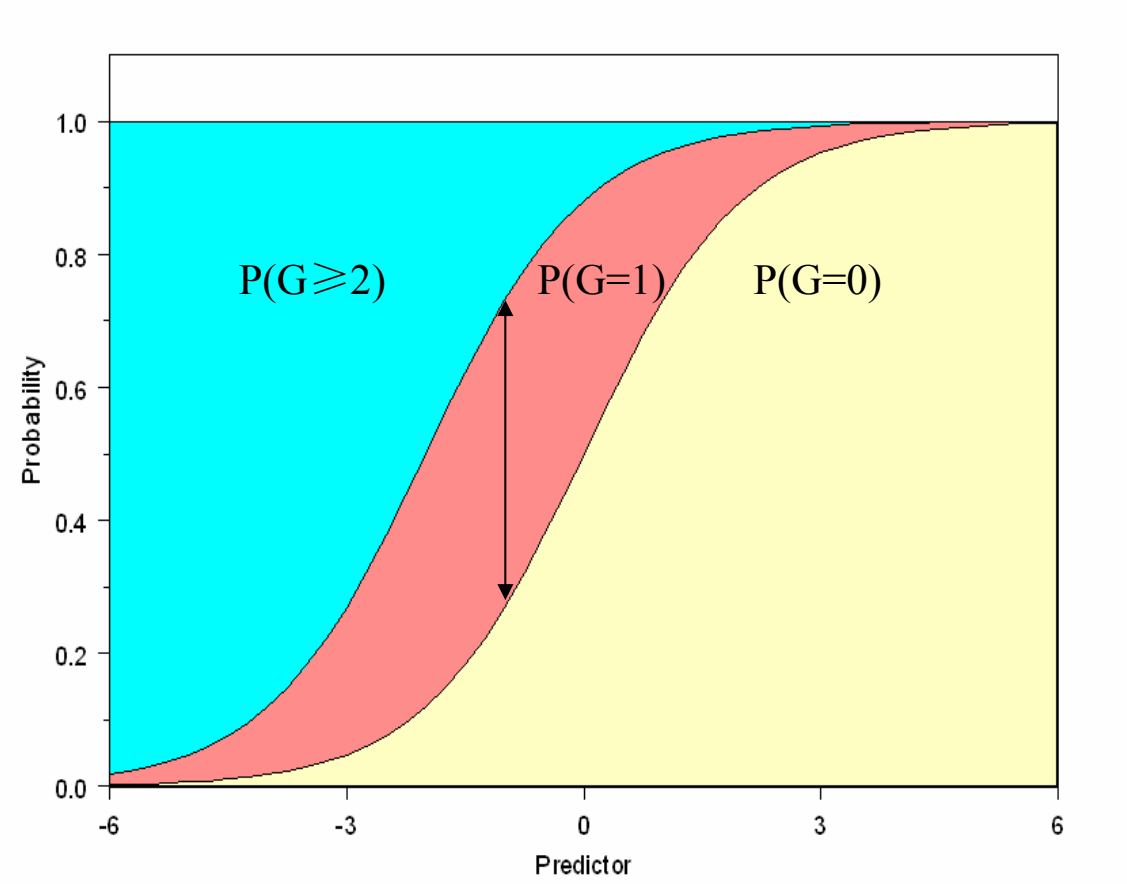
PPC for transitions



Simplex steps



Grade probabilities



Drug exposure

$$\frac{\sum_{t=1}^{T} \text{taken dose}(t)}{\sum_{t=1}^{T} \text{nominal dose}(t)}$$

T – duration of participation in the trial