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# Prior elicitation in early phase clinical trials

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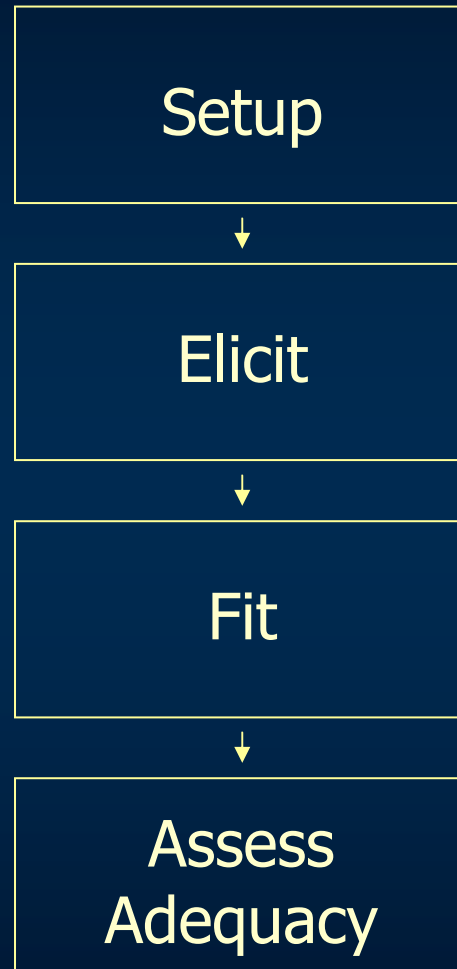
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# Introduction (1)

- Elicitation is the process of formulating a person's knowledge and beliefs about one or more unknown quantities of interest into a probability distribution for those quantities (Garthwaite et al, 2005).
- An elicitation is done well if the distribution that is derived accurately represents the experts' knowledge, regardless of how good this knowledge is.

## The elicitation process (Garthwaite et al, 2005)



# Introduction (2)

## Elicitation of proportions

- direct and relative frequency methods (Berger, 1985)
- parametric approaches (Winkler, 1967)
- non-parametric approaches (Berger and O'Hagan, 1988; Oakley and O'Hagan, 2002)
- semi-parametric approaches (Bornkamp and Ickstadt, 2009 to appear)

# Introduction (3)

Motivation for eliciting prior beliefs in clinical trials:  
(Chaloner and Rhome, 2001)

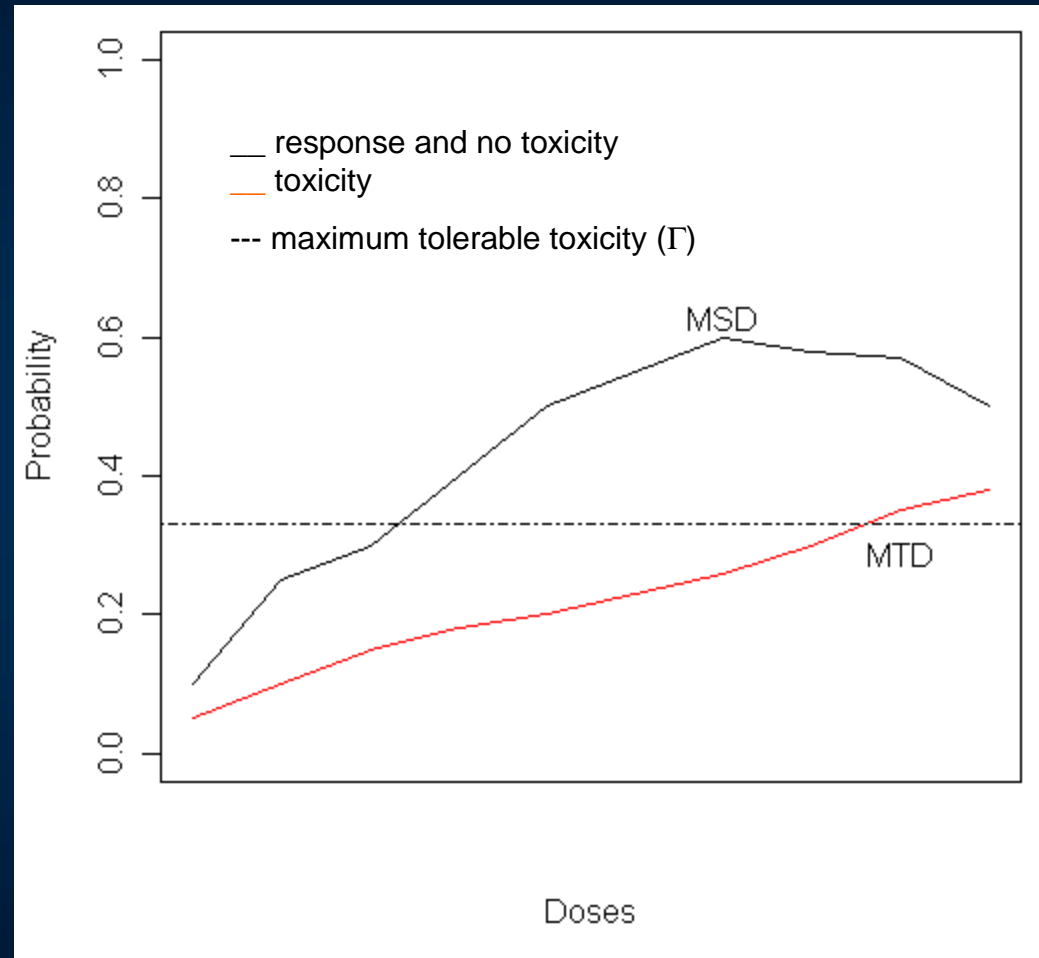
- Design and sample size
- Monitoring
- Bayesian methods
- Hindsight

# Introduction (5)

## Type of early phase drug development trial designs (Piantadosi, 1997; Zohar et al., 2007)

- Phase I: trial design that has as a primary objective identifying the maximum tolerated dose (MTD) to administer
- Phase II: trial design with safety and efficacy estimation as a primary objective
- Phase I/II: aims to locate the most successful dose (MSD) i.e. the dose that maximizes the probability of observing a therapeutic response without toxicity

## Possible relationship between MSD and MTD.



# Objectives

- Commonly used phase I/II dose-finding designs use a Bayesian approach in order to determine the MSD. In this context, Bayesian inference requires incorporation of prior information on the dose-toxicity and dose-success relationships (Legezda 2001; Chaloner 2001).
- The aim of this study was to elicit prior probability distribution from physician's opinion about the available dose levels planned for phase I/II dose-finding clinical trials on human DNA vaccine in HER2 tumours (Zohar et al, submitted).

# Materials and Methods (1)

Prior elicitation process in four stages (O'Hagan 1998; Garthwaite 2005):

1. Expert's selection and identification of the aspects of the problem to elicit:

13 researchers and physician selected

initial guesses about toxicity and efficacy probability of the treatment per dose level (direct method)

2. Interaction with the experts:

Questionnaire sent to the experts with a short cover letter

They were asked not to discuss their answers with one another

# Materials and Methods (2)

## 3. Fit of probability distributions to the expert's summaries:

Different priors for each dose level according to the choice of the percentile of the dose-toxicity distribution of the expert's opinion

- enthusiastic prior 1 – the 10<sup>th</sup> p
- enthusiastic prior 2 – the 25<sup>th</sup> p
- informative prior – median p
- skeptical prior 1 – the 75<sup>th</sup> p
- skeptical prior 2 – the 90<sup>th</sup> p

# Materials and Methods (3)

## 4. Assessing the adequacy of the elicitation:

Simulation study investigating 100 different scenarios (each under the five different priors separately) in terms of dose-toxicity and dose-success relationship.

A phase I/II allocation scheme using a Bayesian inference (Ivanova, 2003) was chosen:

- nonparametric response-adaptive design for the dose allocation scheme
- estimation of the dose–toxicity relationship made using the Bayesian parametric modelling proposed for the continual reassessment method (O’Quigley et al, 1990).

# Materials and Methods (4)

Phase I/II design

Dose space:  $\Omega_d = \{d_1, \dots, d_k\}$

$\Gamma$ =maximal toxicity target

Binary indicators for toxicity ( $Y=1$  if toxicity,  $Y=0$  otherwise) and response ( $V=1$  if response,  $V=0$  otherwise)

$Q(d)$ =probability of toxicity at dose  $d$

$P(d)$ =probability of response without toxicity at dose  $d$

MSD: dose  $d^*$  such that  $P(d^*) = \max_{d \in \{d_1, \dots, d_k\} \& Q(d) \leq \Gamma} P(d)$

# Materials and Methods (5)

Allocation scheme:

Assuming that the most recent subject was treated with dose  $d_j$   
the dose level to be assigned to the next patient is:

- Dose  $d_{j-1}$  if the most recent subject had toxicity
- Dose  $d_j$  if the most recent subject had response with no toxicity
- Dose  $d_{j+1}$  if the most recent subject had no response and no toxicity

# Materials and Methods (6)

The allocation scheme is adjusted by monitoring  $Q(d)$ .

Dose–toxicity relationship:

$$Q(d_j) = \alpha_j^a$$

$(\alpha_1, \dots, \alpha_k)$ : reflects elicited prior beliefs

$a$  : parameter with prior density taken to be  $g(a) = e^{-a}$

# Materials and Methods (7)

After each patient's response, posterior toxicity probabilities at each dose are updated using Bayesian methods.



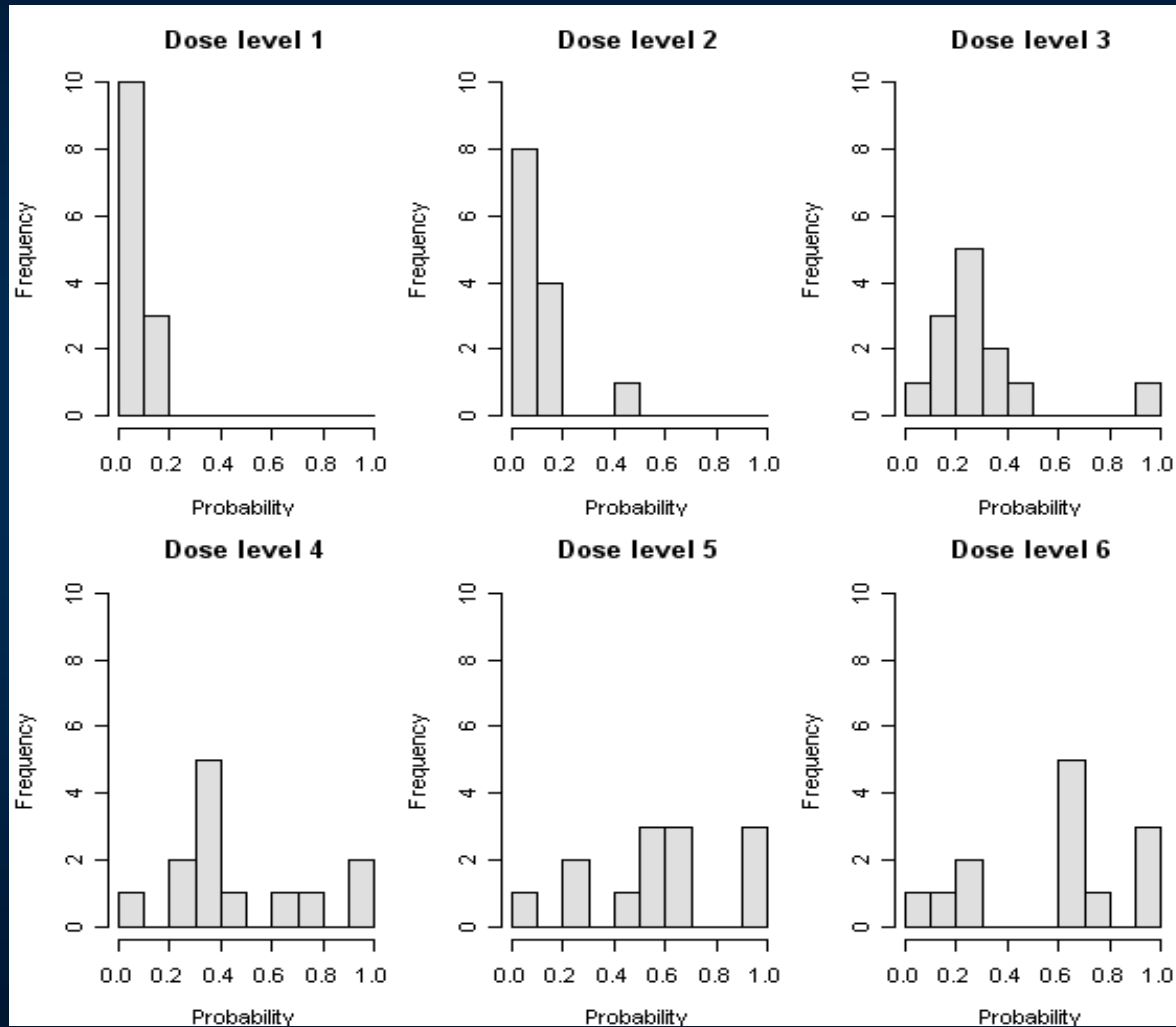
$d^{**}$  : maximum dose-level such that  $P(d^{**}) \leq \Gamma$



Next patient assigned to the dose  $\min(d^{**}, d_{allocation\ scheme})$

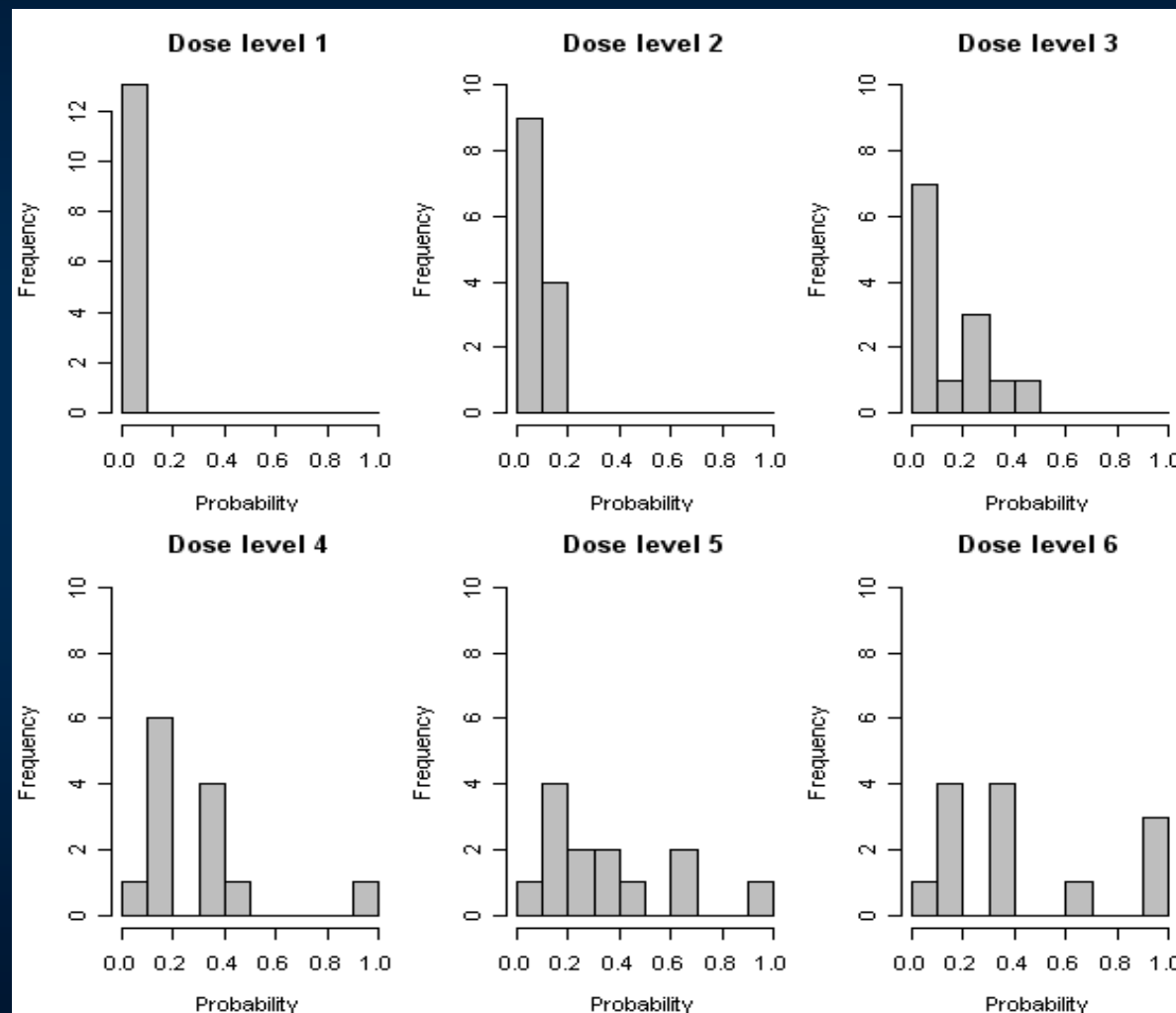
# Results (1)

Response distribution according to the expert's opinion by dose level.



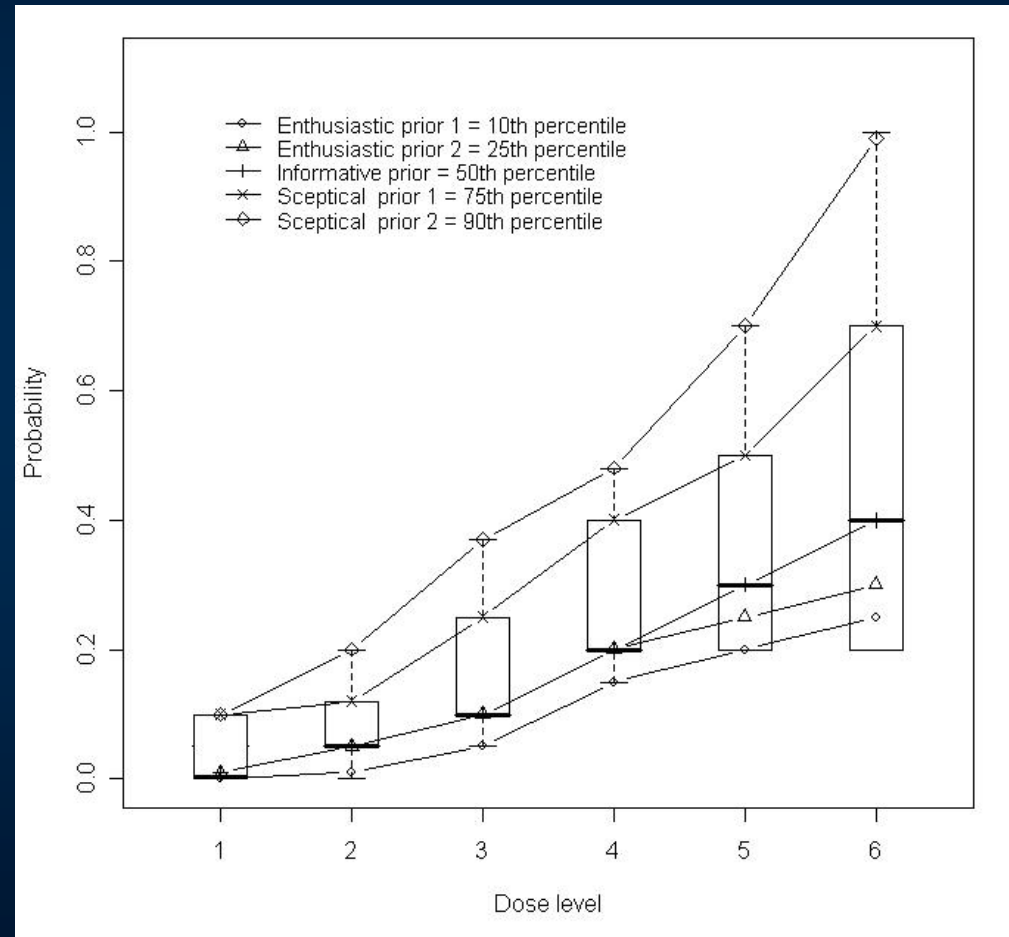
# Results (2)

Toxicity distribution according to the expert's opinion by dose level.



# Results (3)

Prior dose-toxicity relationships defined according to the expert's dose-toxicity distribution.



# Results (4)

<b>PRIOR (DOSE-TOXICITY)</b>	<b>MSD-1</b>	<b>MSD</b>	<b>MSD+1</b>	<b>Median sample size at stopping (Q1-Q3)</b>	<b>Mean % observed toxicities</b>
<b>Enthusiastic prior 1: 0.001 , 0.01 , 0.05 , 0.15 , 0.2 , 0.25</b>	<b>0.19</b>	<b>0.69</b>	<b>0.06</b>	<b>42 (36-54)</b>	<b>10.8</b>
<b>Enthusiastic prior 2: 0.01 , 0.05 , 0.1 , 0.2 , 0.25 , 0.3</b>	<b>0.21</b>	<b>0.65</b>	<b>0.09</b>	<b>44 (37-54)</b>	<b>11.6</b>
<b>Informative prior: 0.01 , 0.05 , 0.1 , 0.2 , 0.3 , 0.4</b>	<b>0.24</b>	<b>0.59</b>	<b>0.12</b>	<b>30 (28-34)</b>	<b>8.1</b>
<b>Skeptical prior 1: 0.1 , 0.12 , 0.25 , 0.4 , 0.5 , 0.7</b>	<b>0.21</b>	<b>0.63</b>	<b>0.07</b>	<b>38 (33-50)</b>	<b>9.3</b>
<b>Skeptical prior 2: 0.1 , 0.2 , 0.37 , 0.48 , 0.7 , 0.99</b>	<b>0.26</b>	<b>0.58</b>	<b>0.07</b>	<b>40 (33-49)</b>	<b>8.4</b>

# Results (5)

- The rate of finding the true MSD is not higher than 70%.
- Enthusiastic prior 1 always gave the higher percentage of correct selection (mean MSQ=0.006)
- Enthusiastic prior 2 always gave the higher median sample size at stopping.
- The informative prior gave the lower percentage of correct selection with the lower median sample size.

# Conclusion

- Introducing subjectivity into a scientific process by using expert opinion is a controversial issue.
- Caution must be taken when using predefined questionnaires since appropriate training for the clinicians to properly understand what exactly is expected from them is required.
- Including in a trial protocol a detailed section on the conduct of the elicitation process and the resulting assessments could be a first step to make the use of assessed distributions acceptable.