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Improving Design, Evaluation and Analysis of Early Drug Development Studies (IDEAS)

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Disclaimer

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Current Statistics training

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Traditional training in Statistics is often

- very general (MSc level)
- highly specialised (PhD level)
- completely isolated from practice
- neglecting transferable skills

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What is IDEAS

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- Pan-European training network
- Focus on early drug development
- Close interaction between academia

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Objectives

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a) train early-stage researchers in state of the art methods for designing, evaluating and analysing early phase studies

b) develop novel methodology for early phase studies through individually supervised, collaborative, research projects

c) provide an international, collaborative environment in which the academic research experience is paired with the challenges of undertaking drug development within the private sector

d) raise awareness about cutting edge methods for designing and analysing early phase studies among trialists and clinicians alike

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Set-up

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- 5 academic partners
- 3 industry partners
- Several associated partners (all industry)
- 14 early stage researchers (ESRs)

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Training

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(i) individually supervised research projects

(ii) transnational, cross-sectorial secondments

(iii) network-wide training activities

(iv) individual training activities

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Secondments

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- Cross-sectorial
- Cross-national
- Minimum 3 months
- Research and daily work

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Network-wide training

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- A week-long kick-off event
- three week-long summer schools
- e-learning courses in statistical methodology
- a think tank
- surgery sessions
- dissemination workshop

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Network-wide training

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- Statistics
- Practical skills
- Networking

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More on IDEAS

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Website	www.ideas-itn.eu
email	ideas@lancaster.ac.uk
Twitter	@IDEAS_ITN

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Two projects on translation

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- Translational aspects in clinical development

ESR:	Eleni Vradi (Bayer)
Industry supervisor:	Dr Richardus Vonk
Clinical advisor:	Prof Damian OConnell (Bayer)
Academic collaborator:	Prof Thomas Jaki (Lancaster University)

- Using pre-clinical information to establish a safe dose in first-in-man studies

ESR:	Haiyan Zheng (Lancaster University)
Academic supervisor:	Dr Lisa Hampson
Clinical advisor:	Dr Malcolm Mecleod (Edinburgh University)
Industry collaborator:	Dr Alun Bedding (AstraZeneca)

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Biomarkers

EFFECTIVE INCORPORATION AND UTILIZATION OF BIOMARKERS IN NONCLINICAL STUDIES

MICHAEL R. BLEAVINS, PhD, DABT
White Crow Innovation, LLC, Dexter, MI

The Role of the Study Director in Nonclinical Studies: Pharmaceuticals, Chemicals, Medical Devices, and Pesticides, First Edition. Edited by William J. Brock, Barbara Mounho, and Lijie Fu.

- WHY we study Biomarkers in preclinical research?
  - Optimize drug development, reduce overall animal use.
  - Test a new biomarker from preclinical studies with the intention of incorporating it into future clinical trials.
  - Not every study or drug has to have a biomarker.
- There are numerous instances where biomarkers offer no value $\Rightarrow$ high attrition rates.
- A poorly choosen biomarker may confound the outcome.

Translation

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Research in Translation

Can Animal Models of Disease Reliably Inform Human Studies?

H. Bart van der Worp[1]*, David W. Howells[2], Emily S. Sena[2,3], Michelle J. Porritt[2], Sarah Rewell[2], Victoria O'Collins[2], Malcolm R. Macleod[3]

- Animal studies do not predict with sufficient certainty what will happen in humans.
- Often fundamental for understanding disease mechanisms, but sometimes less useful in predicting human diseases.
  - Insufficient power to detect a true benefit,
  - Inadequate animal data and overoptimistic interpretation
  - Lack of generalisability
  - Neutral/negative animal studies more likely are unpublished than clinical trials.

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Why translation fails

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- Publication Bias
  - What gets published
- Selection bias
  - What gets published
- Statistics
  - Lack of sample size calculation
  - Wrong analysis (means for ordinal data...)
  - Treating multiple observations from one animal as independent
  - …
- Lack of external validity

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What can be done

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Better

- animal models
- decision making about progression (scoring systems?)
- methods for indentification of biomarkers
  - Eleni's current focus around sparse selection methods
- ...

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Q: How can we use pre-clinical toxicology and pharmacology data to improve Phase I dose-escalation trials?

Current approaches use pre-clinical data to determine a maximum recommended starting dose (MRSD) using allometric scaling:

- Using toxicology data: Human dose $(\mathrm{mg}|\mathrm{kg}^{-1})$= NOAEL $\times(W_A/W_H)^{0.33}$)
- Using PK data: Estimate human PK parameters using allometric scaling, e.g., $Cl_H = Cl_A(W_A/W_H)^b$
- Scale doses by a safety factor of 10 in case of size-independent differences.

Simply allometry can produce inaccurate predictions of human doses (e.g., diazepam, warfarin) leading to conservative or toxic starting doses.

- May be uncertainty about the best choice of allometric exponent
- Likely to be data on several animal species - which species is most relevant?

Investigation interest

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Objectives: To establish a safe dose in phase I first-in-man studies based on a Bayesian model that uses pre-clinical information

Within this Bayesian framework, pre-clinical evidence is incorporated dynamically according to a weight that

- considers the degree of agreement with the dose-toxicity relationship in humans:
  Is the drug predicted more (or less) potent in humans than it actually is?
- will be gradually reduced as increasing human data become available

Note that such a weight is to be computed at each interim analysis.

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Pre-clinical toxicology data

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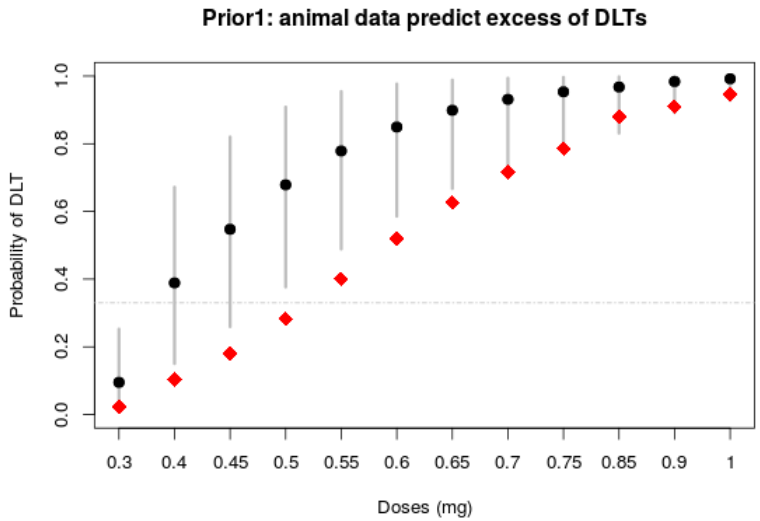
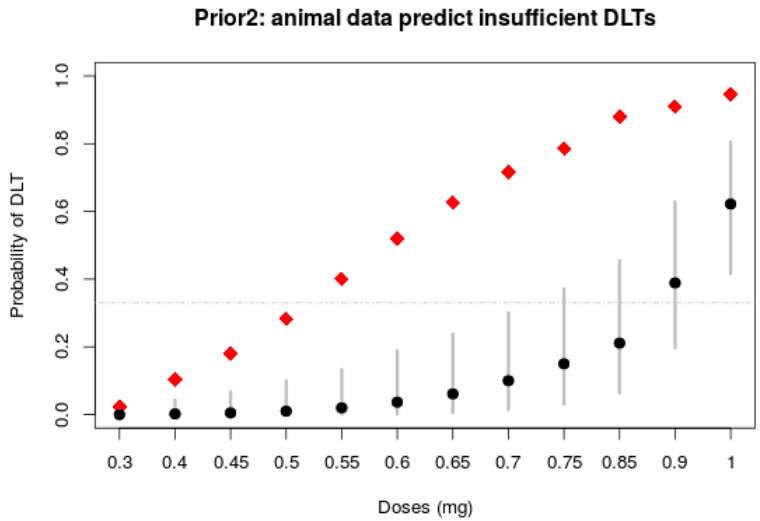
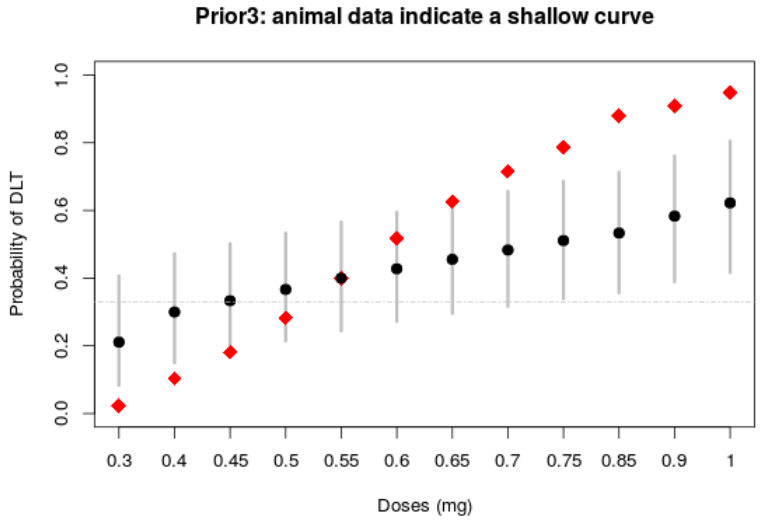
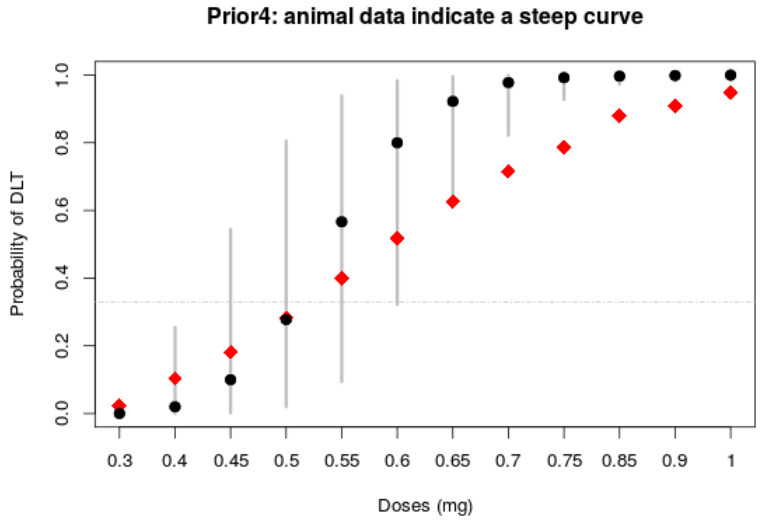
Commensurability issues









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Addressing the potential prior-data conflict

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1. Future observation of DLT ($\tilde{y} = 1$) or not ($\tilde{y} = 0$) are predicted using the prior predictive distribution of $\tilde{y}$,

$$\mathcal{P}\{Y = \tilde{y}\} = \int_{p_j} f(\tilde{y}|p_j)g(p_j)\mathrm{d}p_j,$$

   where $f(\cdot)$ is the link function with the DLT probability p_j, and the pior $g(p_j)$ is formed from pre-clinical studies.

2. Predictions are **optimal** in the sense of maximising the prior expected utility

$$\bar{u}(\eta) = \sum_{\tilde{y}} u(\tilde{y}, \eta)\mathcal{P}\{Y = \tilde{y}\},$$

   where $u(\tilde{y}, \eta)$ is the utility function that rewards/penalises predictions of $\tilde{y}$ as η:

$$u(\tilde{y}, \eta) = \begin{cases} 0, & \text{if } \eta = 0 \text{ while } \tilde{y} = 1 \\ c, & \text{if } \eta = 1 \text{ while } \tilde{y} = 0 \\ 1, & \eta = \tilde{y} \in \{0, 1\} \end{cases}.$$

   Note that $0 < c < 1$.

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Addressing the potential prior-data conflict (*Cont'd*)

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3. The optimal prediction $\hat{\eta}$ is therefore chosen out of the whole decision set $\mathcal{H} = \{0, 1\}$ by maximising the expected utility $\bar{u}(\eta)$:

$$\hat{\eta} = \arg\max_{\eta \in \mathcal{H}} \sum_{\tilde{y}} u(\tilde{y}, \eta) \mathcal{P}\{Y = \tilde{y}\}.$$

4. A 2×2 contingency table for the actual versus predicted DLTs and no-DLTs

		Rewards and Penalties		Counts	
		Actual (y)			
		No-DLT	DLT		
Predicted ($\hat{\eta}$)	No-DLT	u_{00}	u_{10}	n_{00}	n_{10}
	DLT	u_{01}	u_{11}	n_{01}	n_{11}

5. The predictive utility is then calculated at dose d_j as $U^j_{\text{pred}} = \sum_{l=0}^{1} \sum_{m=0}^{1} u_{lm} n_{lm}$, and the predictive accuracy as

$$a_j = \frac{U^j_{\text{pred}}}{\sum_{l=0}^{1} \sum_{m=0}^{1} n_{lm}}.$$

6. The average $\bar{a} = \sum a_j / j$ will be used to down-weight the pre-clinical data.

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Prior tuning

- $\bar{a} \in [0, 1)$, computed at each interim analysis, quantifies the degree of agreement between animal and human toxicology data
- Mixture prior with a weakly informative component will be considered

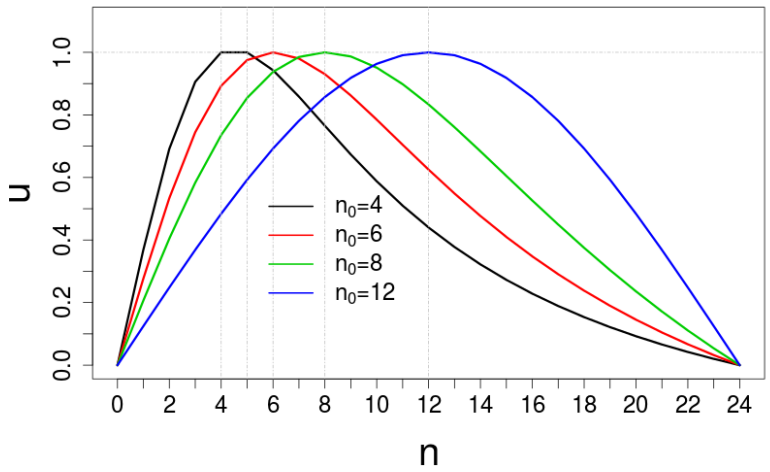
$$f(\theta) = w \times \underbrace{g(\theta)}_{\text{pre-clinical data}} + (1 - w) \times \underbrace{p(\theta)}_{\text{weakly-informative}},$$

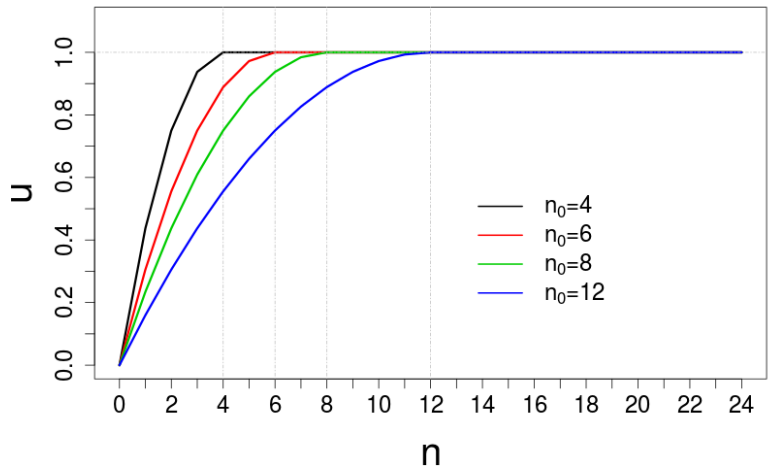
- the weight w is a function of $\bar{a}$, allowing for a flexible borrowing especially when the human data is sparse at the beginning of a trial
- $p(\theta)$ can be either a minimally informative prior (Neuenschwander et al., 2008) or an operational prior (Whitehead and Williamson, 1998)

The pre-clinical data weight

Define the weight as $w = u \times \bar{a}$, where the multiplicative factor u governs how influential the pre-clinical data are as the trial proceeds.

- Two possible forms of the multiplicative factor u, expressed as a function of the information time n/N (say, $N = 24$)





Note that n_0 denotes the length of a run-in period, during which w ranges from 0 to $\bar{a}$. *The left indicates the impact of the pre-clinical data is gradually reduced relative to the weakly-informative component afterwards, while the right suggests $w = \bar{a}$ right after the run-in period and till the end.*

Bayesian logistic regression method

A fully Bayesian approach will be used for dose escalation decisions.

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