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A search for an ethically attractive dose-finding design for a drug with expected narrow therapeutic interval.

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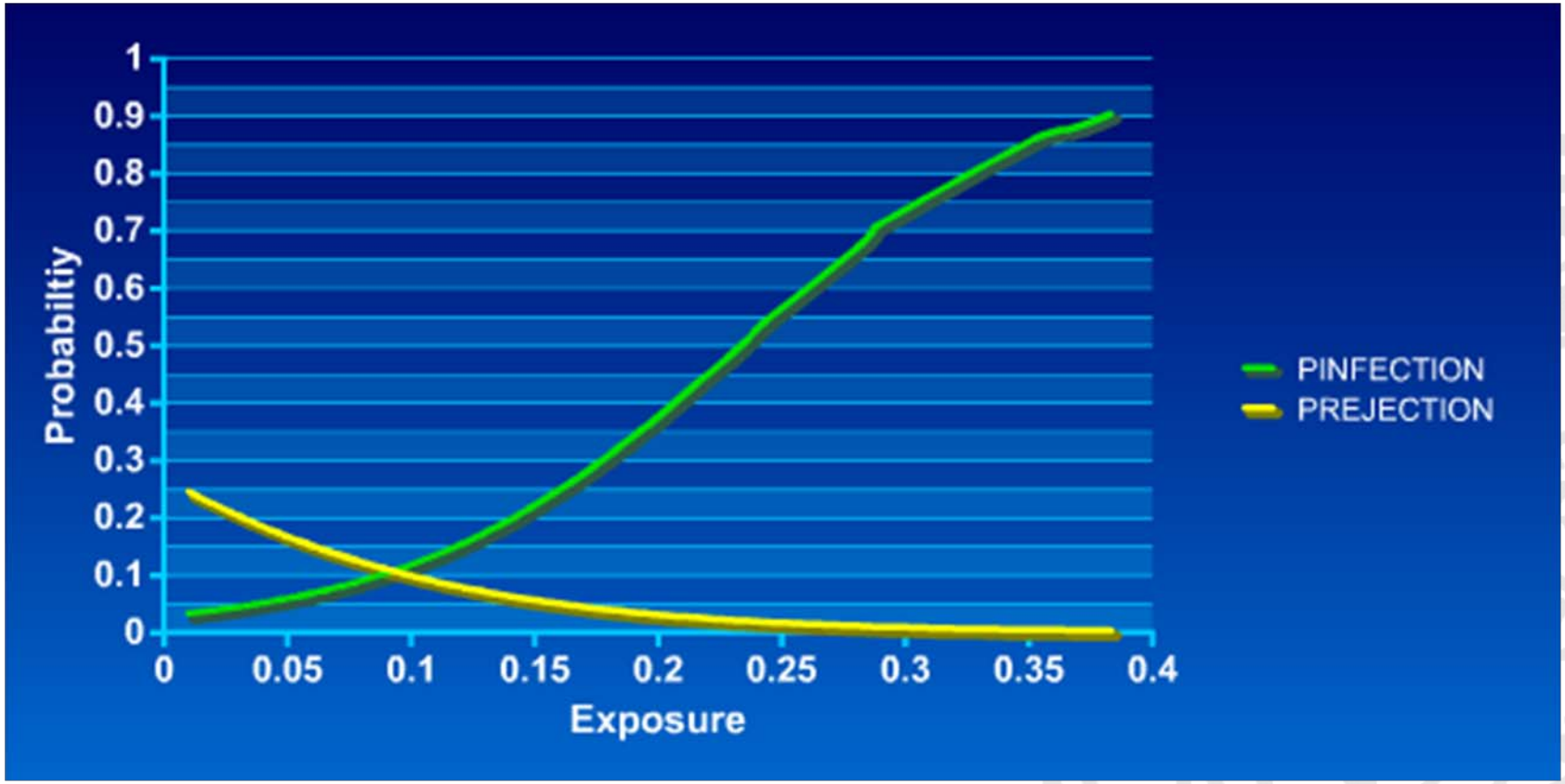
Exposure-response relations



• Methods- 1) PKPD model

PK model	• CL=20L/h var=0.2025 (CV=45%)
Clinical Endpoint models: INFECTIONS & REJECTIONS	• Infections: $Logit_i = Binf + Sinf * C$ $PINF = e^{Logit_i}/(1+e^{Logit_i})$ Binf=-3.5, Sinf=15 • Rejections: $Logit_i = Brej + Srej * C$ $PREJ = e^{Logit_i}/(1+e^{Logit_i})$ Brej=-1, Srej=-12

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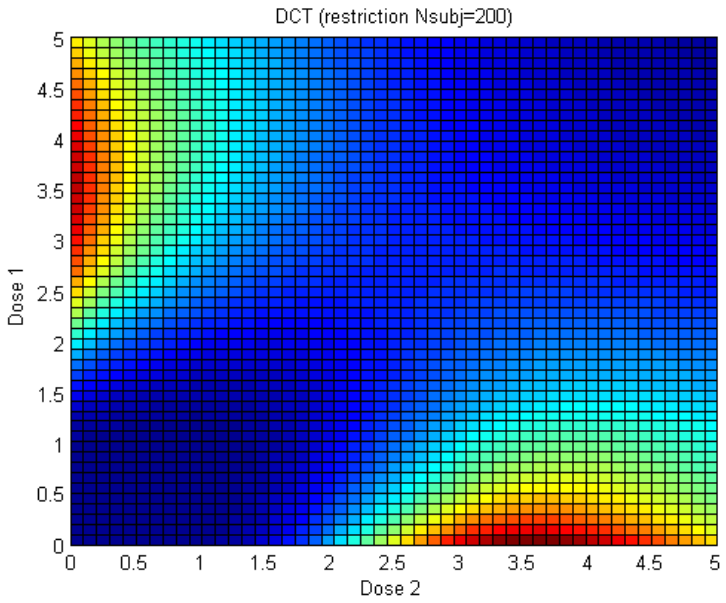
Aims

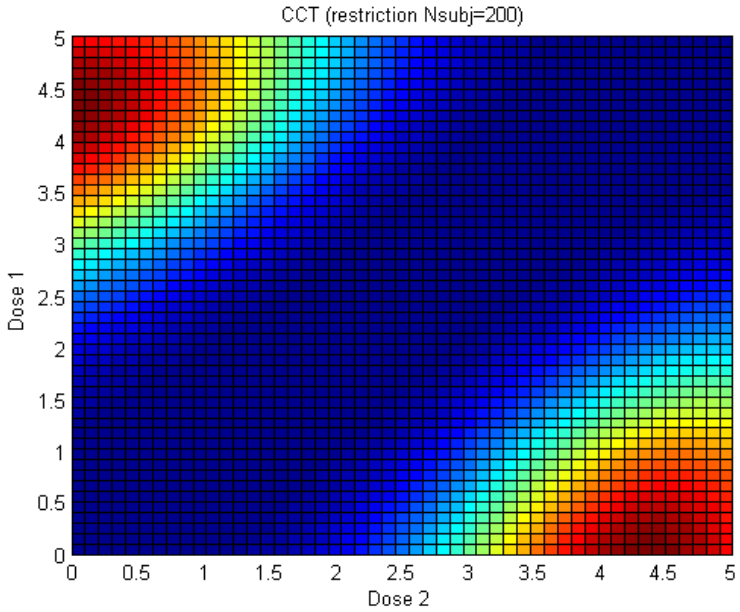
1. Constrast DCT versus CCT
2. Suggestions for a good design that is ethically attractive

Default settings

- D-optimal design for PD parameters (Brej, Srej, Binf, Sinf)
- Optimised across the CL distribution using ED-optimality
- Nsubj = 200
- 2 arms (doses for DCT; concentrations for CCT)
- Equal sized arms
- CLi assumed to be determined without imprecision
- Concentrations perfectly achieved in the CCTs
- No random effects parameters to be determined

- Results
- Optimal designs





CONDITIONS
- 50% of subjects in each group
- Max.subj=200
- Rest of variables (doses,events): unlimitted

	DCT	CCT
Det(FIM)	9.38E-04	2.80E-04
Doselow	0	0
Dosehigh	3.52	4.30
Nsubj Dose low	100	100
Nsubj Dose high	100	100
CV_binf	50%	99%
CV_sinf	55%	110%
CV_brej	51%	51%
CV_srej	125%	148%
#Event_constraint	none	none
#Events	72	75
Num ind	**200**	**200**

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Expected number of events

$$\#Events = \Sigma(Pinf,i) + \Sigma(Prej,i)$$

$$Pinf,i = f(Conc,Binf,Sinf)$$

$$Conc = Dose/CLi$$

$$Prej,i = f(Conc,Brej,Srej)$$

$$Conc = Dose/CLi$$

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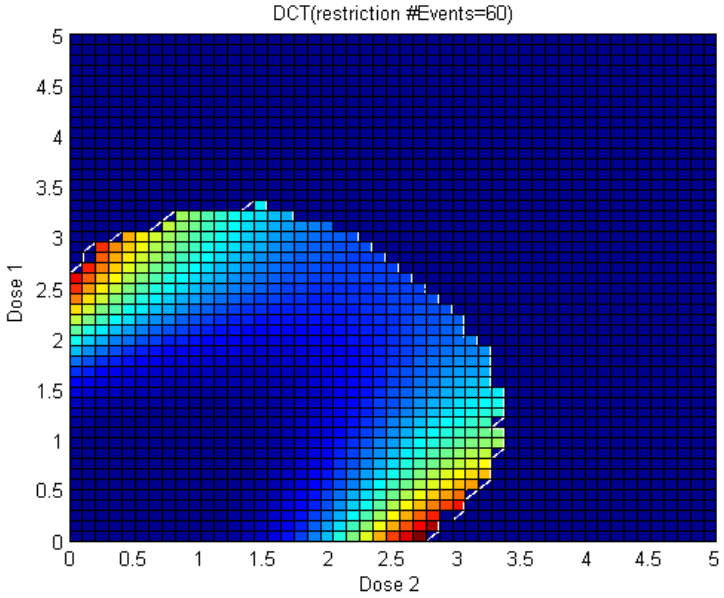
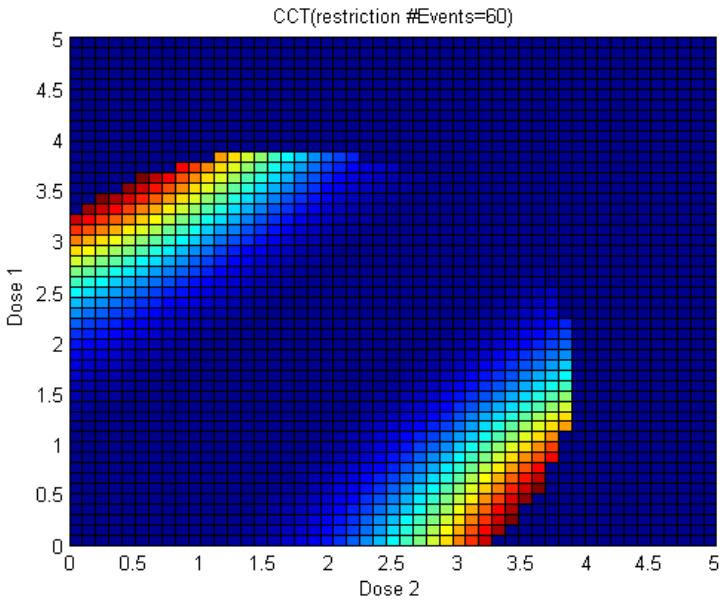
Cost-based designs

- In general, designs can be optimised based on a certain price for each sample, subject, center, dose, etc.
- Design aim can be: Give me the best design for 1M €!
- Alternative view, see the occurance of an unwanted event (rejection or infection) as a ”cost”
- Design aim: Give me the best design allowing X number of unwanted events!

• Results- Event-restricted design

• Optimal designs





CONDITIONS
- 50% of subjects in each group
- Max.events=60
- Rest of variables (doses,subjects): unlimitted

	DCT	CCT
Det(FIM)	7.70E-04	1.81E-04
Doselow	0	0.302
Dosehigh	2.74	3.45
Proportion total	0.5	0.5
Nsubj Dose low	99	100
Nsubj Dosehigh	99	100
CV_binf	50%	89%
CV_sinf	61%	122%
CV_brej	51%	65%
CV_srej	114%	129%
#Event_constraint	60	60
#Ind_constraint	none	none
Num ind	**198**	**200**
#Events	60	60

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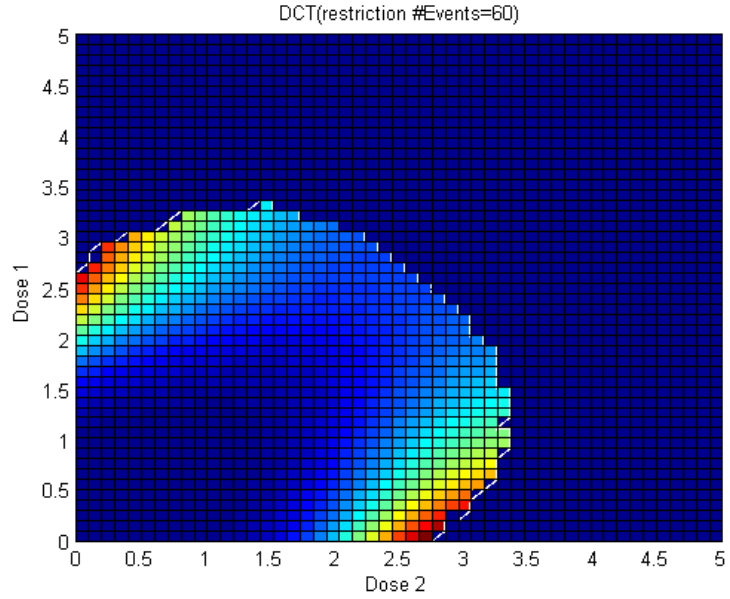
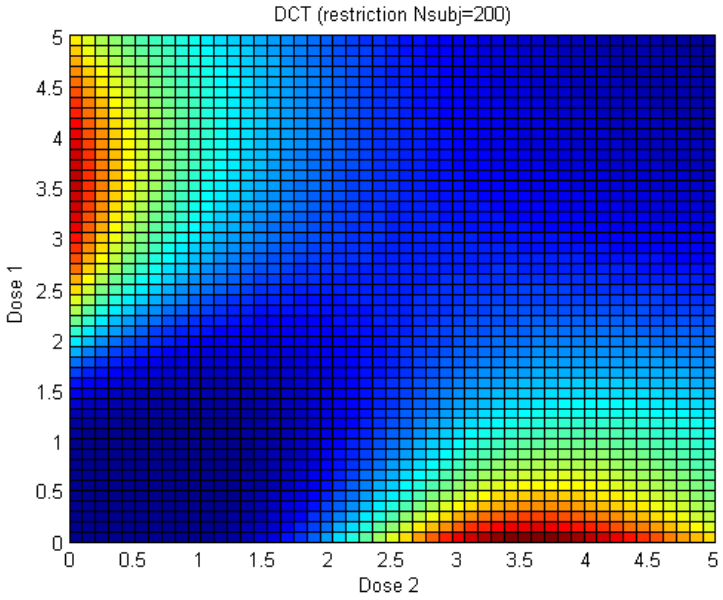
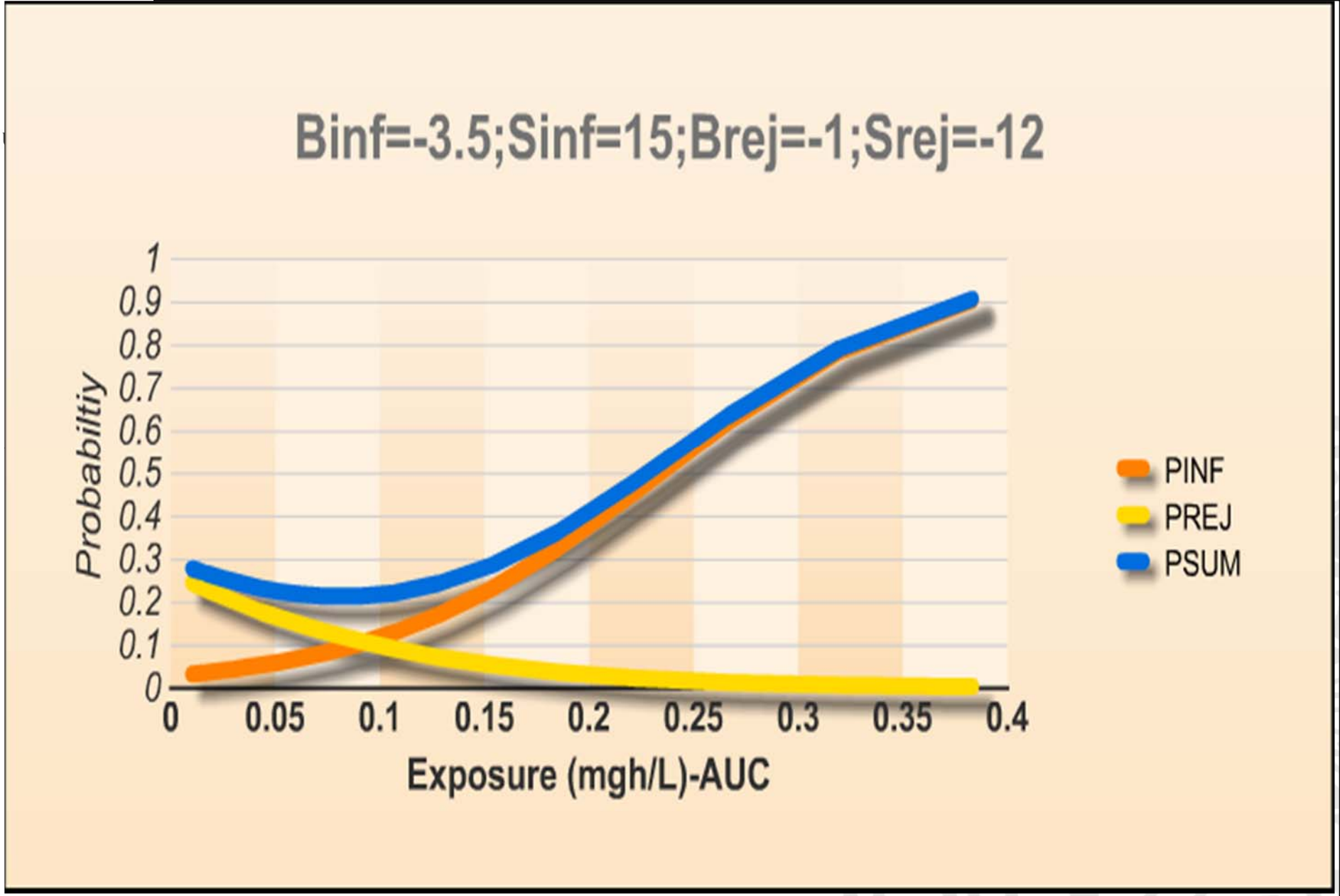
• Comparison for DCTs





	DCT -event	DCT -subj
Det(FIM)	7.70E-04	9.38E-04
Doselow	0	0
Dosehigh	2.74	3.52
Nsubj Dose low	99	100
Nsubj Dosehigh	99	100
CV_binf	50%	50%
CV_sinf	61%	55%
CV_brej	51%	51%
CV_srej	114%	125%
#Event_constraint	60	none
#Ind_constraint	none	200
Num ind	**198**	**200**
#Events	**60**	**72**



Ideal target: 0.082 mgh/L→ PSUM(PINF+PREJ): 0.214

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Ethical dilemma

To obtain information about exposure-response (Brej, Srej, Binf, Sinf), the optimal designs results in a high individual risk (Psum) for an event

A design that minimises individual risk (Psum) will result in a much higher number of events to learn about exposure-response

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Ethical dilemma – aid in making the trade-off

Provide quantitative information about the trade-off between capping the individual risk and total number of events for a given information about the exposure-response

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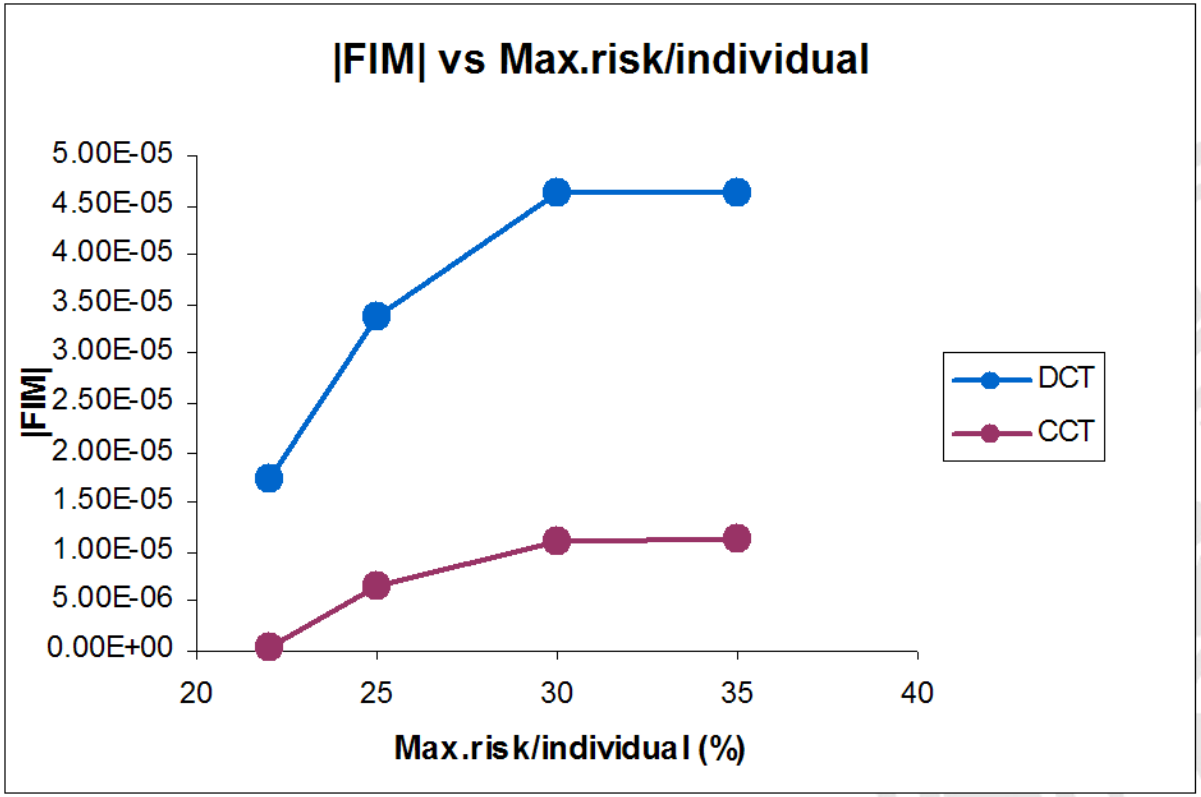
• Results- Part II

iii) restriction in Max.risk/ind.

How much information I gain while increasing the risk/individual?



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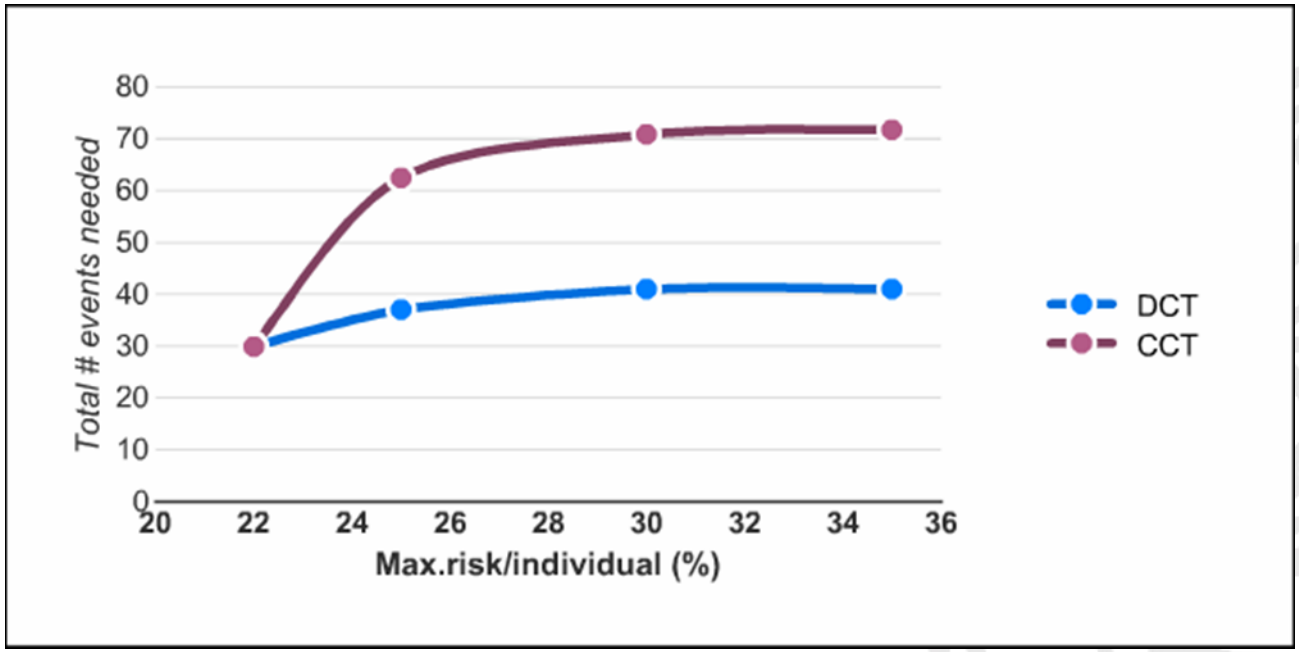
• Results- Part II

iii) restriction in Max.risk/ind.

CONDITIONS
- 50% of subjects in each group
- Optimal doses corresponding to a risk/ind. of 22%

How many events do I need in a trial with max.risk of 22% conditions, to get the same information as when taking higher risk/individual?



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Introduce prior information

Optimise design for use of prior info also in analysis

Weak prior on Brej and Binf

Method used to introduce prior as described by Mentré and co-workers

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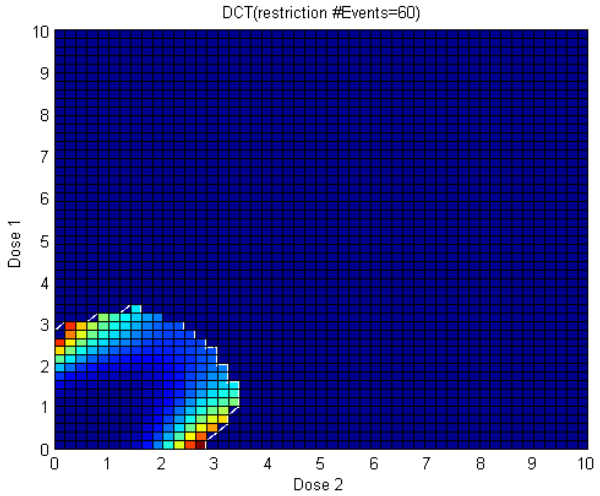
• Results- Part II
• Optimal designs

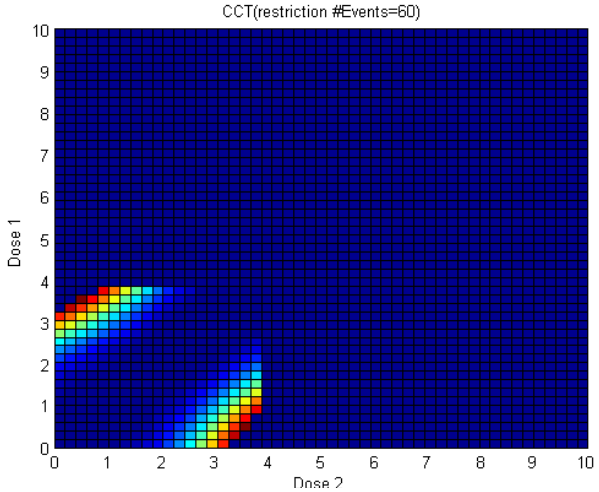
iv) Prior
ii) restriction in #events=60

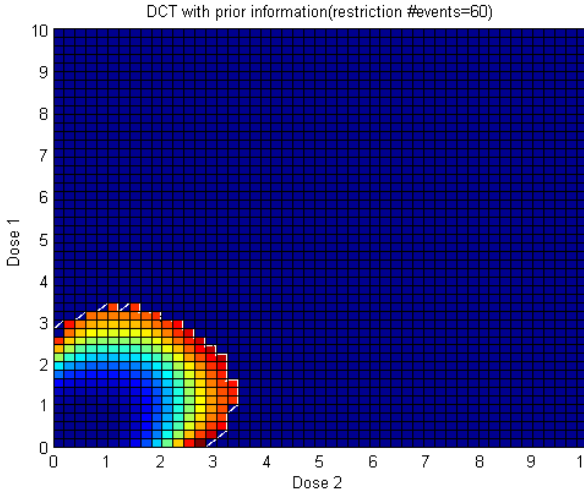
CONDITIONS
- 50% of subjects in each group
- Max.events=60
- Rest of variables (doses,subjects): unlimitted

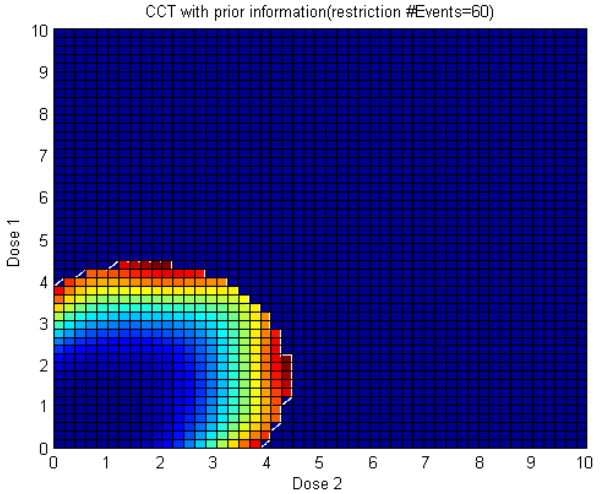
REFERENCE	DCT	CCT
Det(FIM)	7.70E-04	1.81E-04
Doselow	0	0.302
Dosehigh	2.74	3.45
CV_binf	50%	89%
CV_sinf	61%	122%
CV_brej	51%	65%
CV_srej	114%	129%
Num ind	**198**	**200**
#Events	60	60

PRIOR	DCT	CCT
Det(FIM)	3.74E-03	3.15E-03
Doselow	0	1.97
Dosehigh	2.73	4.3
CV_binf	25%	26%
CV_sinf	36%	32%
CV_brej	46%	100%
CV_srej	113%	110%
Num ind	**196**	**177.0**
#Events	**60.0**	**59.9**
EFF (respect to without PRIOR)	**148%**	**204%**









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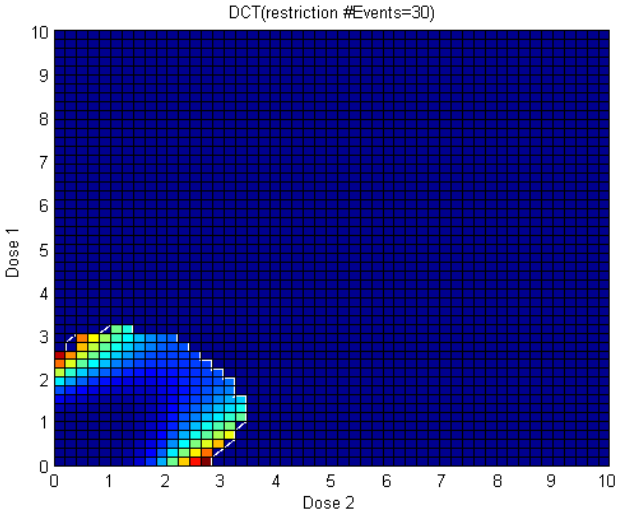
• Results- Part II
• Optimal designs

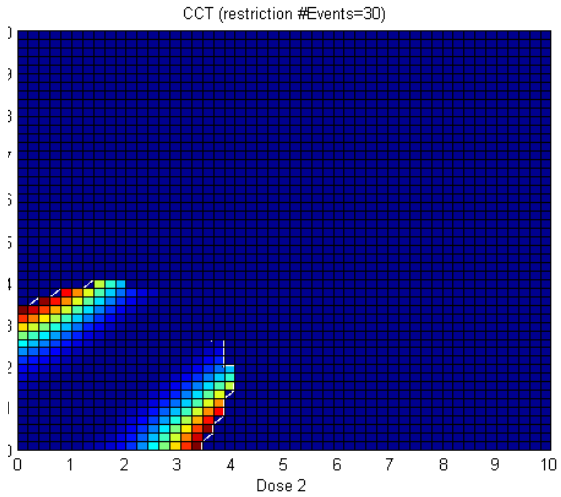
iv) Prior
ii) restriction in #events=30

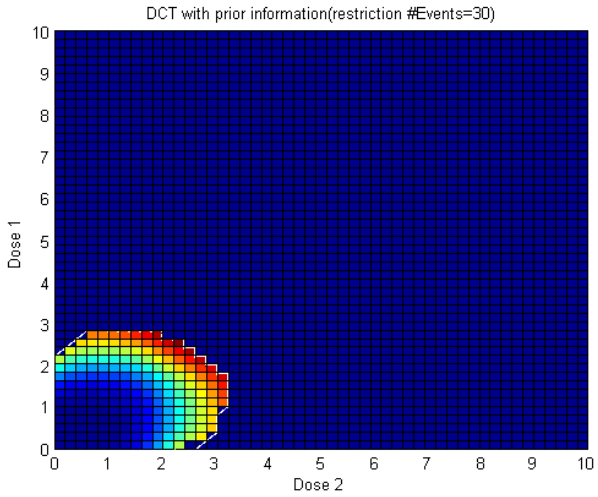
CONDITIONS
- 50% of subjects in each group
- Max.events=30
- Rest of variables (doses,subjects): unlimitted

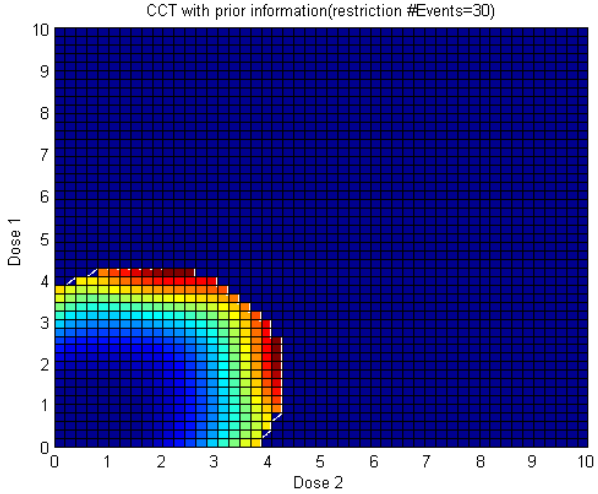
REFERENCE	DCT	CCT
Det(FIM)	4.96E-05	1.12E-05
Doselow	0	0.360
Dosehigh	2.51	3.57
CV_binf	68%	127%
CV_sinf	84%	171%
CV_brej	71%	93%
CV_srej	160%	185%
#Events	30	30
Num ind	**102**	**98**

With PRIOR	DCT	CCT
Det(FIM)	6.71E-04	6.84E-04
Doselow	2.42	1.98
Dosehigh	2.50	4.23
CV_binf	26%	27%
CV_sinf	40%	37%
CV_brej	99%	101%
CV_srej	126%	136%
#Events	30	30
Num ind	**106**	**90**
EFF (respect to without PRIOR)	**192%**	**279%**









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Not shown

Designs with unequal group sizes

Extension to full ED-optimality

Optimisation across many samples of the CL distribution

Ds-designs (e.g. Focus on Srej, Sinf)

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Conclusions

- DCT is generally superior to CCT
- Seeing events as ”cost” is feasible
- ”Ethical” trade-off can be quantified
- Use of prior information about Brej and Binf in estimation can lead to ethically more attractive designs