CONSIDERATIONS WHEN DERIVING TIME-AVERAGED EXPOSURE FOR CENSORED SUBJECTS FOR LOGISTIC REGRESSION EXPOSURE-RESPONSE ANALYSES

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Background

- Exposure-response (ER) information is at the heart of determining the safety and effectiveness of drugs during drug development
- ER evaluates the risk-to-benefit ratio for **dose selection, justification, and confirmation**
- ER has become an integral part of clinical drug development and regulatory decision making, however regulatory guidance is still lacking behind

FDA Guidance for Industry - Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, 2003
Overgaard et al. Establishing Good Practices for Exposure–Response Analysis of Clinical Endpoints in Drug Development. CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 565–575

ER Analysis

- Variety of different analysis methods contribute to determining the ER relationships, depending on the type of the response variable
  - Logistic regression – binary endpoints
  - Time to event – time-varying endpoints
  - Longitudinal analysis – progression endpoints

Patel K, Lin YW, Largajolli A, Edwards AY, Cheung SYA, Hennig S. Impact of Exposure Metric on Binary Endpoints in Exposure-Response Analysis. ACOP13 (2022) PMX-365 [www.go-acop.org/?abstract=365]

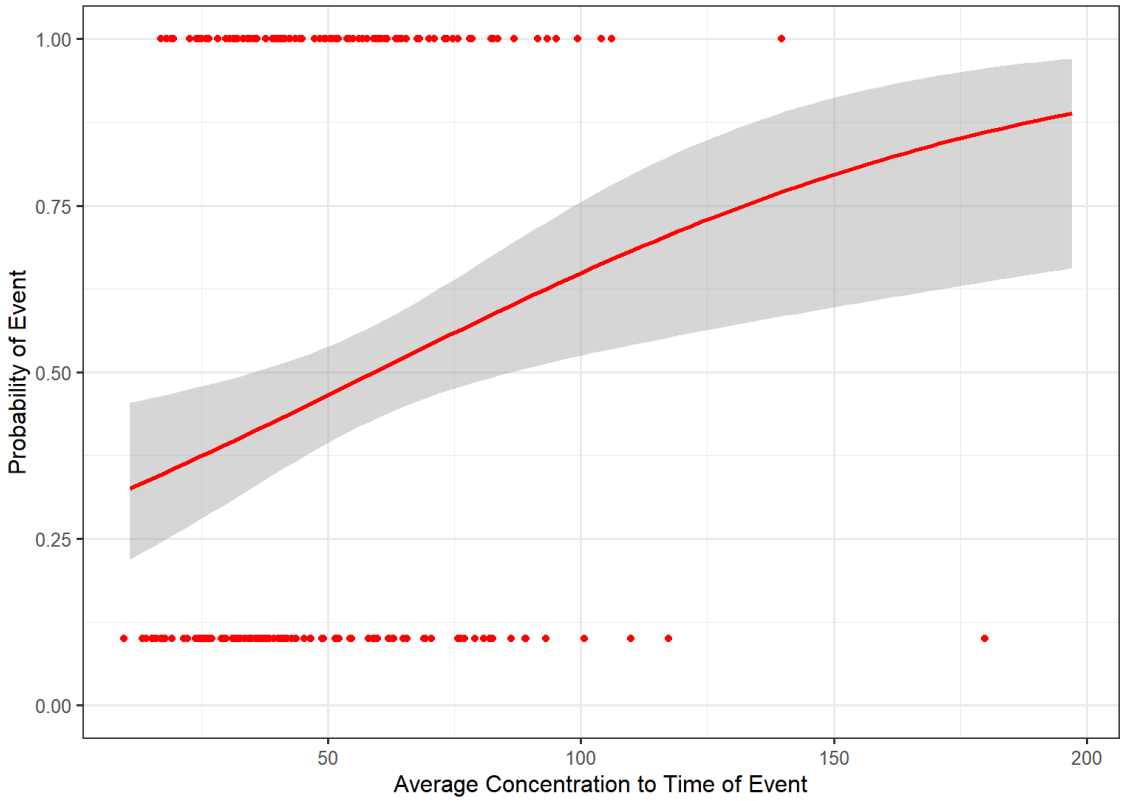
Logistic Regression Analysis

Simple univariate model

- Binomial response variables (yes/no)
- Can handle multiple exploratory variables
- Focus on drug exposure only

$$\text{logit}(P_{i,event}) = \log\left(\frac{P_{i,event}}{1-P_{i,event}}\right) = \beta_0 + \beta_1 \times PK_i$$

  - $P_{i,event}$ is the probability of the i^{th} endpoint of interest
  - β_0 is the intercept
  - β_1 is the slope, exposure effect parameter
  - PK_i is the i^{th} exposure metrics



Choice of Exposure Metric

Difference between $Cavg_{ss}$ & $Cavg_{TE}$

At steady-state

$$AUC_{ss} = \frac{Dose_{ss} \times Bioavialbility}{Clearnace}$$

$$Cavg_{ss} = \frac{AUC_{ss}}{Dosing\ Interval}$$

At any time – time-averaged exposure

$$Cavg_{TE} = \frac{AUC_{cum}}{Time}$$

- AUC_{cum} = actual cumulative exposure since start of treatment
- Time = time since start of treatment

- $Cavg_{TE}$ accounts for dose interruptions, modifications, and reductions
- What *Time* should be used for censored subjects to derive $Cavg_{TE}$?

Several exposure metrics are typically investigated

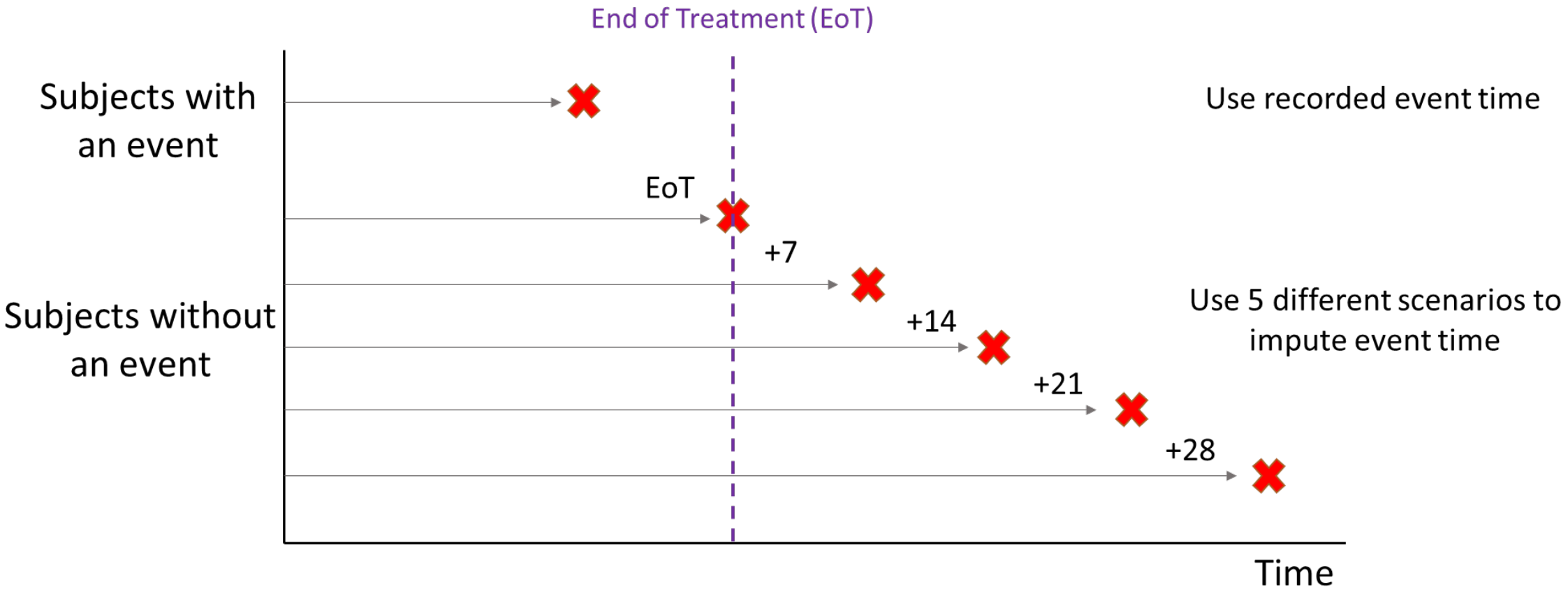
- Based on pharmacological plausibility
- Prior analysis findings
- Timing of the event

Objective

Evaluated the impact of different derivations of $Cavg_{TE}$ for subjects without events on the modeled ER relationships

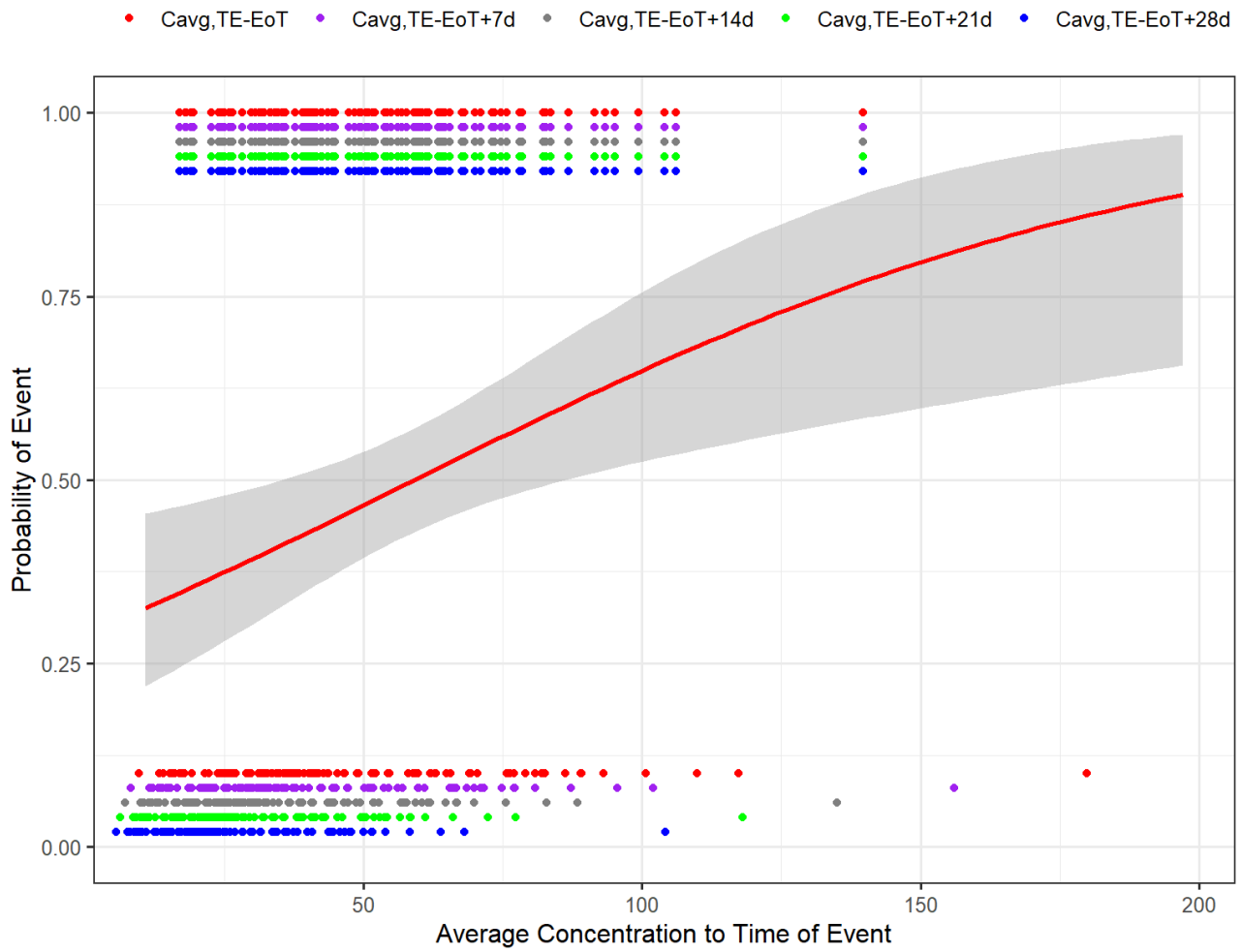
Derivation of $Cavg_{TE}$

Time value imputed to derive $Cavg_{TE}$ for censored subjects

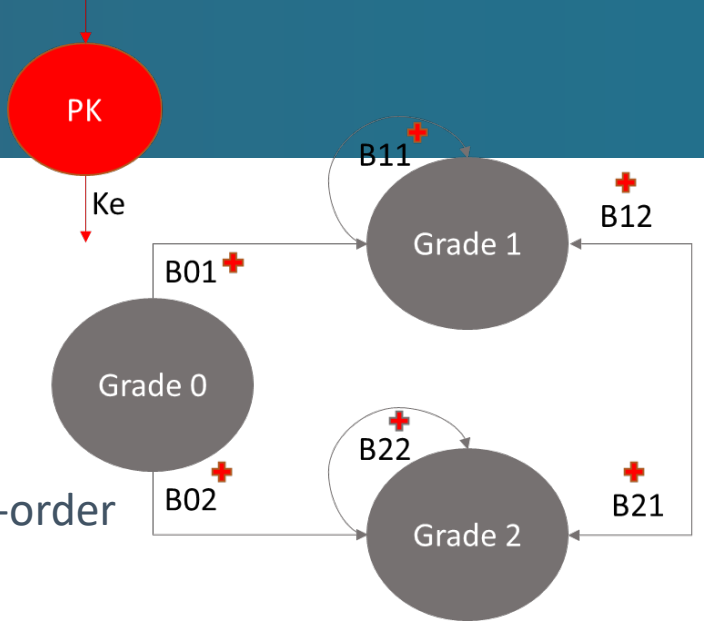


Derivation of $Cavg_{TE}$

Impact of the Time value on $Cavg_{TE}$



Example - Methods



- Data: 3 virtual populations with sample size of 50, 100 or 200
- Exposures:
  - Dose = 60 mg QD for 4 cycles of 28 days
  - Exposure was maximum concentration based on a 1-compartment model with first-order elimination rate
- Events:
  - Events were simulated based on a proportional odds model with Markov components
  - Subjects with Grade 0 - no event
  - Subjects with Grade 1 or 2 - first event/subject selected
- ER relationship:
  - Varying strengths ranging from 0.05-fold to 1.00-fold of the original ER relationship by varying the Emax parameter
- All simulations and logistic regression were performed in R (v 4.1.0 +) within RStudio.

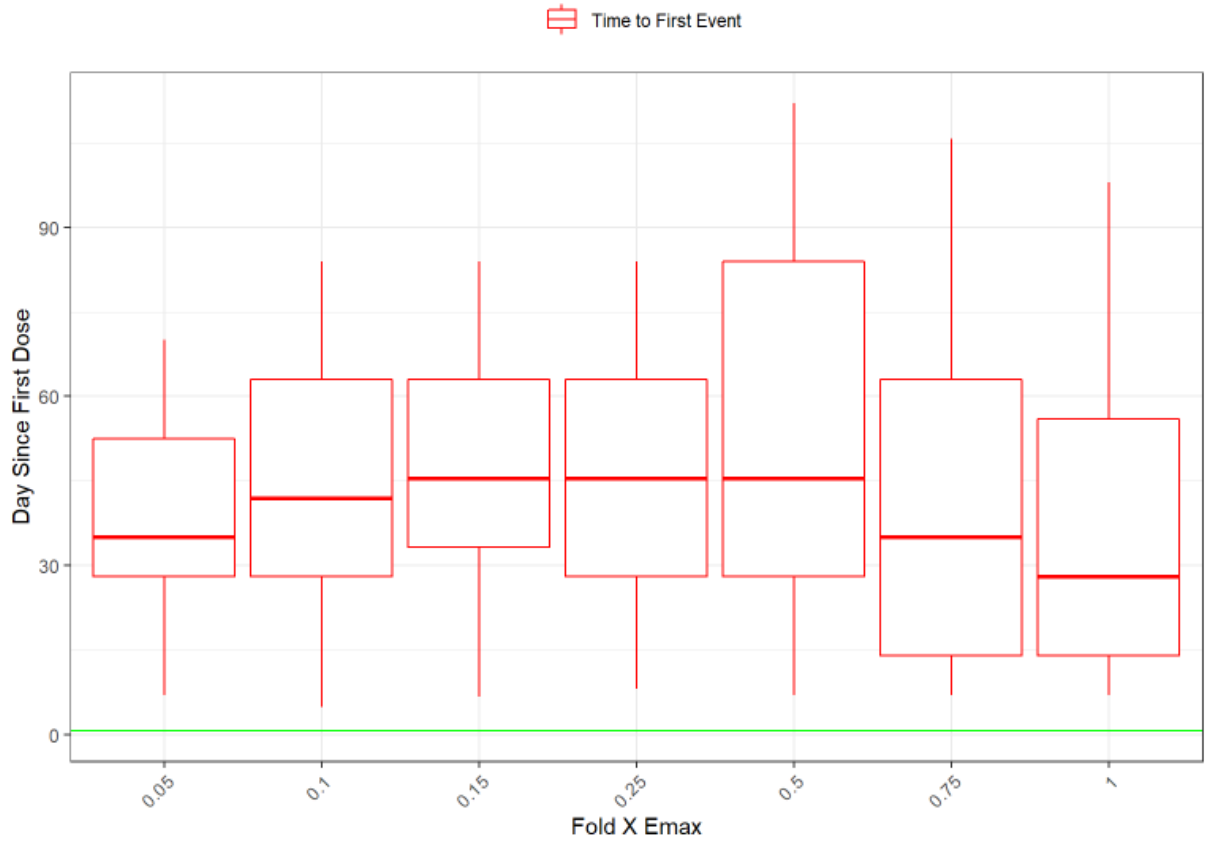
Example - Results

- Increased event rate with increased drug effect
- Event rate similar across the three study sizes

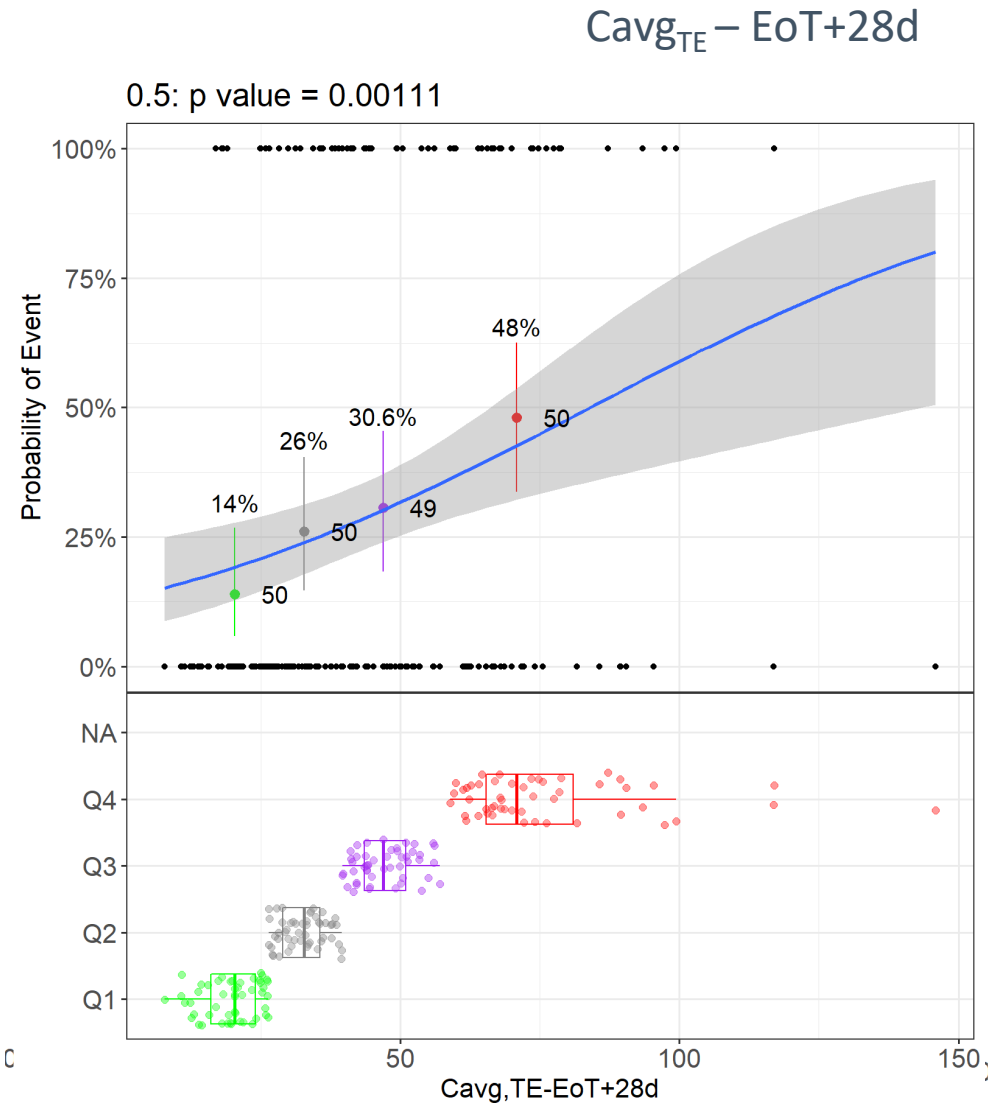
Drug Effect Factor	Event Rate (%) (95% CI)		
	N =50	N=100	N=200
0.05	6 (1.25 – 16.5)	5 (1.64 – 11.3)	5.5 (2.78 – 9.63)
0.10	8 (2.22 – 19.2)	9 (4.20 – 16.4)	7.5 (4.26 – 12.1)
0.25	8 (2.22 – 19.2)	15 (8.62 – 23.5)	12.0 (7.84 – 17.3)
0.50	32 (19.5 – 46.7)	32 (23.0 – 42.1)	30.0 (23.7 – 36.9)
0.75	52 (37.4 – 66.3)	49 (38.9 – 59.2)	49.5 (42.4 – 56.6)
1.00 (reference)	78 (64.0 – 88.5)	72 (62.1 – 80.5)	75.5 (68.9 – 81.3)

Example - Results

- Distribution of time to first event similar across all varying ER relationship strengths
- Time to first event > Time to Steady-state (green line)



Change in Relationship



Example: N= 200, 0.5-fold effect size of ER relationship

- *p*-values for the slope parameter ($\beta_1 \times PK_i$) decreased with increasing time values used to derive Cavg$_{TE}$ for censored subjects

N=200					
Drug Effect	Cavg$_{TE}$	Cavg$_{TE}$+7d	Cavg$_{TE}$+14d	Cavg$_{TE}$+21d	Cavg$_{TE}$+28d
0.5	0.485	0.192	0.0441	0.00766	0.00111

p-values on slope

Quartiles : Green = Q1, Grey = Q2, Purple = Q3, Red = Q4

All Tested Models

- Same ER relationship trends across all tested data sets
- Irrespective of the sample size
- With increasing sample size significant *p*-values were reached at lower imputed time values

N=50					
Drug Effect	$Cavg_{TE}$	$Cavg_{TE}$+7d	$Cavg_{TE}$+14d	$Cavg_{TE}$+21d	$Cavg_{TE}$+28d
0.05	0.817	0.702	0.566	0.447	0.347
0.1	0.457	0.355	0.251	0.175	0.121
0.25	0.457	0.355	0.251	0.175	0.121
0.5	0.41	0.267	0.149	0.0806	0.0436
0.75	0.329	0.204	0.109	0.0582	0.0315
1	0.0137	0.0114	0.00964	0.00853	0.00772

N=100					
Drug Effect	$Cavg_{TE}$	$Cavg_{TE}$+7d	$Cavg_{TE}$+14d	$Cavg_{TE}$+21d	$Cavg_{TE}$+28d
0.05	0.737	0.592	0.432	0.303	0.205
0.1	0.855	0.662	0.451	0.288	0.173
0.25	0.277	0.155	0.0685	0.0281	0.0112
0.5	0.18	0.0797	0.0262	0.00814	0.00255
0.75	0.0467	0.0171	0.0049	0.00146	0.000472
1	0.00044	0.000227	0.000119	0.0000705	0.000046

N=200					
Drug Effect	$Cavg_{TE}$	$Cavg_{TE}$+7d	$Cavg_{TE}$+14d	$Cavg_{TE}$+21d	$Cavg_{TE}$+28d
0.05	0.502	0.329	0.177	0.0869	0.0402
0.1	0.743	0.501	0.273	0.131	0.0572
0.25	0.523	0.283	0.11	0.036	0.0105
0.5	0.485	0.192	0.0441	0.00766	0.00111
0.75	0.087	0.0186	0.00216	0.000213	0.0000203
1	0.00033	6.23E-05	9.86E-06	1.92E-06	4.64E-07

p-values are colored according to:
>0.2 = light grey,
0.1 – 0.2 = light yellow,
0.05-0.1 = light orange,
0.01 – 0.05 = light red,
<0.01 = red

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Comparison to $Cavg_{ss}$

- Comparison to $Cavg_{ss}$
  - When ER relationships is <u>strong</u>

    $Cavg_{TE}$ and $Cavg_{ss}$ relationships are aligned
  - When ER relationships is <u>weak</u>

    Only a significant ER relationship with $Cavg_{TE}$ is seen

N=50						
Drug Effect	$Cavg_{TE}$	$Cavg_{TE}$+7d	$Cavg_{TE}$+14d	$Cavg_{TE}$+21d	$Cavg_{TE}$+28d	$Cavg_{ss}$
0.05	0.817	0.702	0.566	0.447	0.347	0.655
0.1	0.457	0.355	0.251	0.175	0.121	0.314
0.25	0.457	0.355	0.251	0.175	0.121	0.314
0.5	0.41	0.267	0.149	0.0806	0.0436	0.242
0.75	0.329	0.204	0.109	0.0582	0.0315	0.143
1	0.0137	0.0114	0.00964	0.00853	0.00772	0.0121

N=100						
Drug Effect	$Cavg_{TE}$	$Cavg_{TE}$+7d	$Cavg_{TE}$+14d	$Cavg_{TE}$+21d	$Cavg_{TE}$+28d	$Cavg_{ss}$
0.05	0.737	0.592	0.432	0.303	0.205	0.687
0.1	0.855	0.662	0.451	0.288	0.173	0.868
0.25	0.277	0.155	0.0685	0.0281	0.0112	0.107
0.5	0.18	0.0797	0.0262	0.00814	0.00255	0.0602
0.75	0.0467	0.0171	0.0049	0.00146	0.000472	0.00753
1	0.00044	0.000227	0.000119	0.0000705	0.000046	0.000368

N=200						
Drug Effect	$Cavg_{TE}$	$Cavg_{TE}$+7d	$Cavg_{TE}$+14d	$Cavg_{TE}$+21d	$Cavg_{TE}$+28d	$Cavg_{ss}$
0.05	0.502	0.329	0.177	0.0869	0.0402	0.079
0.1	0.743	0.501	0.273	0.131	0.0572	0.172
0.25	0.523	0.283	0.11	0.036	0.0105	0.0382
0.5	0.485	0.192	0.0441	0.00766	0.00111	0.0836
0.75	0.087	0.0186	0.00216	0.000213	0.0000203	0.00319
1	0.00033	6.23E-05	9.86E-06	1.92E-06	4.64E-07	5.47E-05

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Change in CL

Example: N= 200, 0.5-fold effect size of ER relationship

- *p*-values for the slope parameter ($\beta_1 \times PK_i$) decreased with increasing time values used to derive $Cavg_{TE}$ for censored subjects irrespective of change in CL
- $Cavg_{TE}$ and $Cavg_{ss}$ relationships do not align

N=200						
CL	**$Cavg_{TE}$**	**$Cavg_{TE}$+7d**	**$Cavg_{TE}$+14d**	**$Cavg_{TE}$+21d**	**$Cavg_{TE}$+28d**	**$Cavg_{ss}$**
0.25	0.785	0.838	0.373	0.117	0.0277	0.0137
0.5	0.345	0.134	0.0286	0.00463	0.000631	0.00762
1	0.485	0.192	0.0441	0.00766	0.00111	0.0836
1.5	0.0896	0.0232	0.00364	0.00049	0.0000631	0.0199

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<0.01 = red

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Conclusions

- The time used for censored subjects to derive $Cavg_{TE}$ can have significant impact on the logistic ER relationships

- Caution with **choosing time** to derive time-averaged exposure for censored subjects

- Suggest using time to event analysis with time-varying exposures

- **Consider the PK profile**
  - Exploratory analysis of your exposures across subjects with events/no events
  - Do a sensitivity analysis and evaluate the chosen time
  - Investigate multiple exposures
  - Consider pharmacological plausibility

➢ Impact on subsequent event projection, dose selection and Go/No-Go decisions

Thank you for your attention

Questions?

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