Personalised Synthetic Control

Dr Richard Jackson

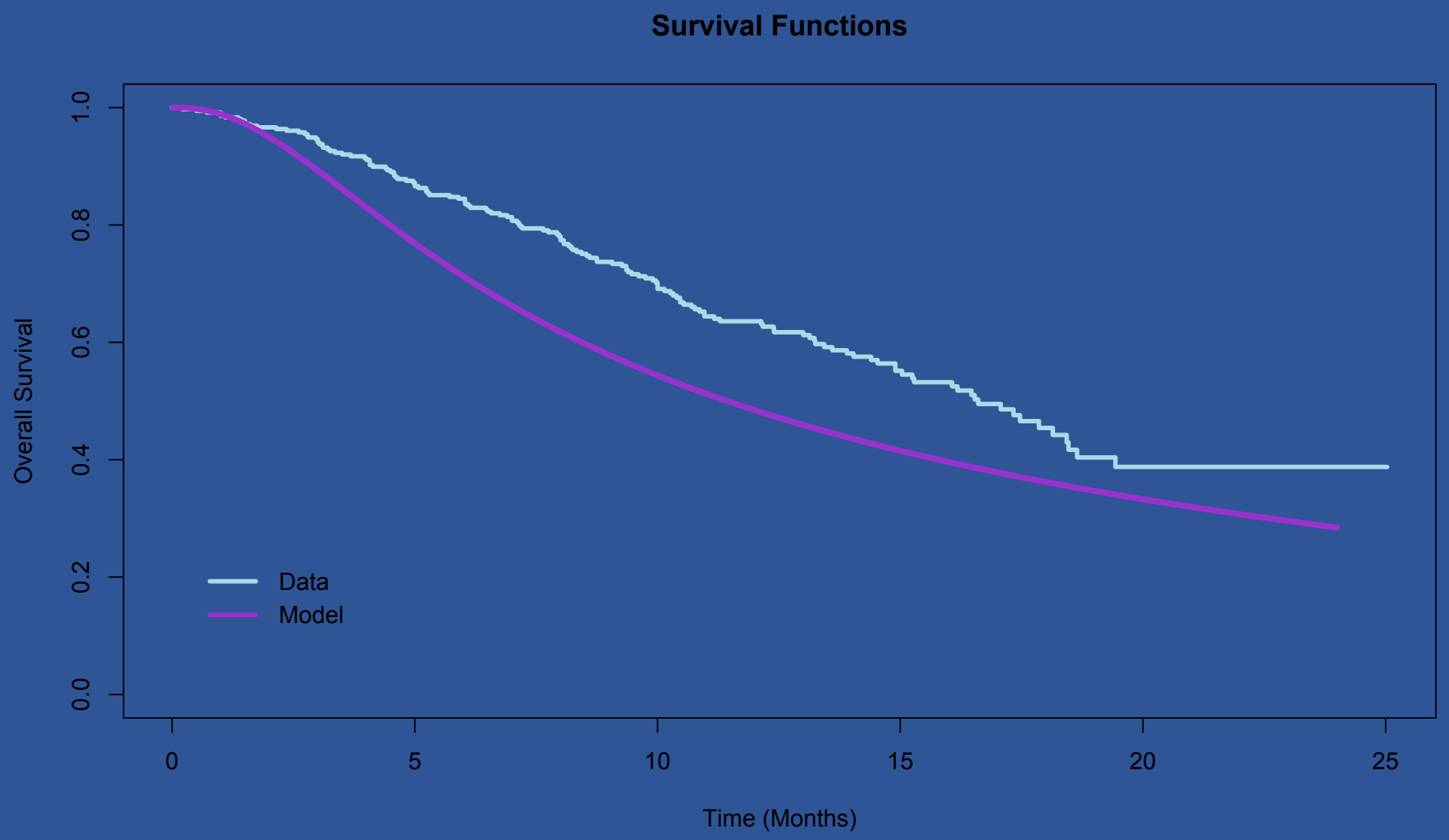
What are they?

How do they Compare?

How can they be useful?

What are they?

Personalised Synthetic Controls



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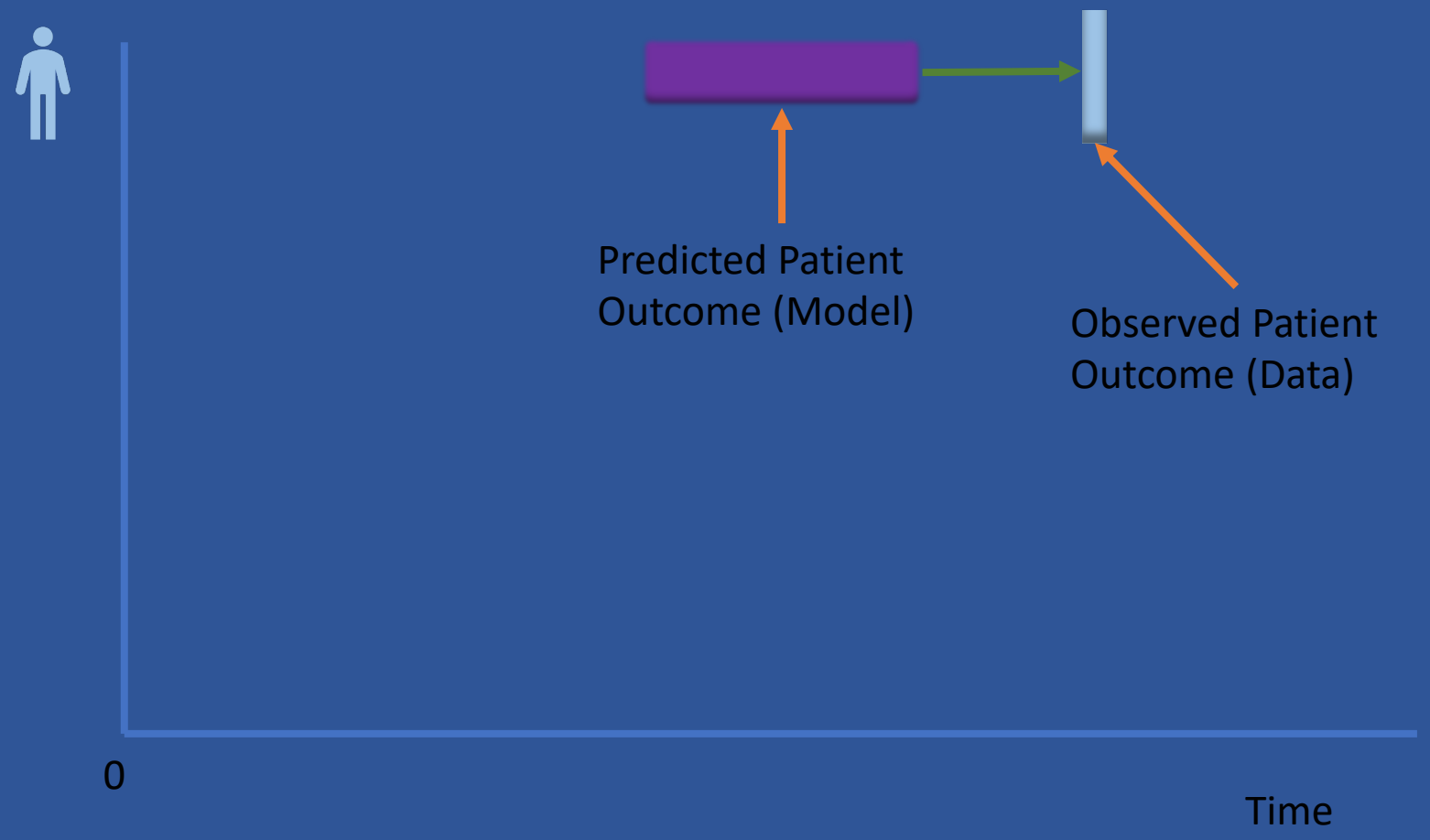

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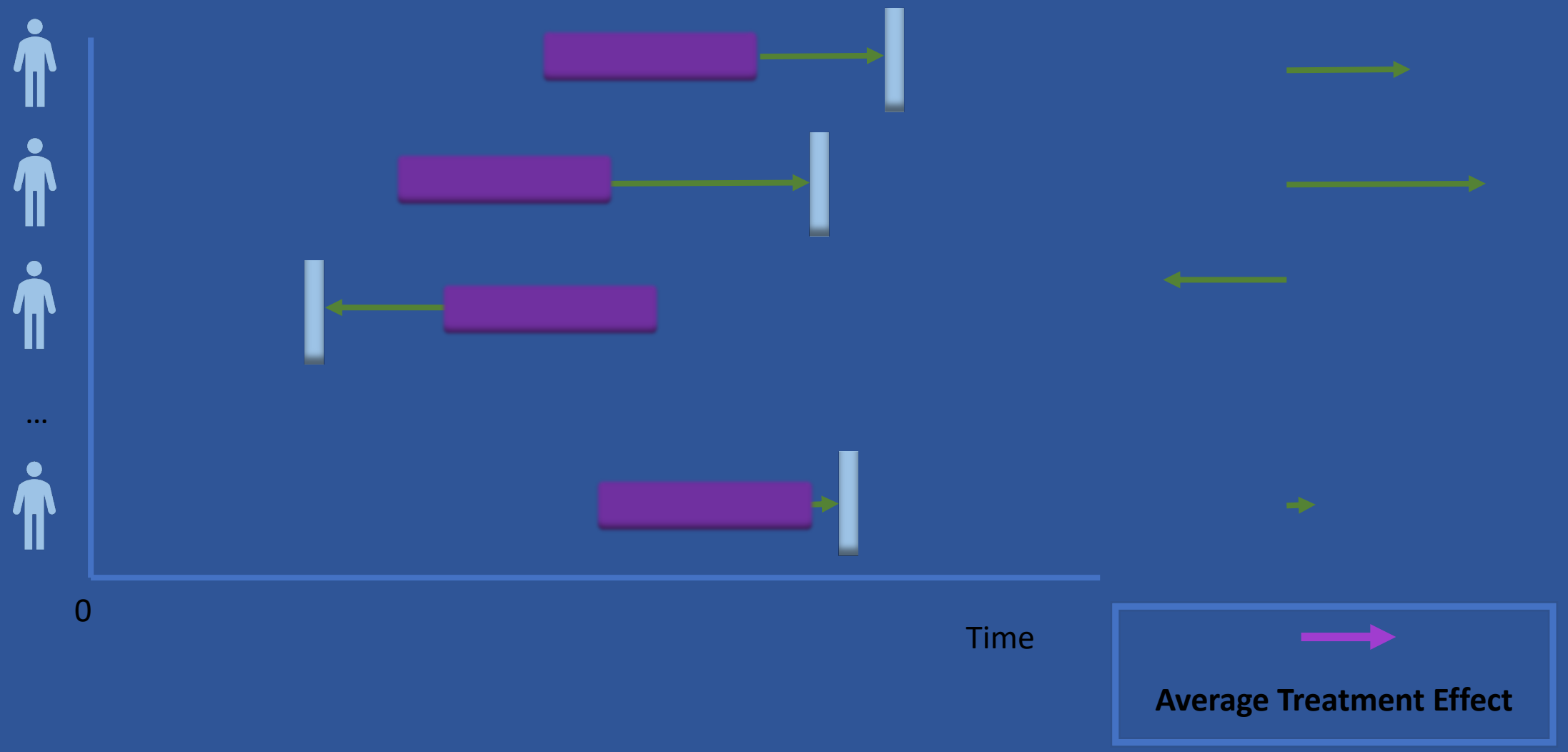
Personalised Synthetic Controls

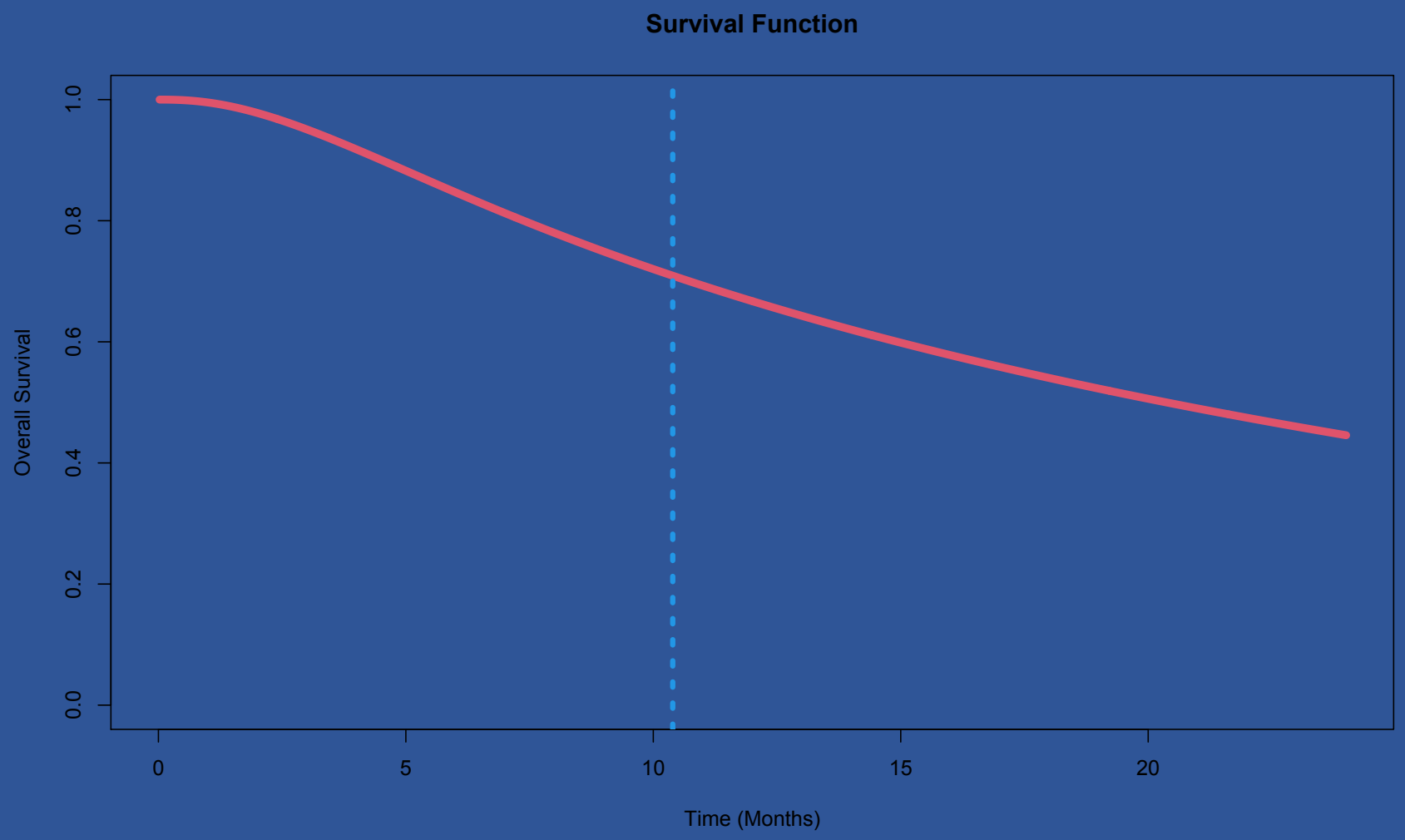


What Are They?

Patient level prediction

Personalised Synthetic Controls

Patient 1

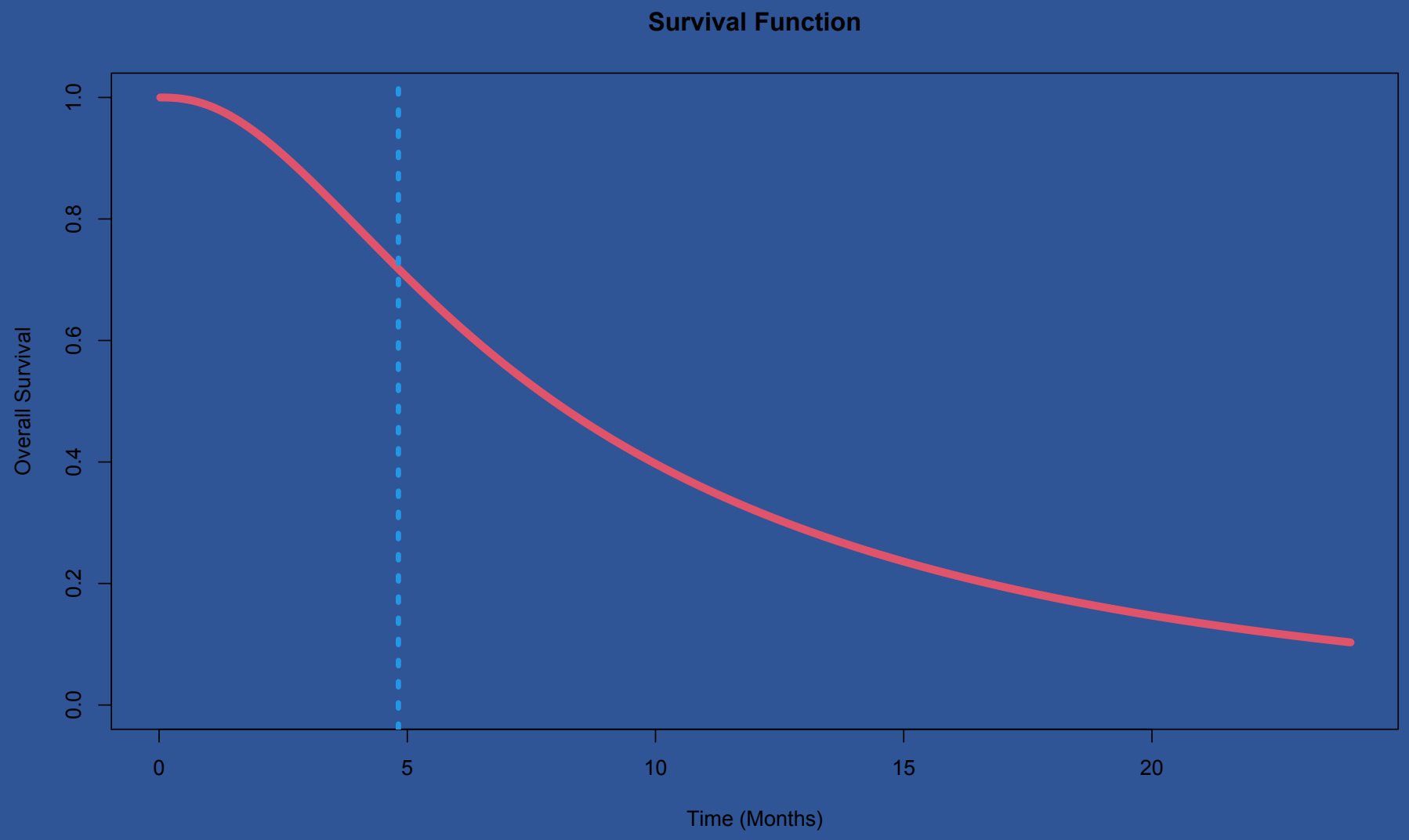


What Are They?

Patient level prediction

Personalised Synthetic Controls

Patient 2

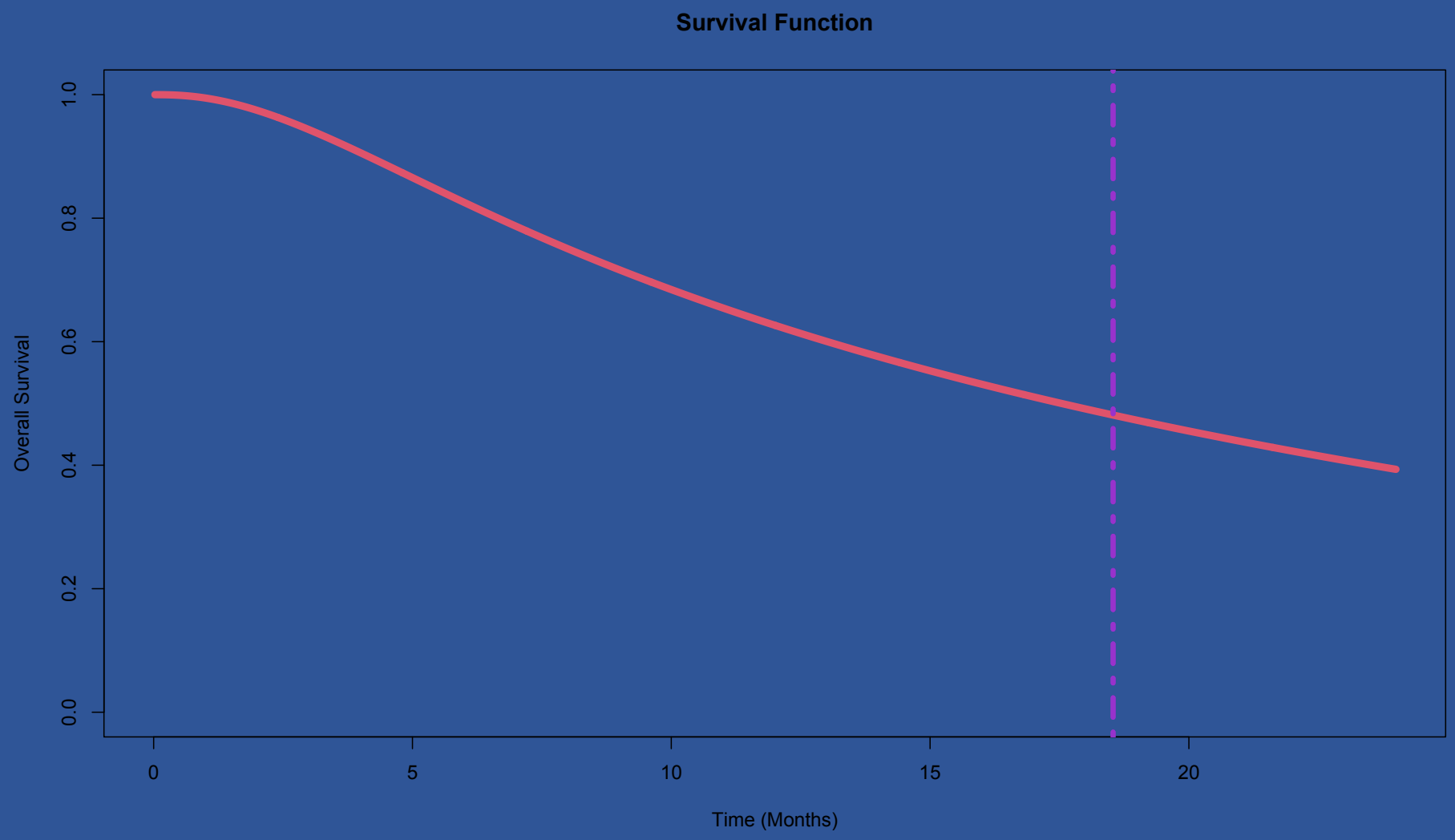


What Are They?

Patient level prediction

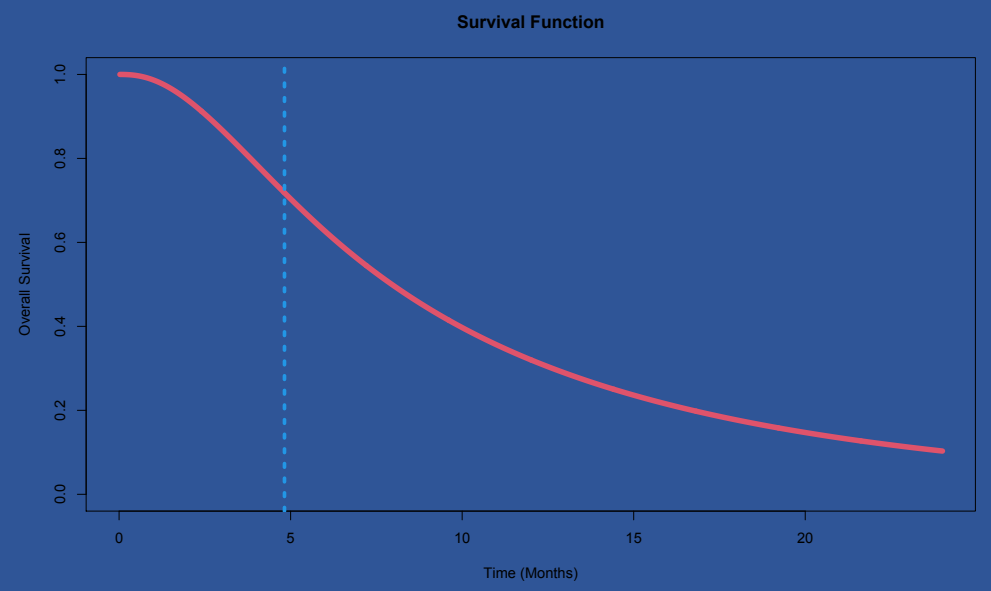
Personalised Synthetic Controls

Patient 3



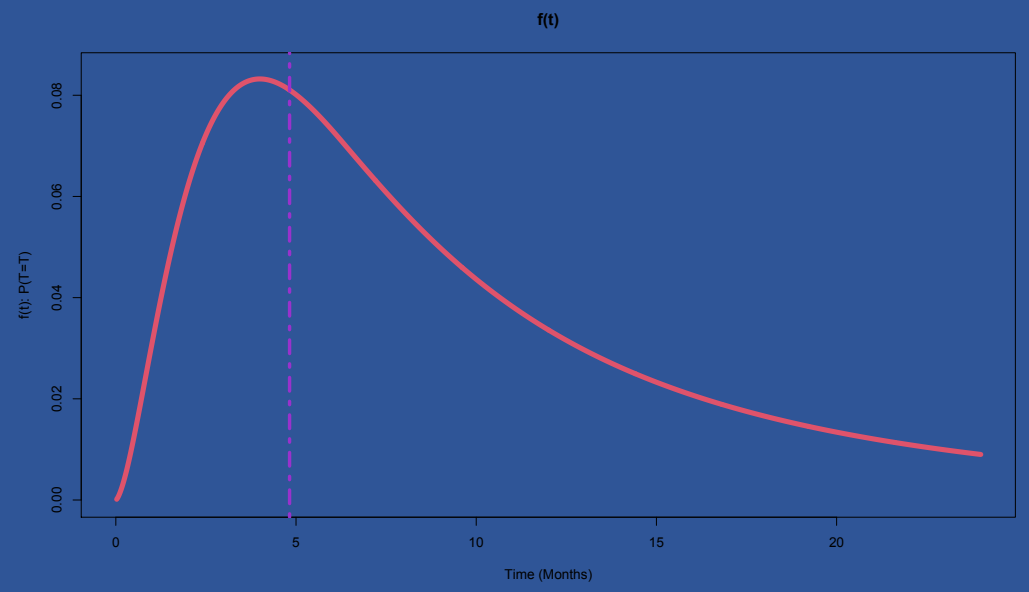
What Are They?

What is the probability a patient died when they did?



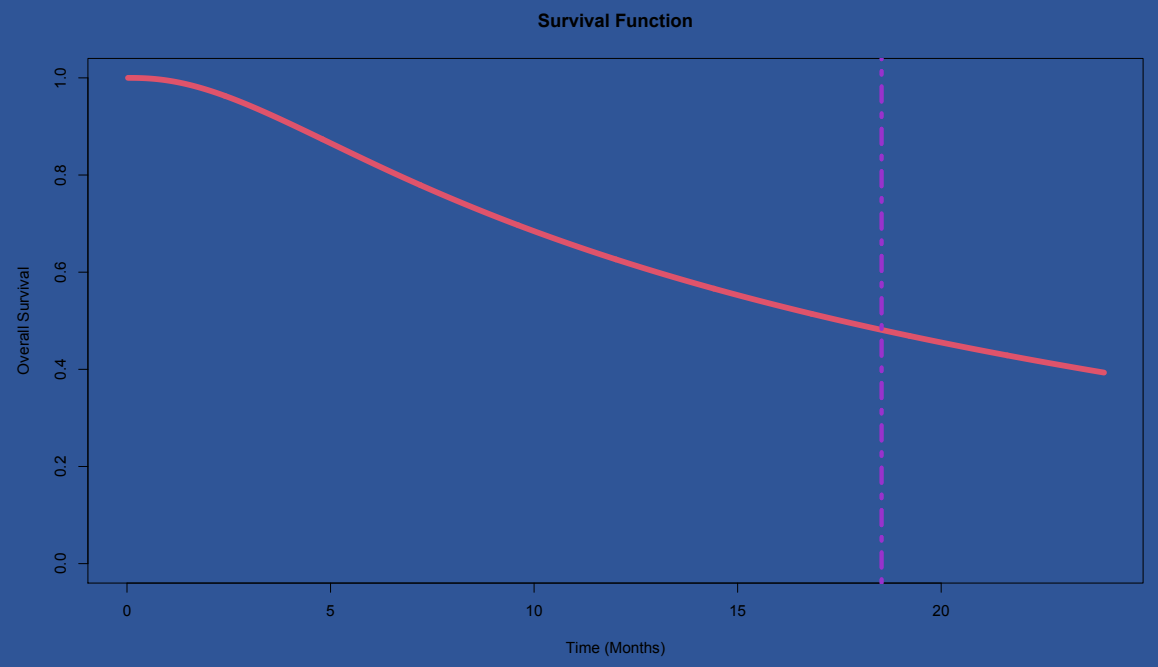
$$\Pr(T = t|x_i, \gamma) \approx f(t|x_i, \gamma)$$

- **NB: f(t) = S(t)h(t)**



What is the probability a patient was censored at a particular time?

$$\Pr(T > t|x_i, \gamma) \approx S(t|x_i, \gamma)$$



Likelihood Definition

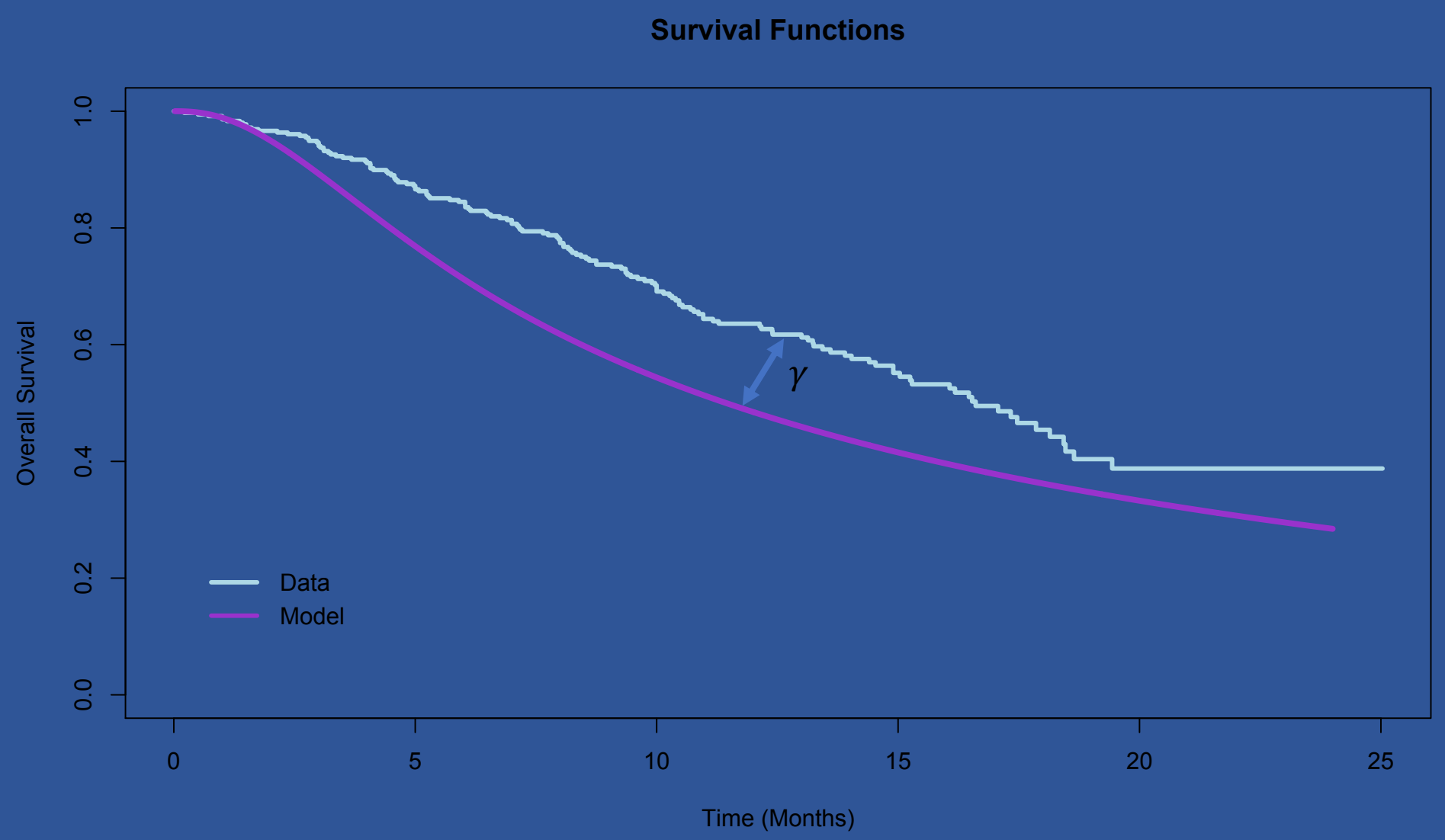
Standard Likelihood for survival data, but conditional on parameters of the predictive model and patient covariates

- $\lambda_i = \alpha + \beta x_i + \gamma$

$$\boldsymbol{L = \prod_{i=1}^{N} P(T = t|\lambda_i)^{\partial_i} P(T > t|\lambda_i)^{(1-\partial_i)}}$$

$$\boldsymbol{L = \prod_{i=1}^{N} f(t|\lambda_i)^{\partial_i} S(t|\lambda_i)^{(1-\partial_i)}}$$

Personalised Synthetic Controls



What Are They?

How do they Compare?

RCT

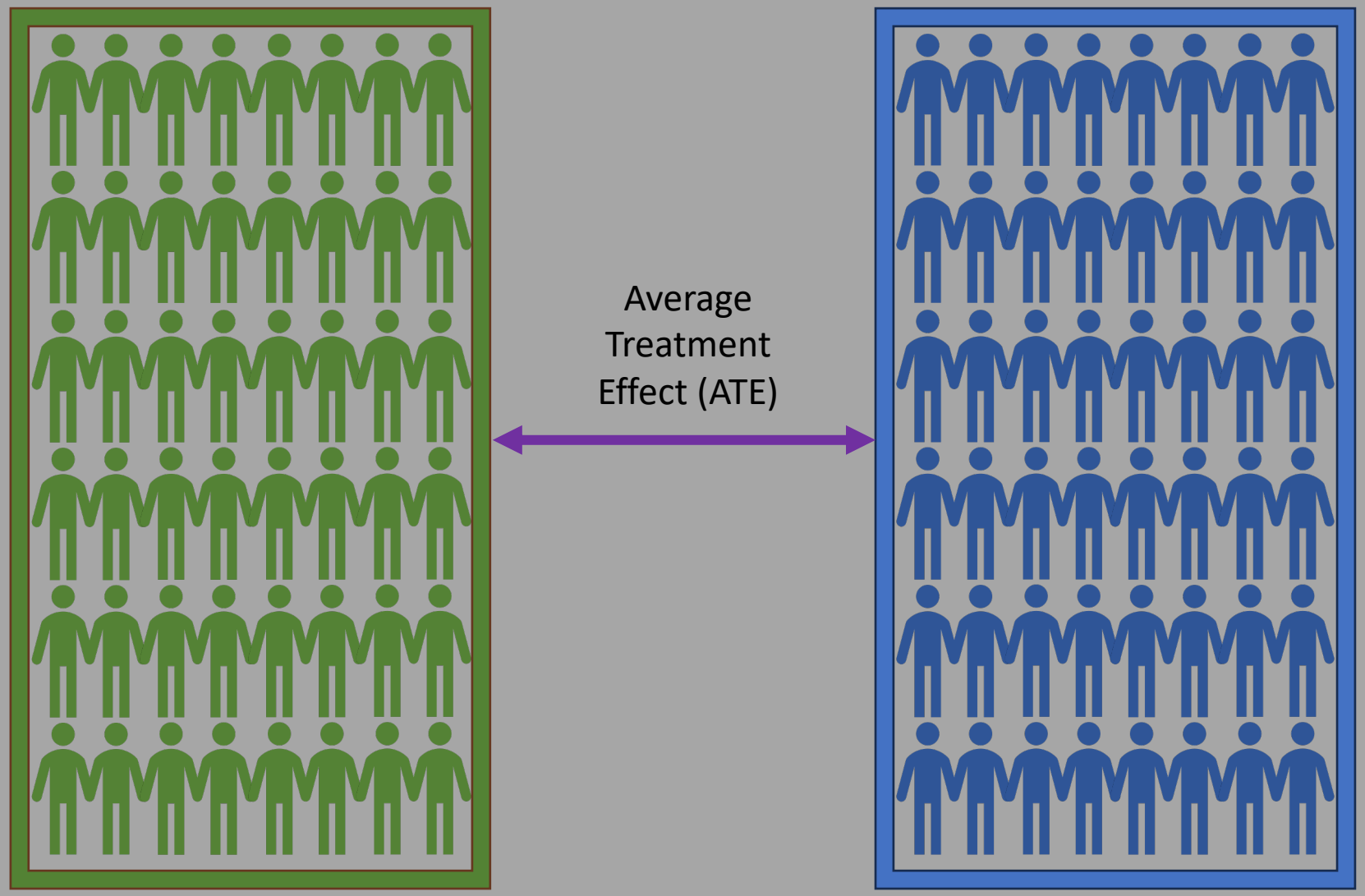
Propensity Score Analysis

(Traditional) Synthetic Controls

Personalised Synthetic Controls

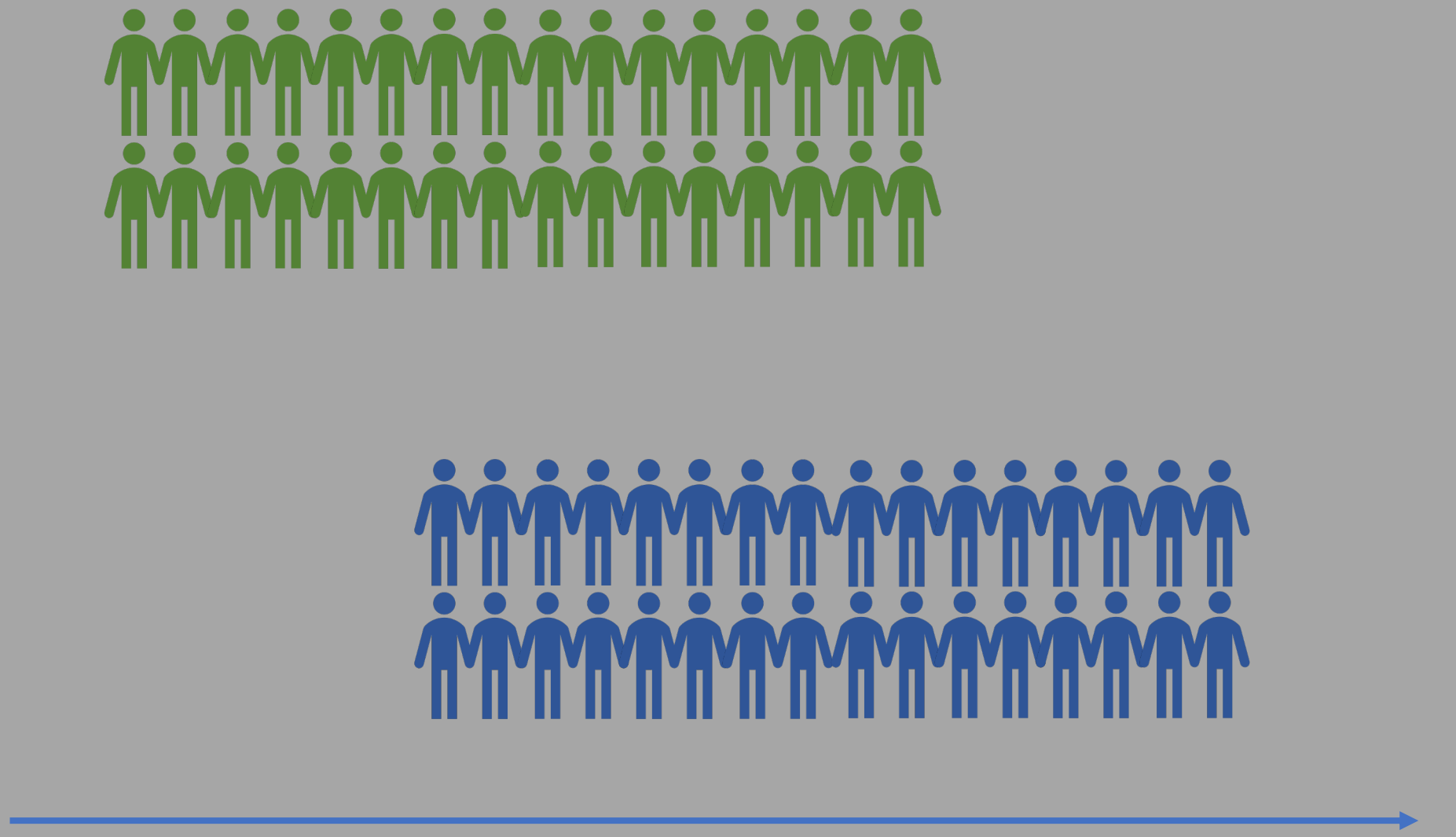
How Do They Compare?

RCT



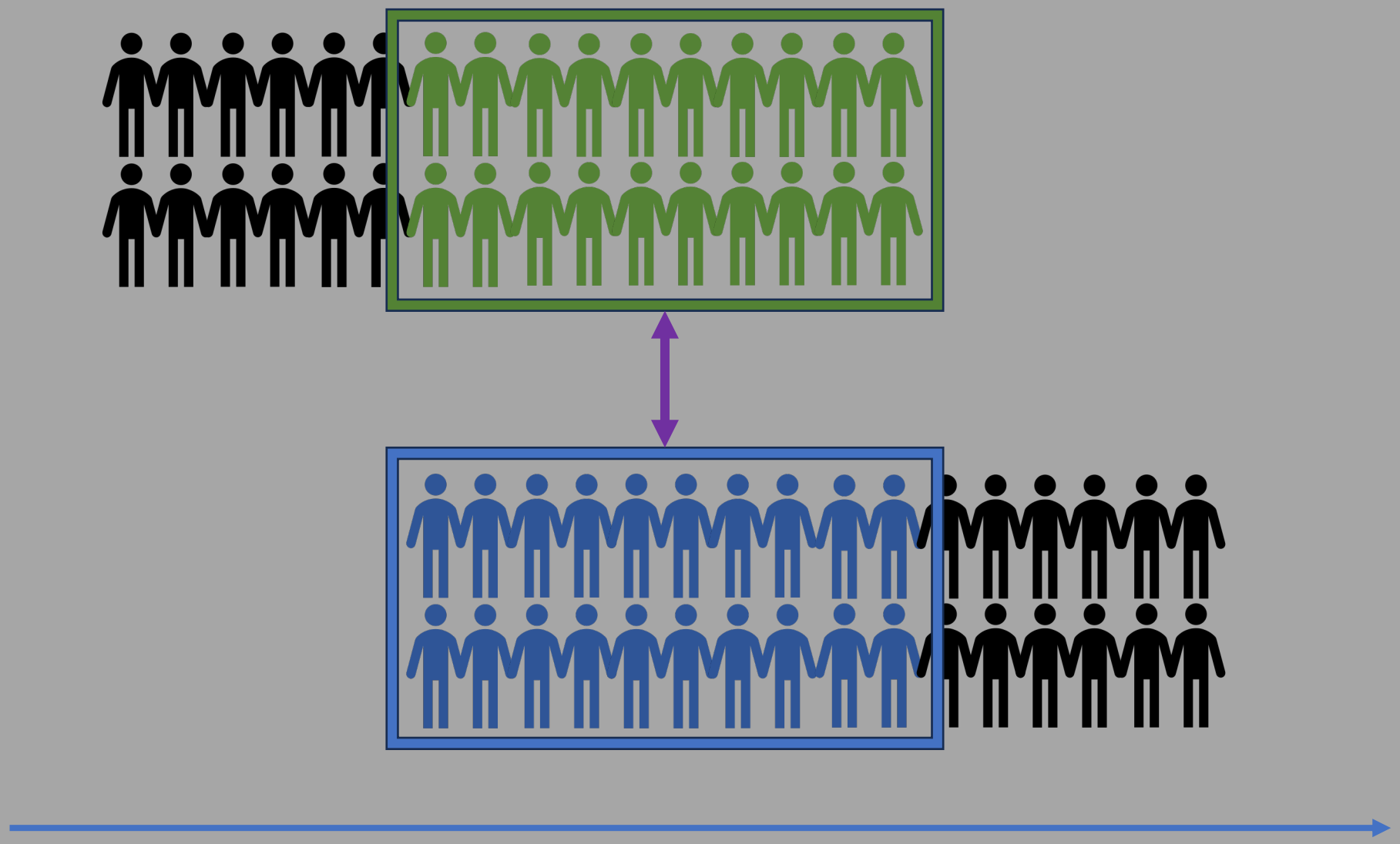
How Do They Compare?

Propensity Scores



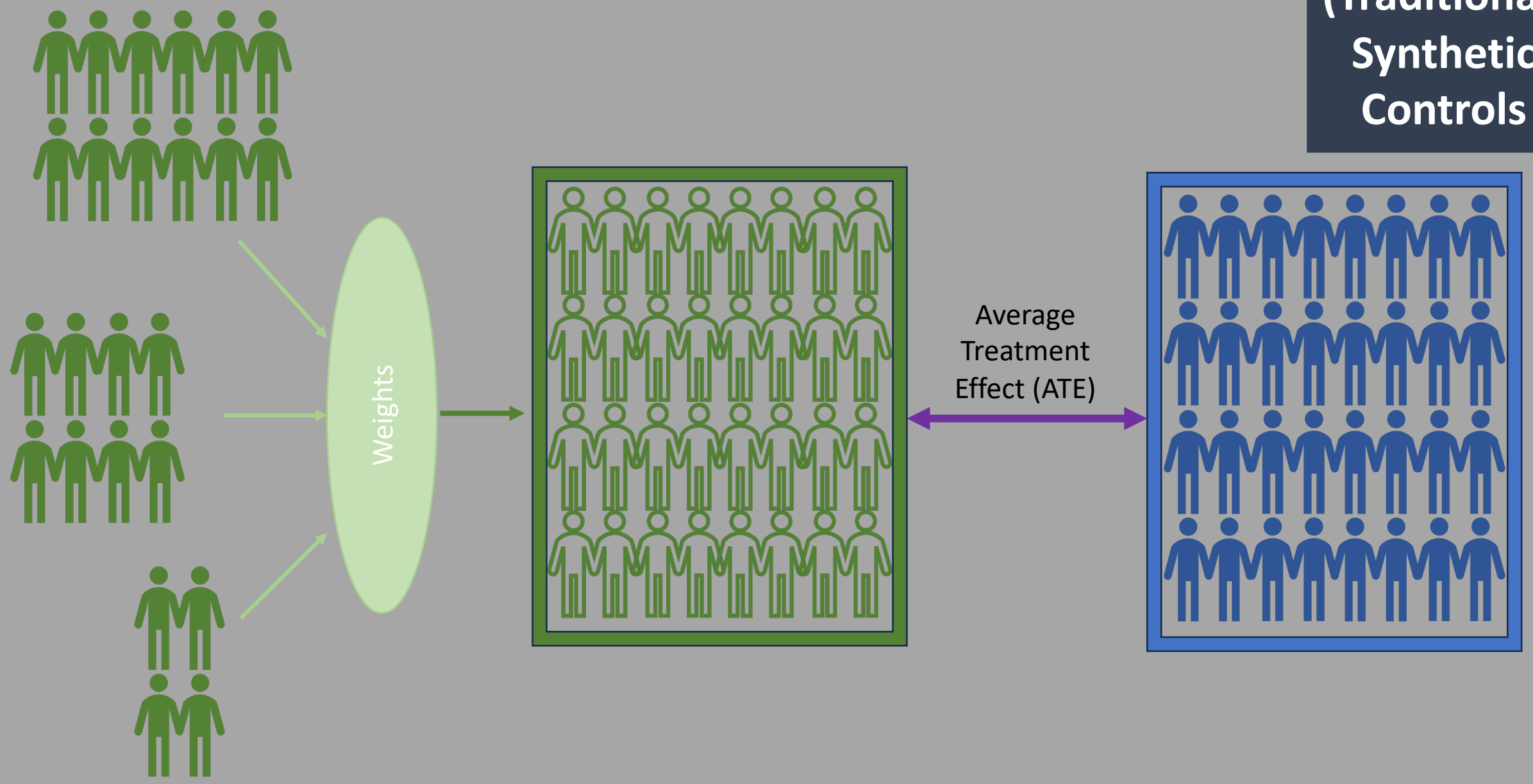
How Do They Compare?

Propensity Scores



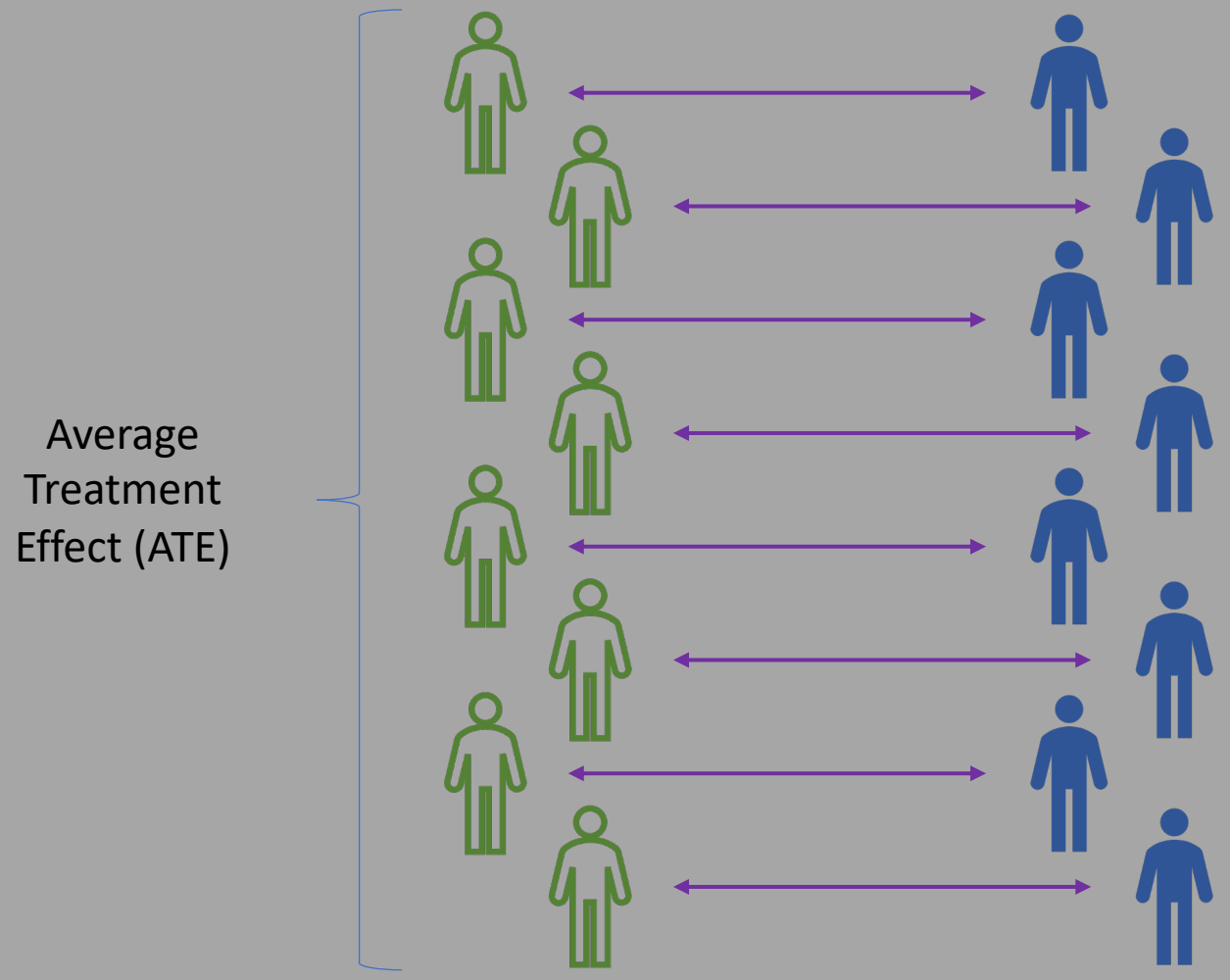
1) Estimate Propensity Model
2) Restrict analysis to ‘regions of common support’
3) Perform analysis conditional on propensity score
   1) Matching
   2) Stratification
   3) Covariate Adjustment
   4) IPW

(Traditional) Synthetic Controls



How Do They Compare?

Personalised Synthetic Controls

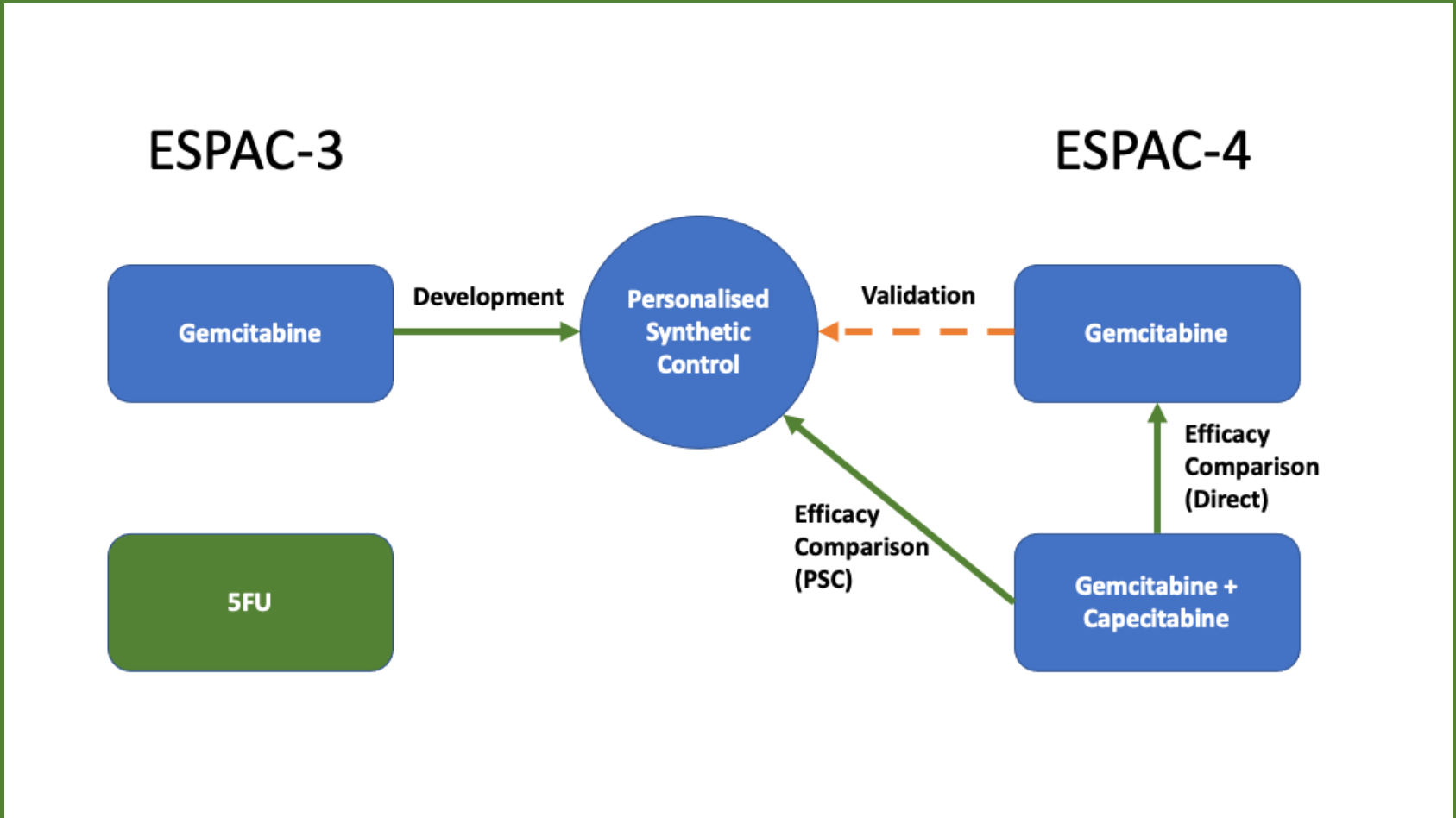


How Do They Compare?

How Can they be Useful?

Compare Treatments Directly

Application: ESPAC Trials

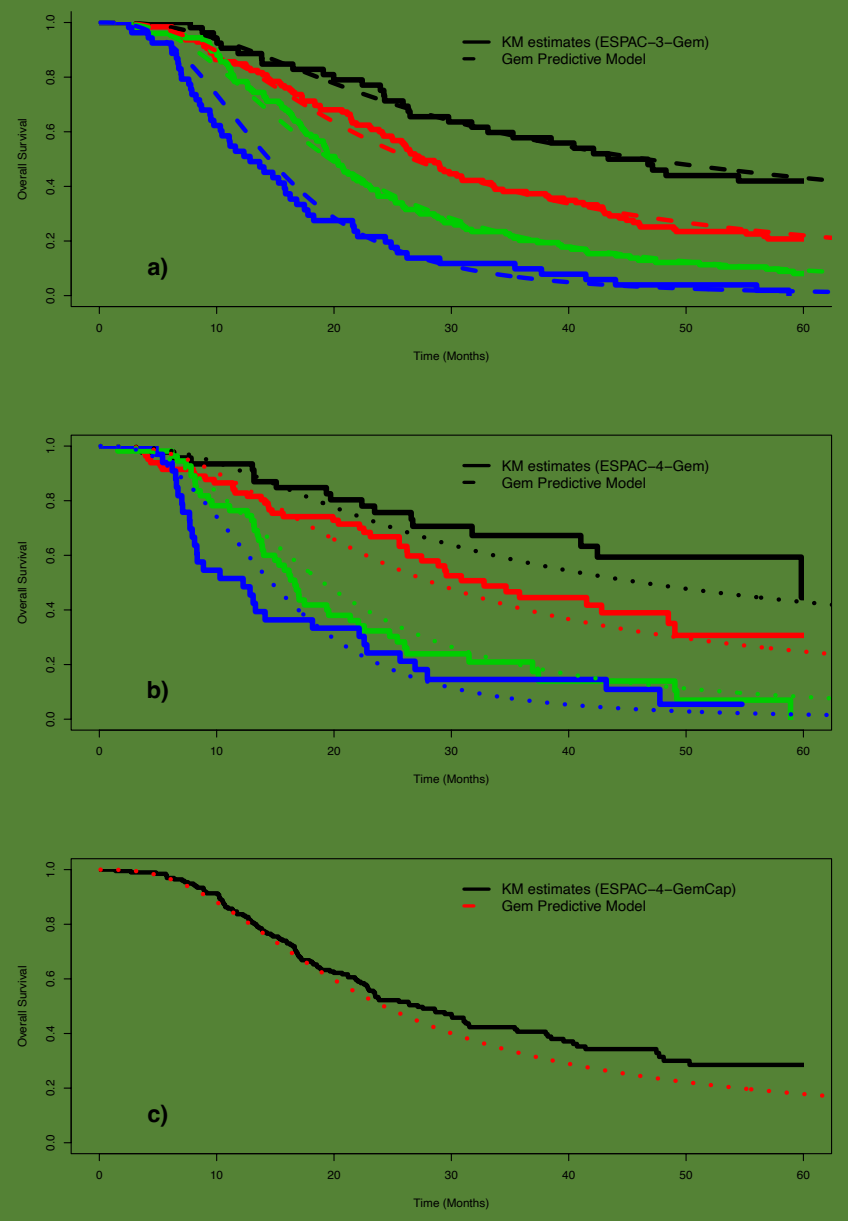


How Can they be useful?

Application: ESPAC Trials

Personalised Synthetic Controls

- Step 1: Study Population
  - Are two datasets comparable
- Step 2: Model Validation
  - Does the model predict 'Gem' survival?
  - Fitting the PSC against the Gem arm allows for a measure of calibration (HR: 0.98)



How Can they be useful?

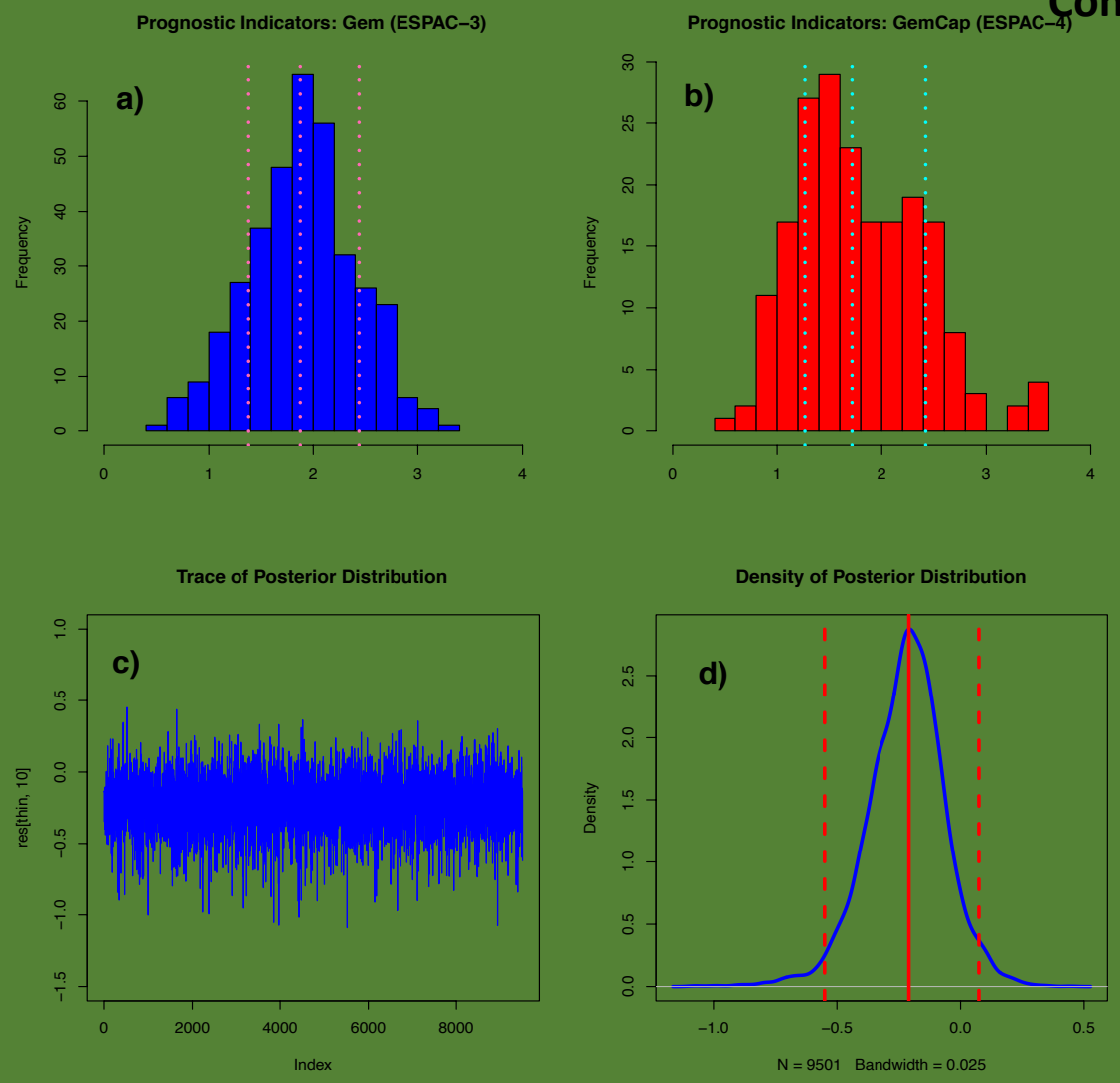
Application: ESPAC Trials

- Step 3: Estimate Hazard Ratio

Model Estimate	$\hat{\beta}$(se)	Hazard Ratio
GemCap Vs Gem (Using PSC)	-0.212 (0.158)	**0.81 (0.58 – 1.08)***
GemCap Vs Gem (Direct Estimation)	-0.239 (0.100)	**0.79 (0.65 – 0.96)****

Conclusion:

- Hazard ratio comparing GemCap to Gemcitabine are comparable using both methods
- Measures of dispersion greater using PSC method (despite a similar number of patients being used in each approach)



Personalised Synthetic Controls

Application: HCC

Atezo Bev Vs Sorafenib

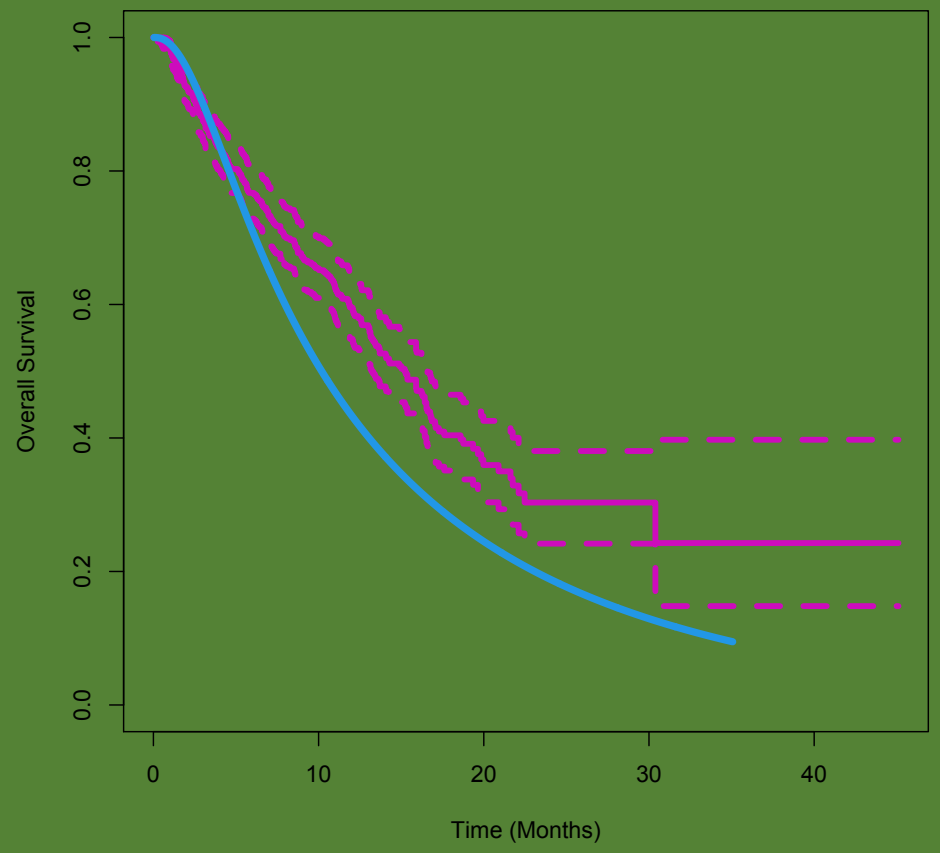


Table 2. Multivariable flexible parametric regression - hazard ratio (with 95% CI) ($n = 500$)

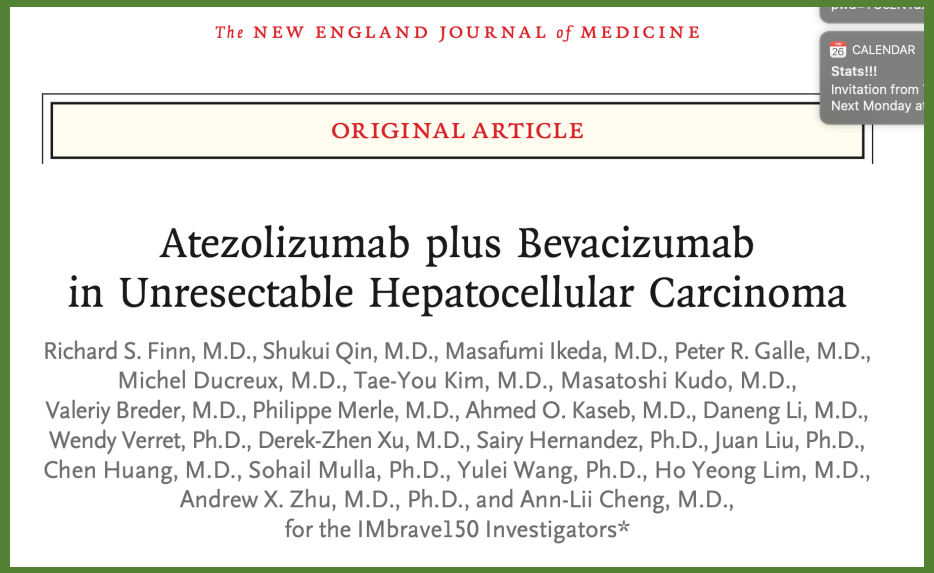
Variables	Hazard ratio	p value
Vascular invasion		
No	1 (reference group)	
Yes	1.387 (1.087, 1.770)	0.008
Age centred at 60 years – No vascular invasion	0.977 (0.966, 0.989)	<0.0001
Age centred at 60 years – With vascular invasion	1.007 (0.992, 1.022)	0.353
ECOG		
0	1 (reference group)	
1	1.576 (1.263, 1.967)	<0.0001
Log (AFP (ng/ml))	1.087 (1.052, 1.123)	<0.0001
Albumin (g/l)	0.946 (0.925, 0.968)	<0.0001
Log (creatinine (μmol/L))	2.032 (1.301, 3.174)	0.002
Log (AST (U/L))	1.418 (1.172, 1.716)	<0.0001
Extra-hepatic spread		
No	1 (reference group)	
Yes	1.348 (1.038, 1.749)	0.025
Aetiology		
HCV	1 (reference group)	
HBV	1.692 (1.210, 2.366)	0.002
Other	1.661 (1.195, 2.308)	0.003
γ_1	11.766 (7.554, 18.327)	<0.0001
γ_2	1.120 (1.075, 1.167)	<0.0001
γ_0 (constant)	2.84×10^{-4} (2.8×10^{-5}, 2.87×10^{-3})	<0.0001

γ_1 and γ_2 are the basis functions of the restricted cubic spline (based here on 2 df). γ_0 is log λ, where λ is the scale parameter.
AFP alpha-fetoprotein, *AST* aspartate aminotransferase, *ECOG* Eastern Cooperative Oncology Group, *g/l* grams per litre, *HBV* hepatitis B, *HCV* hepatitis C, *INR* international normalised ratio, *μmol/L* micromoles per litre.

How Can they be useful?

Atezo Bev Vs Sorafenib

Overall impact suggests improved survival with Atezo Bev [HR: 0.58 (0.44-0.74)]

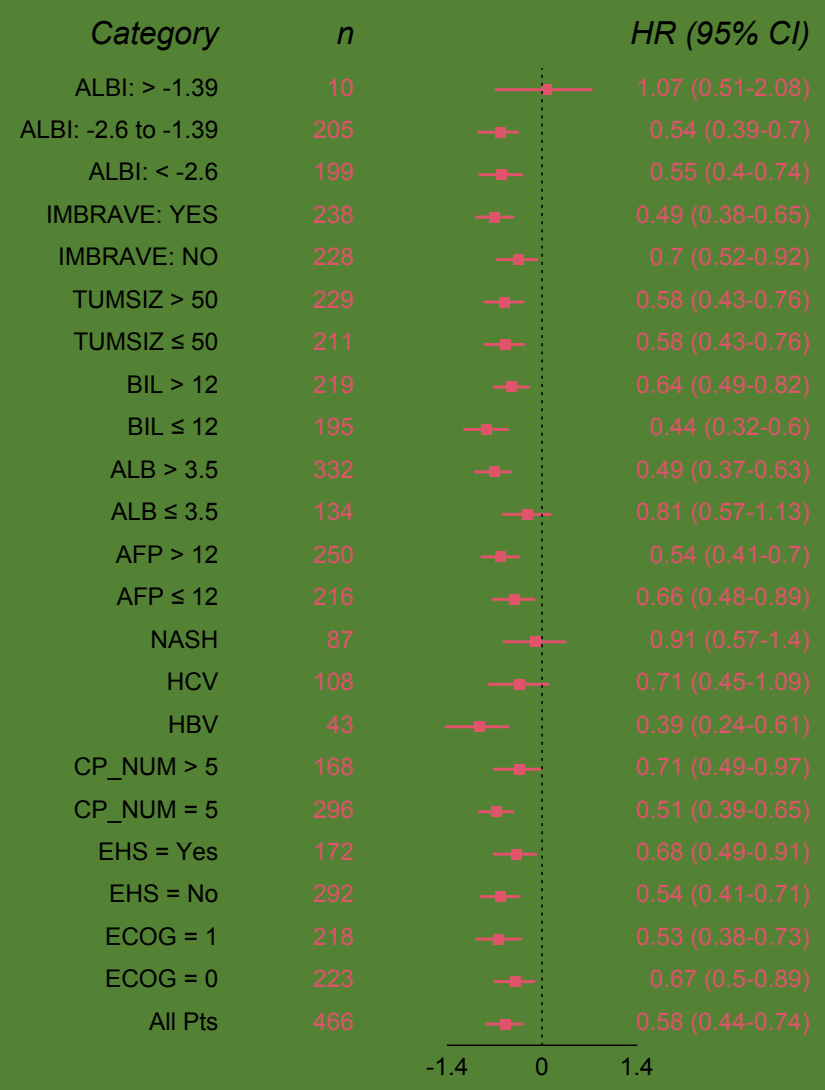


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*



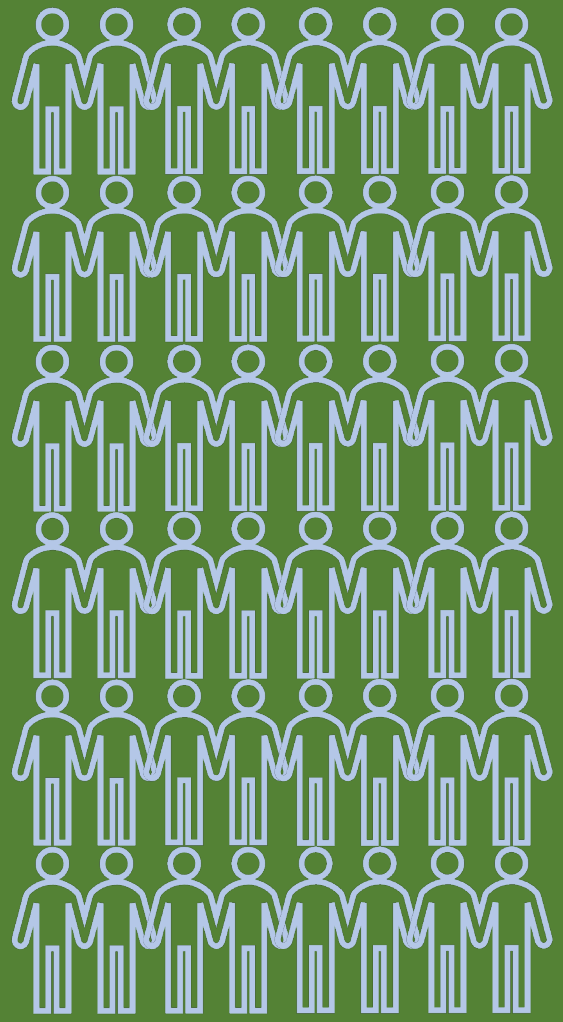
Category	n	HR (95% CI)
ALBI: > -1.39	10	1.07 (0.51-2.08)
ALBI: -2.6 to -1.39	205	0.54 (0.39-0.7)
ALBI: < -2.6	199	0.55 (0.4-0.74)
IMBRAVE: YES	238	0.49 (0.38-0.65)
IMBRAVE: NO	228	0.7 (0.52-0.92)
TUMSIZ > 50	229	0.58 (0.43-0.76)
TUMSIZ ≤ 50	211	0.58 (0.43-0.76)
BIL > 12	219	0.64 (0.49-0.82)
BIL ≤ 12	195	0.44 (0.32-0.6)
ALB > 3.5	332	0.49 (0.37-0.63)
ALB ≤ 3.5	134	0.81 (0.57-1.13)
AFP > 12	250	0.54 (0.41-0.7)
AFP ≤ 12	216	0.66 (0.48-0.89)
NASH	87	0.91 (0.57-1.4)
HCV	108	0.71 (0.45-1.09)
HBV	43	0.39 (0.24-0.61)
CP_NUM > 5	168	0.71 (0.49-0.97)
CP_NUM = 5	296	0.51 (0.39-0.65)
EHS = Yes	172	0.68 (0.49-0.91)
EHS = No	292	0.54 (0.41-0.71)
ECOG = 1	218	0.53 (0.38-0.73)
ECOG = 0	223	0.67 (0.5-0.89)
All Pts	466	0.58 (0.44-0.74)

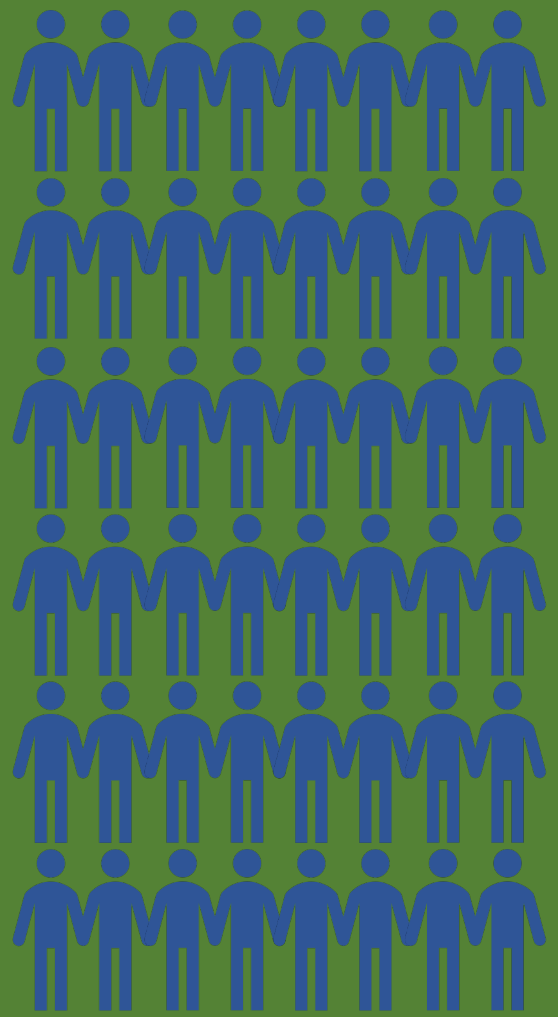
Personalised Synthetic Controls

How Can they be useful?

Personalised Synthetic Controls

Efficient Trial Design





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