Reconstructing Individual Patient Level Survival Data from Aggregate Survival Data using a Simulation Approach

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†research conducted whilst employed at AstraZeneca, UK

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Guyot method

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BMC Medical Research Methodology

TECHNICAL ADVANCE Open Access

Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves

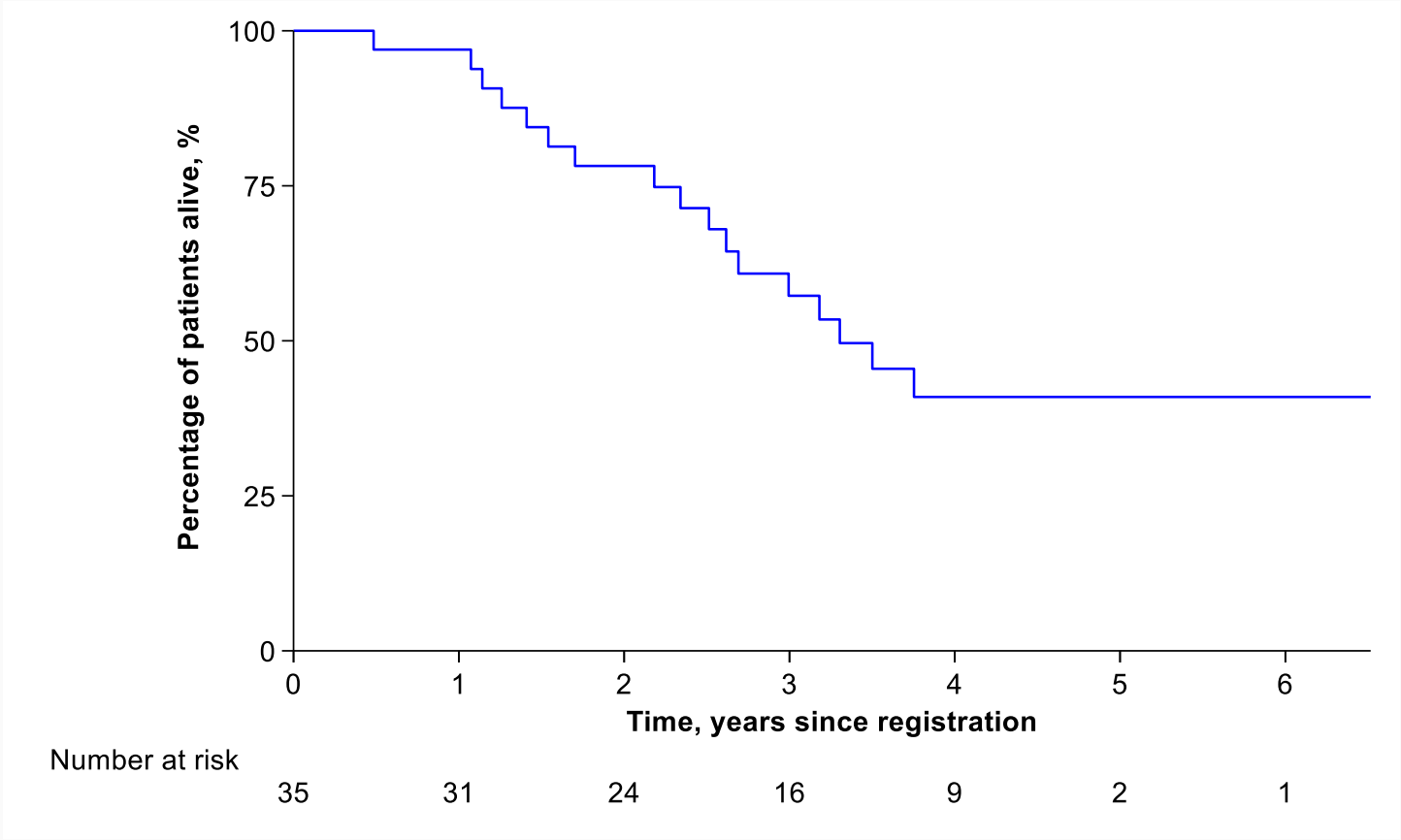
Patricia Guyot[1,2*], AE Ades[1], Mario JNM Ouwens[2] and Nicky J Welton[1]

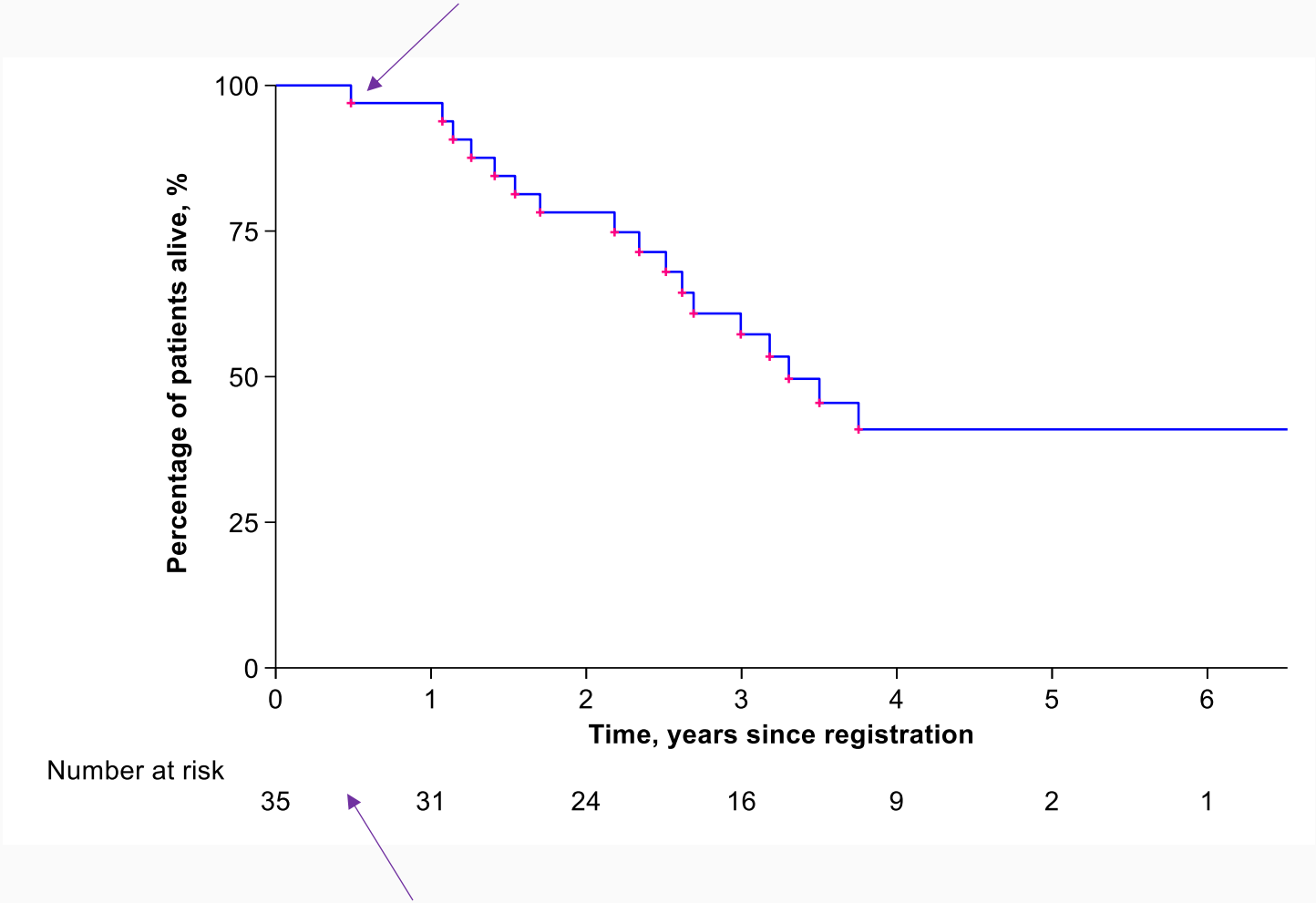
Abstract

Background: The results of Randomized Controlled Trials (RCTs) on time-to-event outcomes that are usually reported are median time to events and Cox Hazard Ratio. These do not constitute the sufficient statistics required for meta-analysis or cost-effectiveness analysis, and their use in secondary analyses requires strong assumptions that may not have been adequately tested. In order to enhance the quality of secondary data analyses, we propose a method which derives from the published Kaplan Meier survival curves a close approximation to the original individual patient time-to-event data from which they were generated.

Methods: We develop an algorithm that maps from digitised curves back to KM data by finding numerical solutions to the inverted KM equations, using where available information on number of events and numbers at risk. The reproducibility and accuracy of survival probabilities, median survival times and hazard ratios based on reconstructed KM data was assessed by comparing published statistics (survival probabilities, medians and hazard ratios) with statistics based on repeated reconstructions by multiple observers.

Results: The validation exercise established there was no material systematic error and that there was a high


100
75
50
25
0
Percentage of patients alive, %
0
1
2
3
4
5
6
Time, years since registration
Number at risk
35
31
24
16
9
2
1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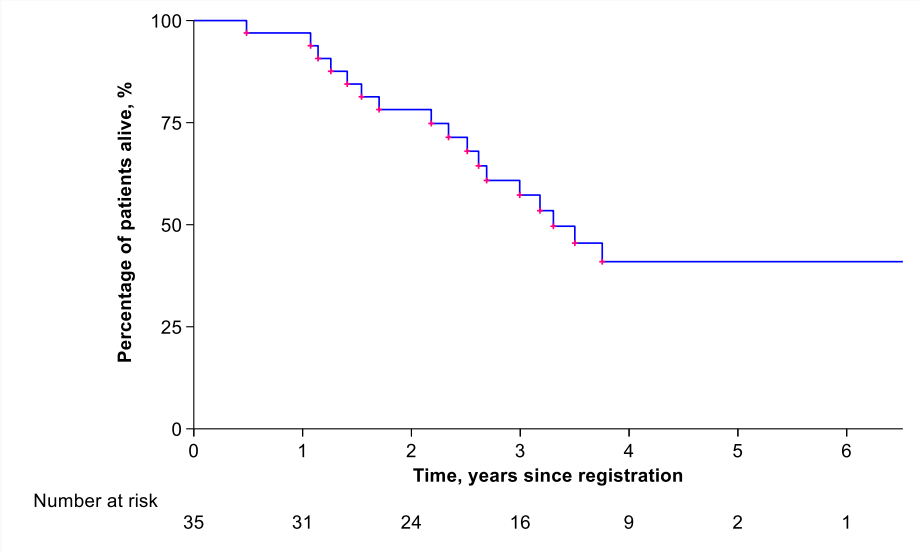
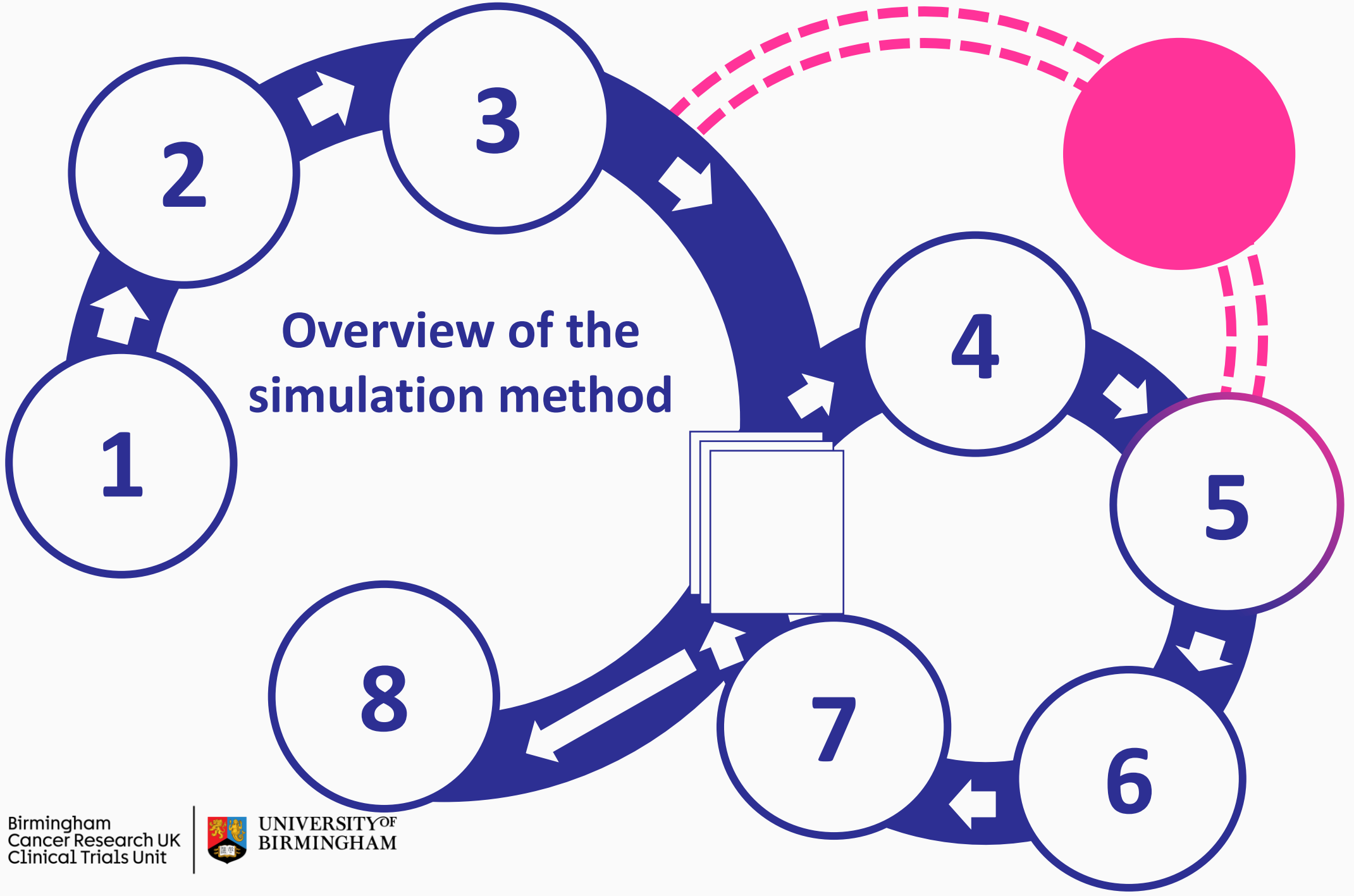
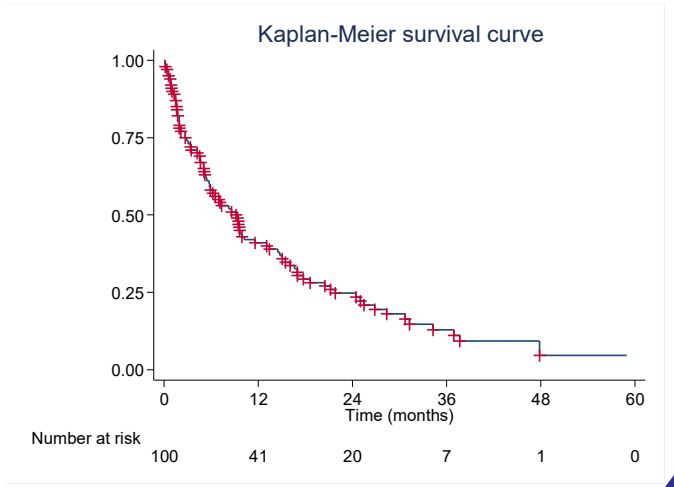


Patient	Survival time	Event
1		
2		
3		
...		

Overview of the simulation method





Extract coordinates

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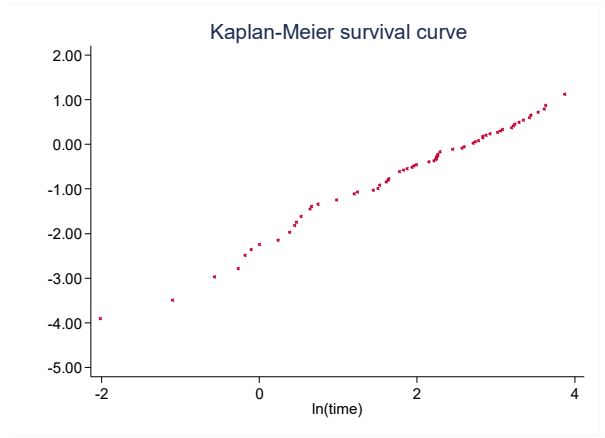
Transform survival



3

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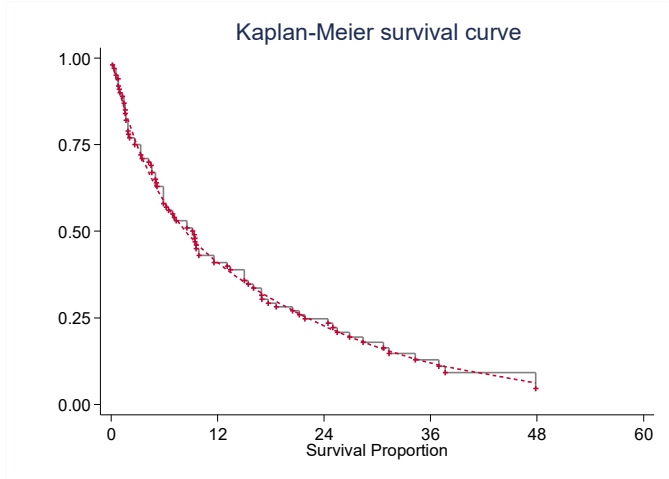
curve

2 4



Model survival distribution

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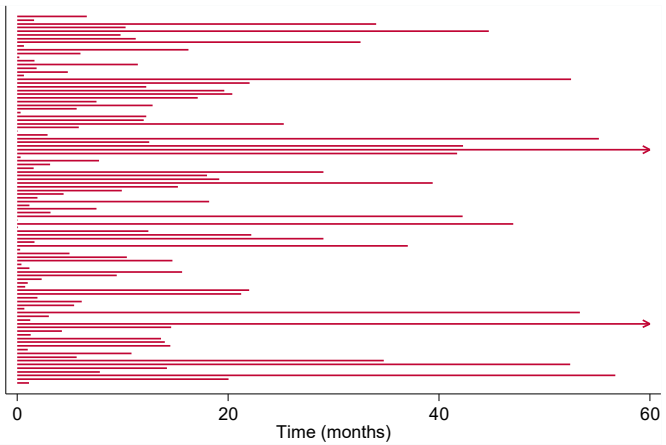
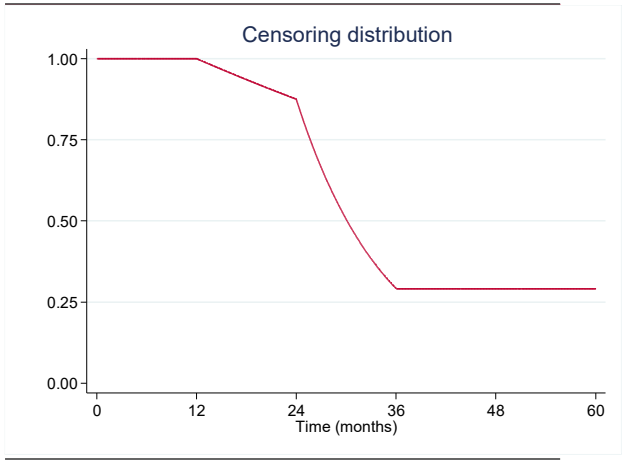
Simulate a survival time for each patient



5

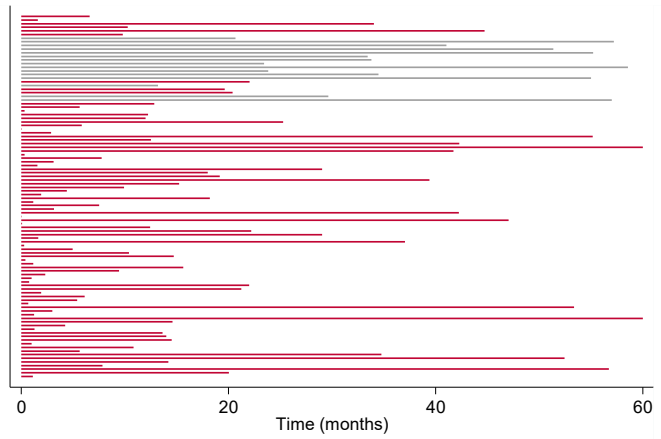
Model censoring



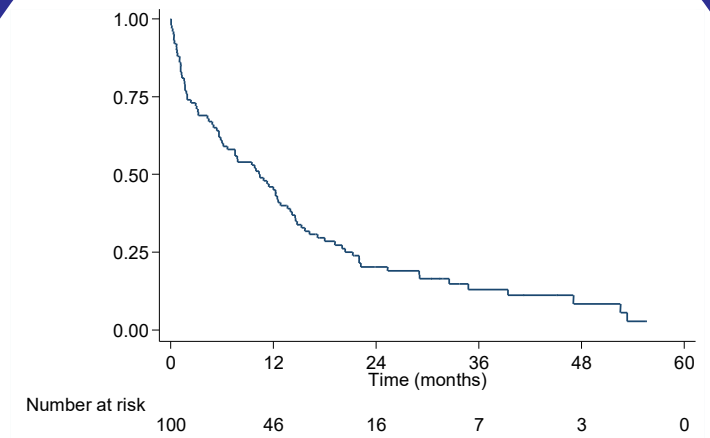
Simulate an event time for each patient

tient
40
60
Time (months)
Simulate a censoring time
for each patient
0
20
40
60
Time (months)

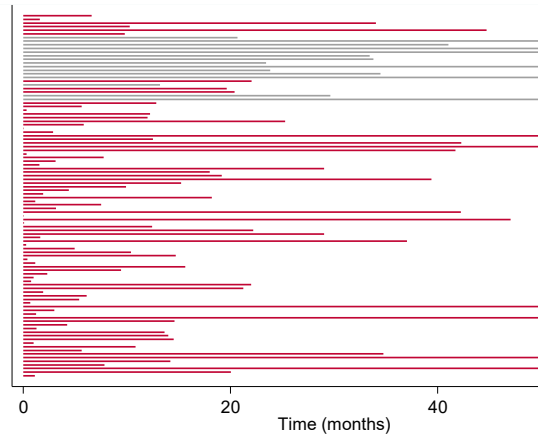
7



Define the survival time and status



Analyse the data



Define the surviv

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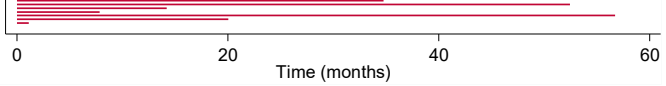
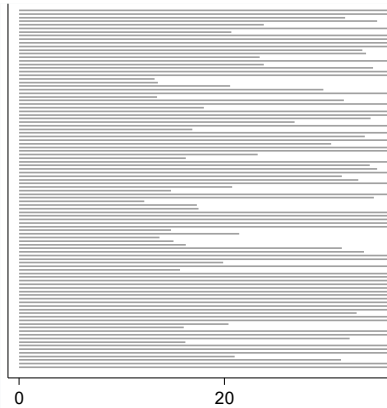
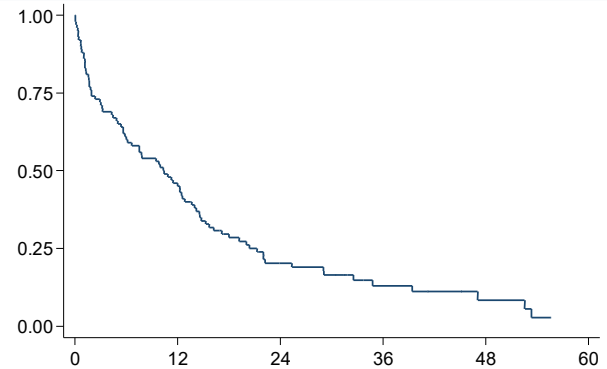
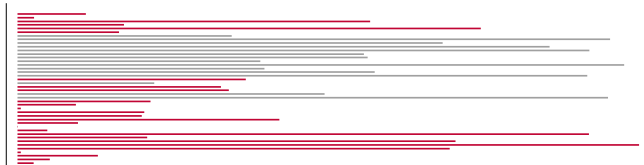
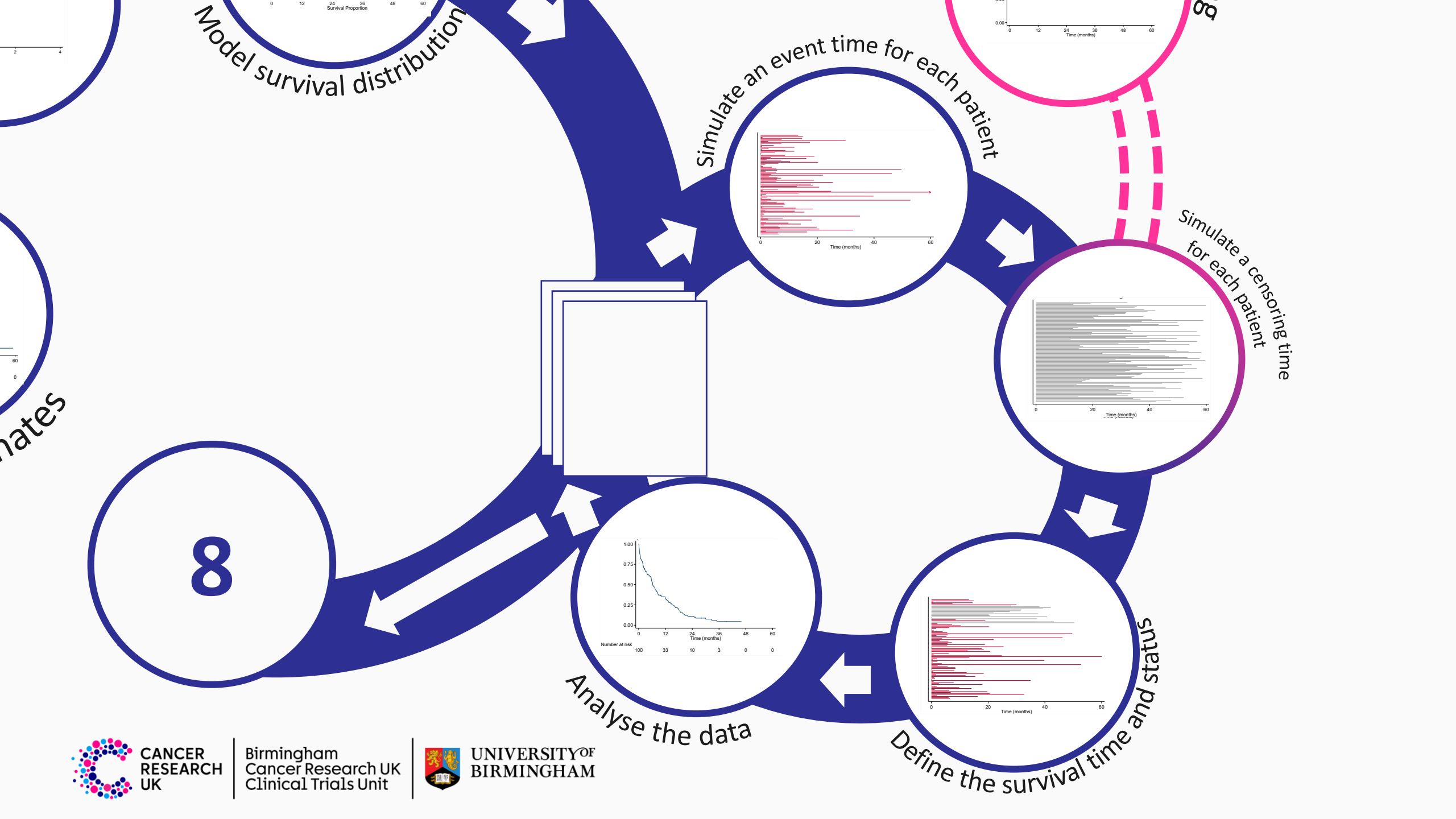

0
20
40
60
Time (months)


0
20
Time (months)


1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60




Model survival distribution
Survival Proportion
Simulate an event time for each patient
Time (months)
Simulate a censoring time for each patient
Time (months)
Define the survival time and status
Time (months)
Analyse the data
Time (months)
Number at risk
100 33 10 3 0 0
8
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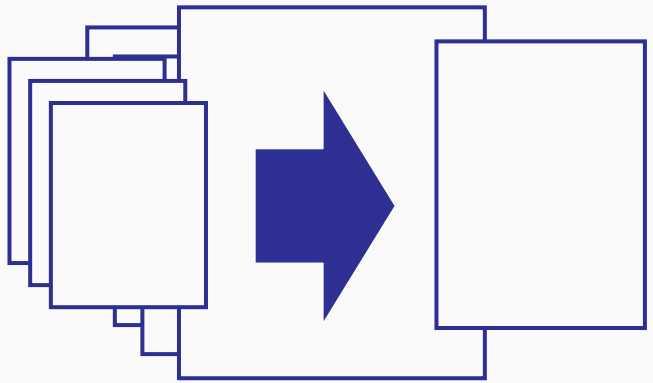
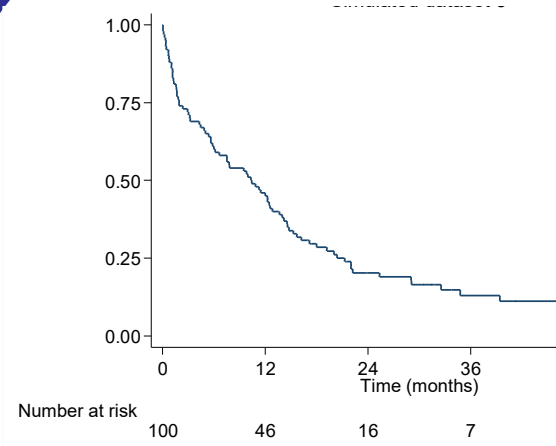
Average over all the datasets





Analyse the data

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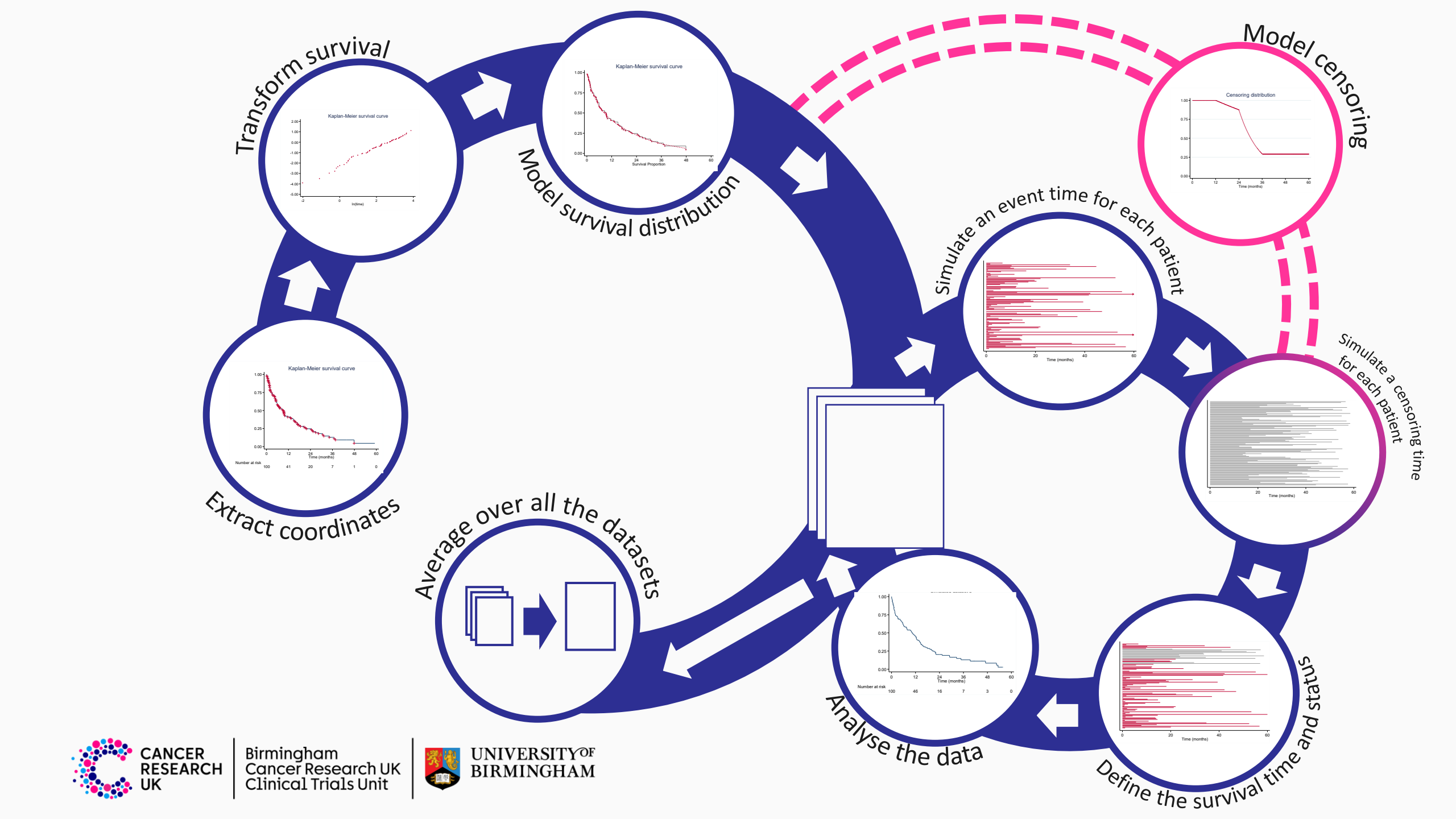

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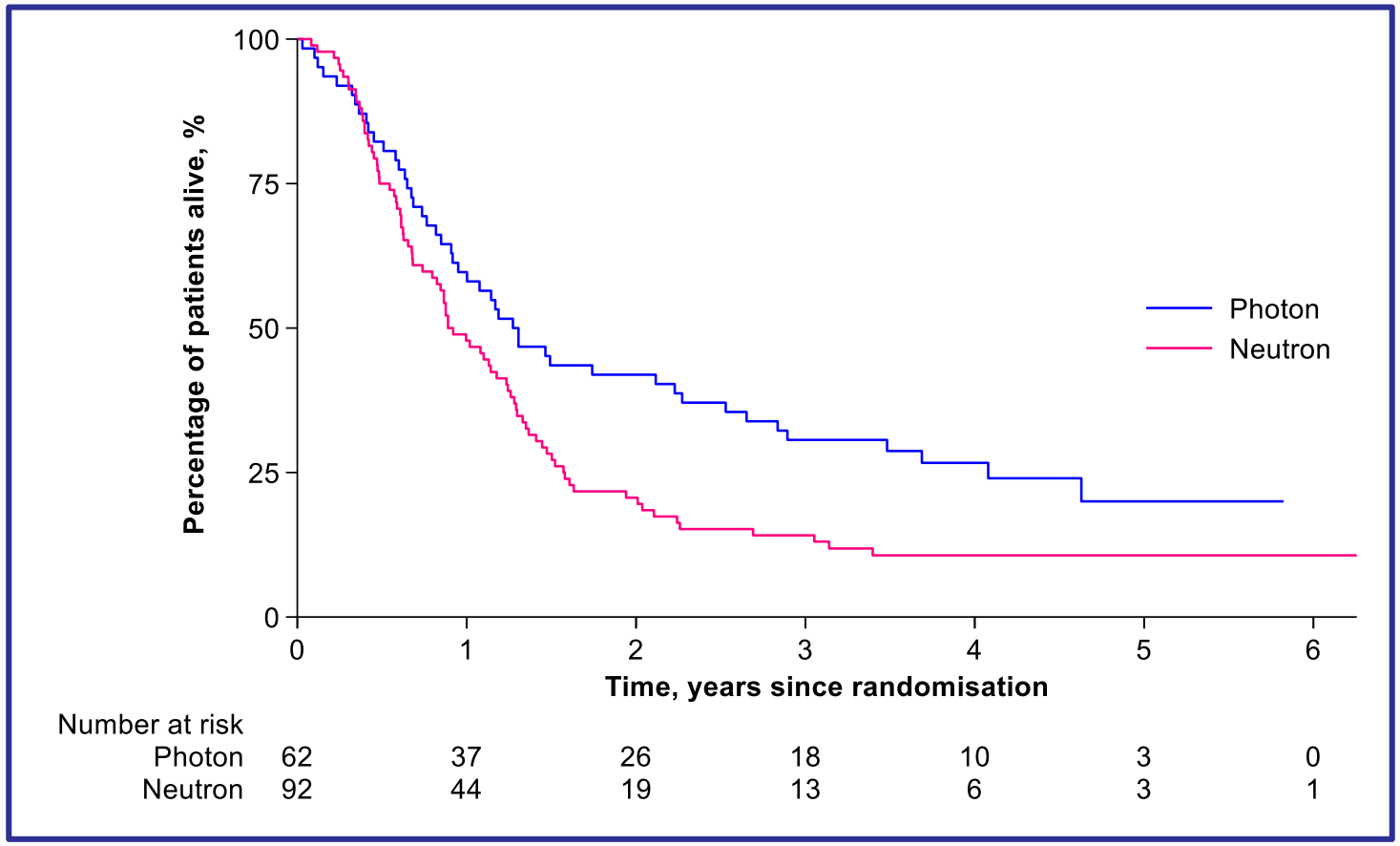
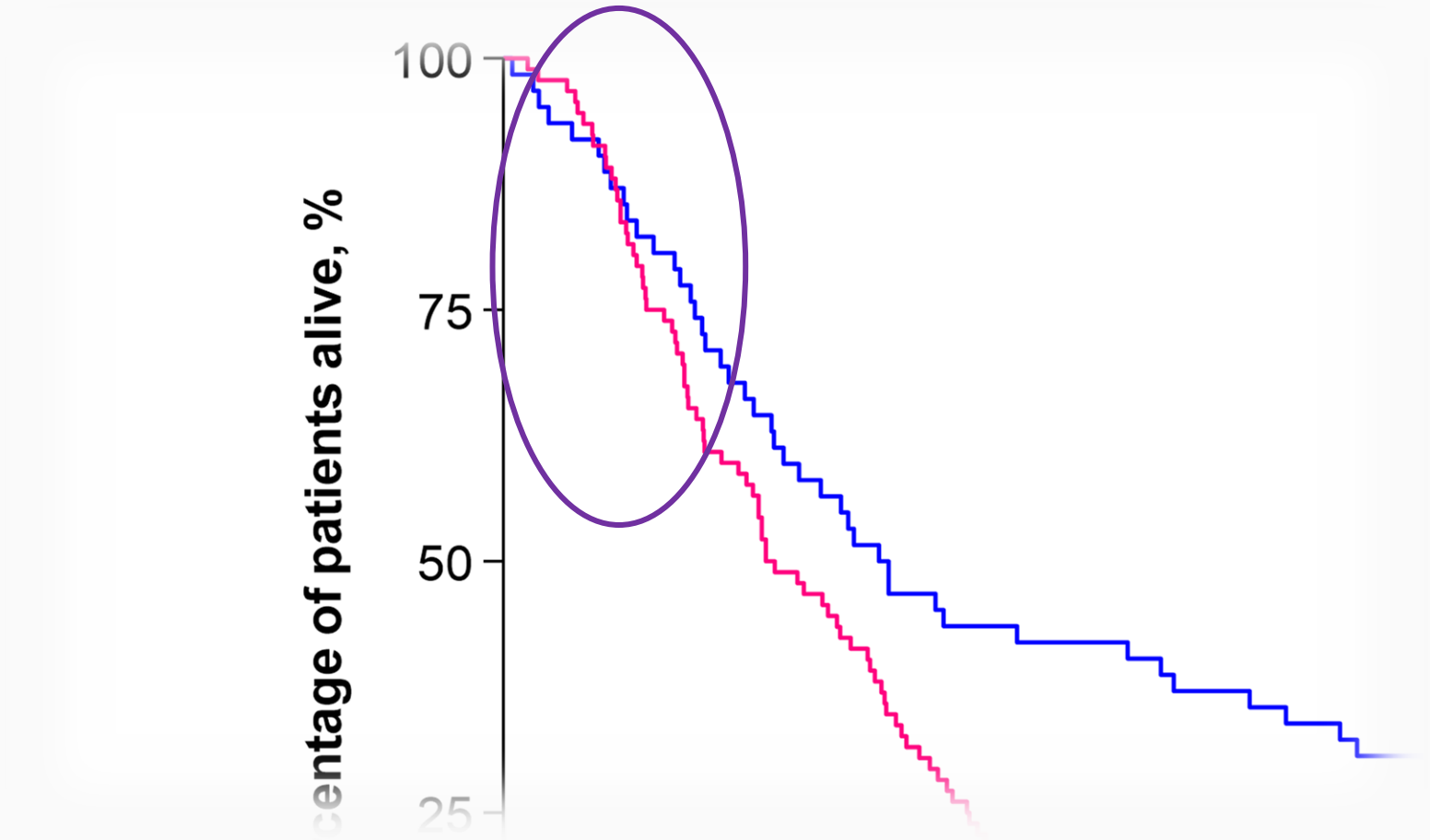


Neutron versus photon therapy for pelvic cancers


100
75
50
25
entage of patients alive, %

How well does it work?

Dataset	Results from initial analysis						
	Number of events		Median survival time		Hazard ratio	Restricted mean survival time*	
	Photon	Neutron	Photon	Neutron		Photon	Neutron
IPD	47 (76%)	82 (89%)	1.27 (0.91, 2.27)	0.89 (0.74, 1.24)	1.57 (1.09, 2.25)	1.80 (1.47, 2.13)	1.29 (1.07, 1.50)
Guyot	47 (76%)	82 (89%)	1.19 (0.86, 2.23)	0.92 (0.70, 1.27)	1.47 (1.03, 2.10)	1.78 (1.55, 2.01)	1.30 (1.15, 1.45)
Simulation (2000 datasets)	47.2 (76%)	82.5 (90%)	1.33 (0.89, 2.11)	0.95 (0.75, 1.16)	1.57 (1.09, 2.32)	1.78 (1.47, 2.11)	1.29 (1.09, 1.49)

* At 3.5 years

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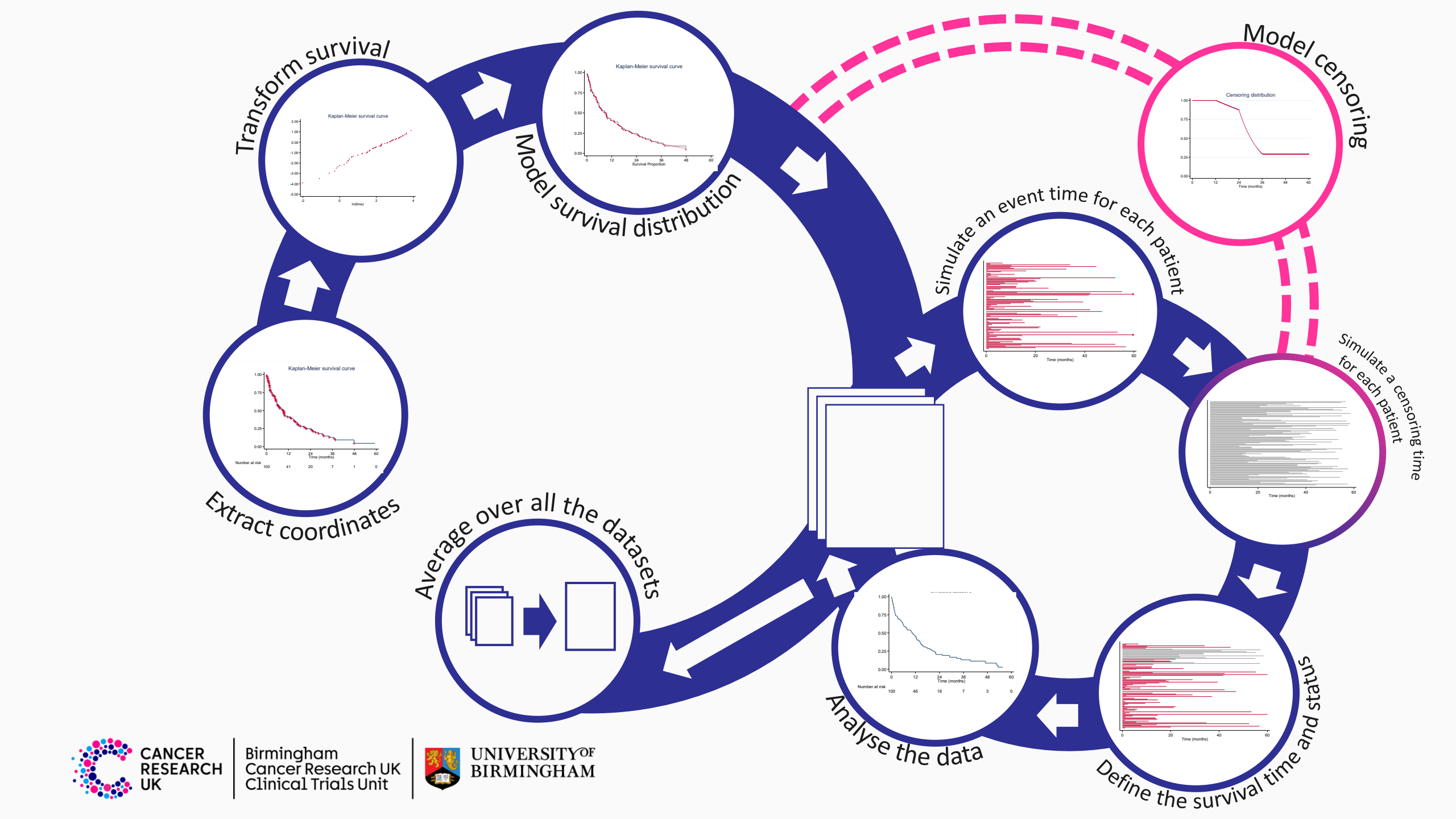
How well does it work?

Dataset	Results from secondary analysis				
	Coefficients from the time-dependent Cox model		Hazard ratios from the piecewise Cox model		
	Main effects	Time dependent effect	0 and 6 months	6 and 12 months	12+ months
IPD	0.482 (-0.115, 0.850)	0.198 (-0.220, 0.617)	1.41 (0.69, 2.90)	1.39 (0.72, 2.68)	1.79 (1.04, 3.08)
Guyot	0.404 (0.045, 0.765)	0.171 (-0.251, 0.594)	1.23 (0.61, 2.48)	1.32 (0.68, 2.55)	1.73 (1.02, 2.93)
Simulation (2000 datasets)	0.489 (0.113, 0.873)	0.188 (-0.288, 0.648)	1.33 (0.62, 3.07)	1.43 (0.77, 2.87)	1.87 (1.07, 3.39)



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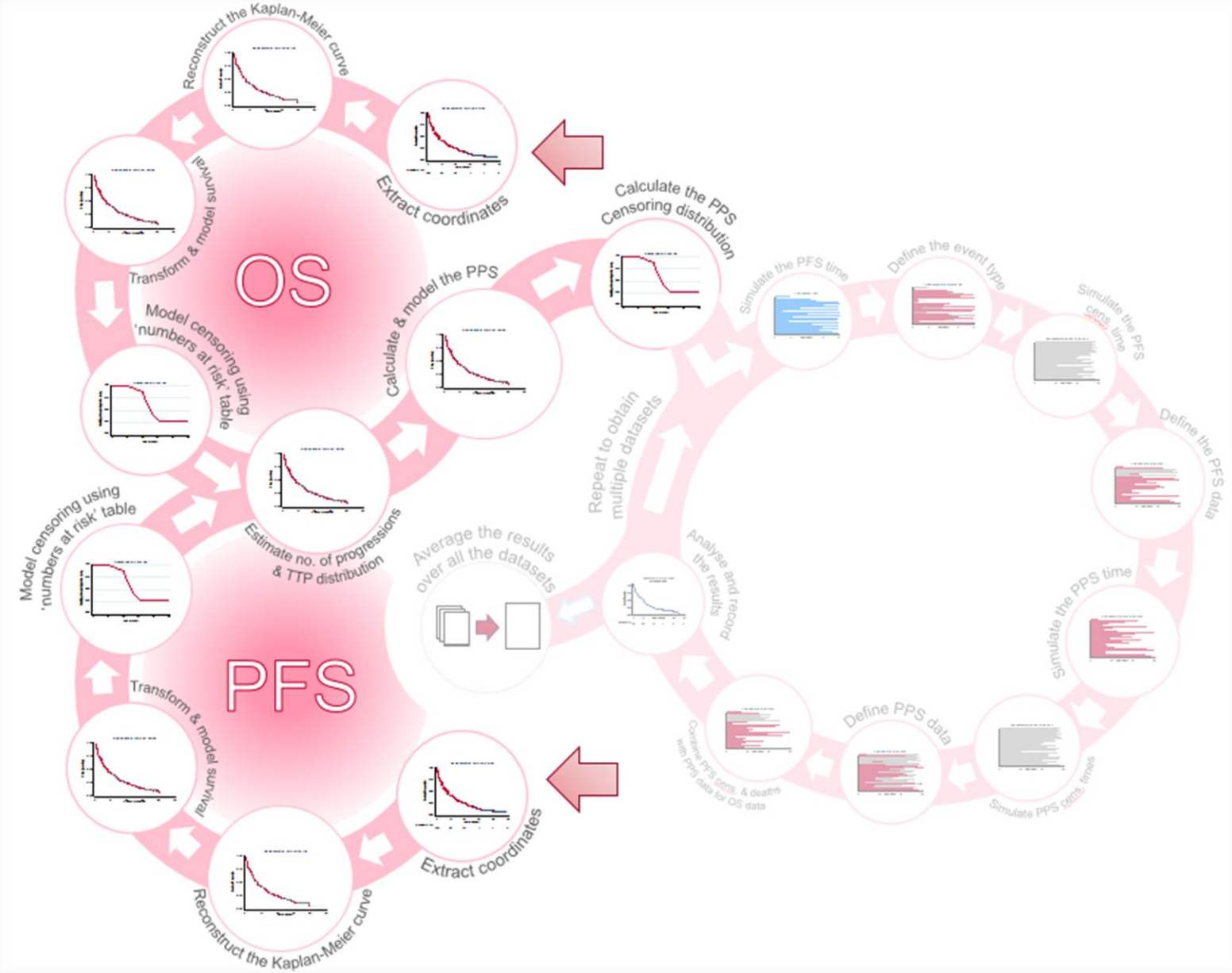

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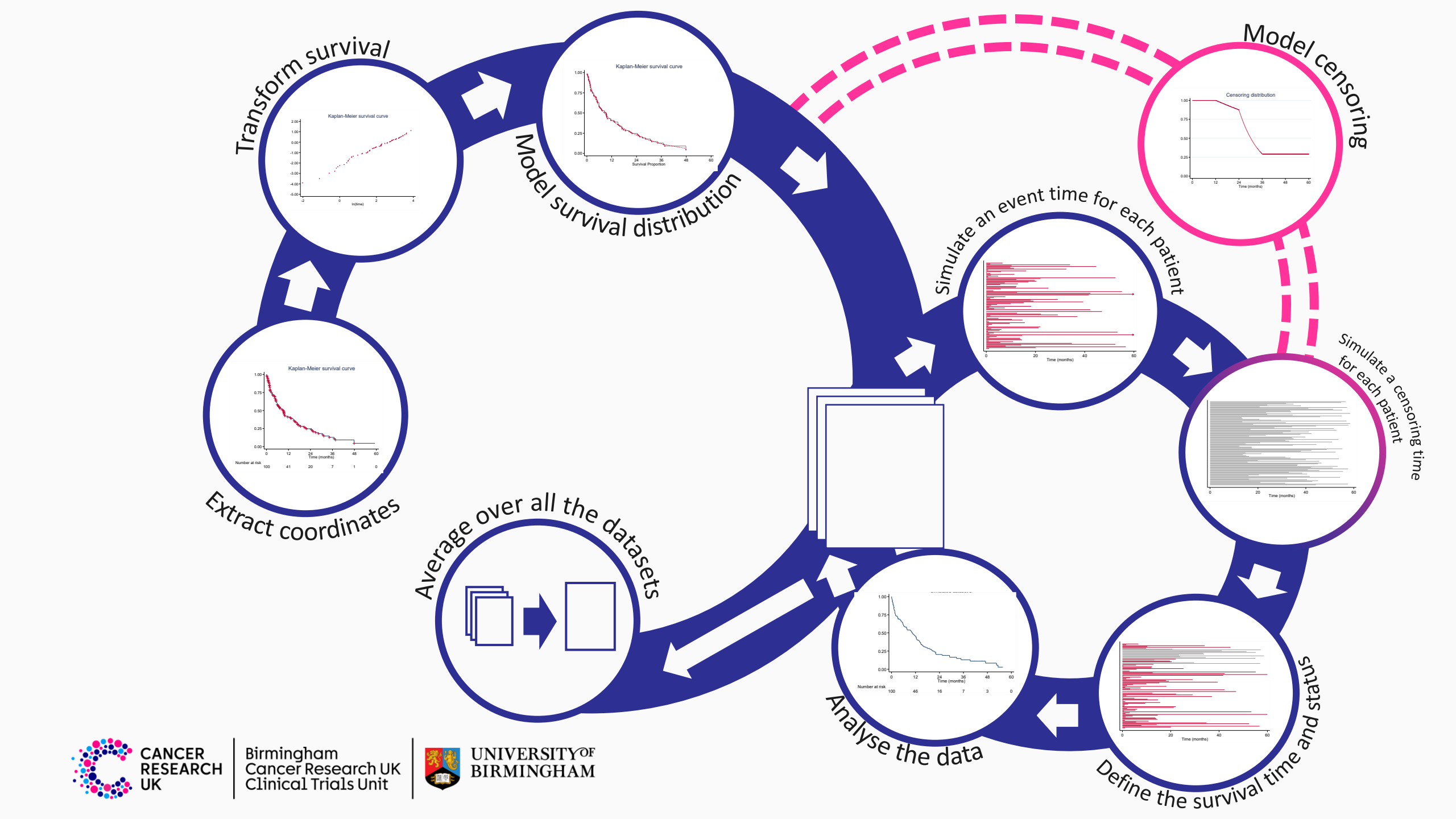

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