Statistically Speaking Lecture Series

Sponsored by the Biostatistics Collaboration Center

Time-to-Event Analysis: A ‘Survival’ Guide

Lauren C Balmert, PhD

Assistant Professor, Department of Preventive Medicine

Northwestern Medicine
Feinberg School of Medicine

BCC: Biostatistics Collaboration Center

Who We Are

Leah J. Welty, PhD
Assoc. Professor
BCC Director

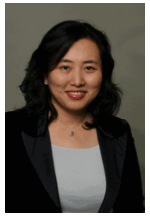
Lauren Balmert, PhD
Asst. Professor

Jody D. Ciolino, PhD
Asst. Professor

Kwang-Youn A. Kim, PhD
Assoc. Professor

Masha Kocherginsky, PhD
Assoc. Professor

Mary J. Kwasny, ScD
Assoc. Professor



Julia Lee, PhD, MPH
Assoc. Professor

David Aaby, MS
Senior Stat. Analyst

Elizabeth Gray, MS
Stat. Analyst

Kimberly Koloms, MS
Stat. Analyst

Amy Yang, MS
Senior Stat. Analyst

Tameka L. Brannon
Financial | Research
Administrator

Biostatistics Collaboration Center (BCC)

Mission: to support investigators in the conduct of high-quality, innovative health-related research by providing expertise in biostatistics, statistical programming, and data management.

How do we accomplish this?

1. Every investigator is provided a **FREE** initial consultation of 1-2 hours, subsidized by **FSM Office for Research**. Thereafter:
   a) Grants
   b) Subscription
   c) Re-charge (Hourly) Rates

2. Grant writing (e.g. developing analysis plans, power/sample size calculations) is also supported by FSM at **no cost to the investigator**, with the goal of establishing successful collaborations.

BCC: Biostatistics Collaboration Center

What We Do

- Many areas of expertise, including:
  - Bayesian Methods
  - Big Data
  - Bioinformatics
  - Causal Inference
  - Clinical Trials
  - Database Design
  - Genomics
  - Longitudinal Data
  - Missing Data
  - Reproducibility
  - Survival Analysis

Many types of software, including:

R

STATA

SAS

SPSS

REDCap
Research Electronic Data Capture

BCC: Biostatistics Collaboration Center

Shared Statistical Resources

Biostatistics Collaboration Center (BCC)

- Supports non-cancer research at NU
- Provides investigators an initial 1-2 hour consultation subsidized by the FSM Office of Research
- Grant, Hourly, Subscription

Quantitative Data Sciences Core (QDSC)

- Supports all cancer-related research at NU
- Provides free support to all Cancer Center members subsidized by RHLCCC
- Grant

Biostatistics Research Core (BRC)

- Supports Lurie Children's Hospital affiliates
- Provides investigators statistical support subsidized by the Stanley Manne Research Institute at Lurie Children's.
- Hourly

BCC: Biostatistics Collaboration Center

Shared Resources Contact Info

- Biostatistics Collaboration Center (BCC)
  - Website: http://www.feinberg.northwestern.edu/sites/bcc/index.html
  - Email: bcc@northwestern.edu
  - Phone: 312.503.2288

- Quantitative Data Sciences Core (QDSC)
  - Website: http://cancer.northwestern.edu/research/shared_resources/quantitative_data_sciences/index.cfm
  - Email: qdsc_rhlccc@northwestern.edu
  - Phone: 312.503.2288

- Biostatistics Research Core (BRC)
  - Website: https://www.luriechildrens.org/en-us/research/facilities/Pages/biostatistics.aspx
  - Email: mereed@luriechildrens.org
  - Phone: 773.755.6328

Northwestern Medicine®
Feinberg School of Medicine

Time-to-Event Analysis: A ‘Survival’ Guide

Studies involving survival analysis

- Time to **death** in a breast cancer trial
- Time to **hospitalization** of children with pneumonia
- Time to **recurrence** of ovarian tumors
- Time to **remission** from depressive symptoms
- Time to **cessation** of postoperative opioids

Objectives of survival analysis

- Estimate survival
  - What is the probability of surviving 5 years post surgery?
- Compare survival between groups
  - Are there differences in survival between treatment groups?
- Assess the relationship of covariates on the time-to-event
  - How do clinical/behavioral characteristics affect survival?

Why do we care about time-to-event?

	Recurrence of Tumor	No Recurrence of Tumor
Treatment A	25	40
Treatment B	30	35

Compare proportion of tumor recurrence between treatment groups: → OR = 0.73

P-value = 0.38

	Treatment A	Treatment B
Time to Recurrence (months)	18.1 ± 2.1	8.5 ± 3.4

Why not traditional methods for time-to-event data?

- Incomplete information
- Not everyone experienced the event of interest

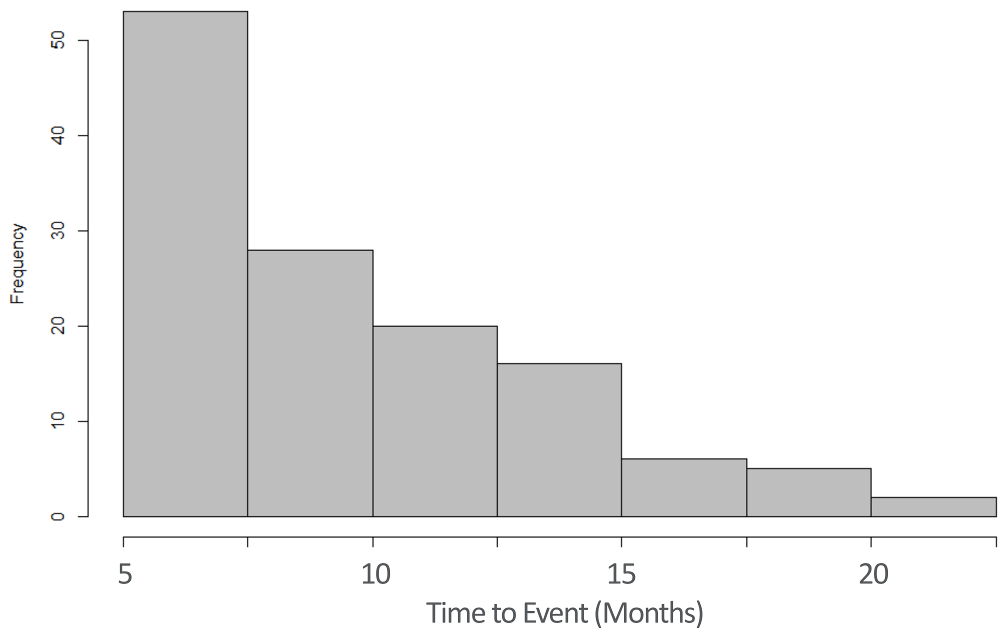
	Recurrence of Tumor	No Recurrence of Tumor
Treatment A	25	40
Treatment B	30	35

No time to event

Why not traditional methods for time-to-event data?

- Compare mean time between groups?

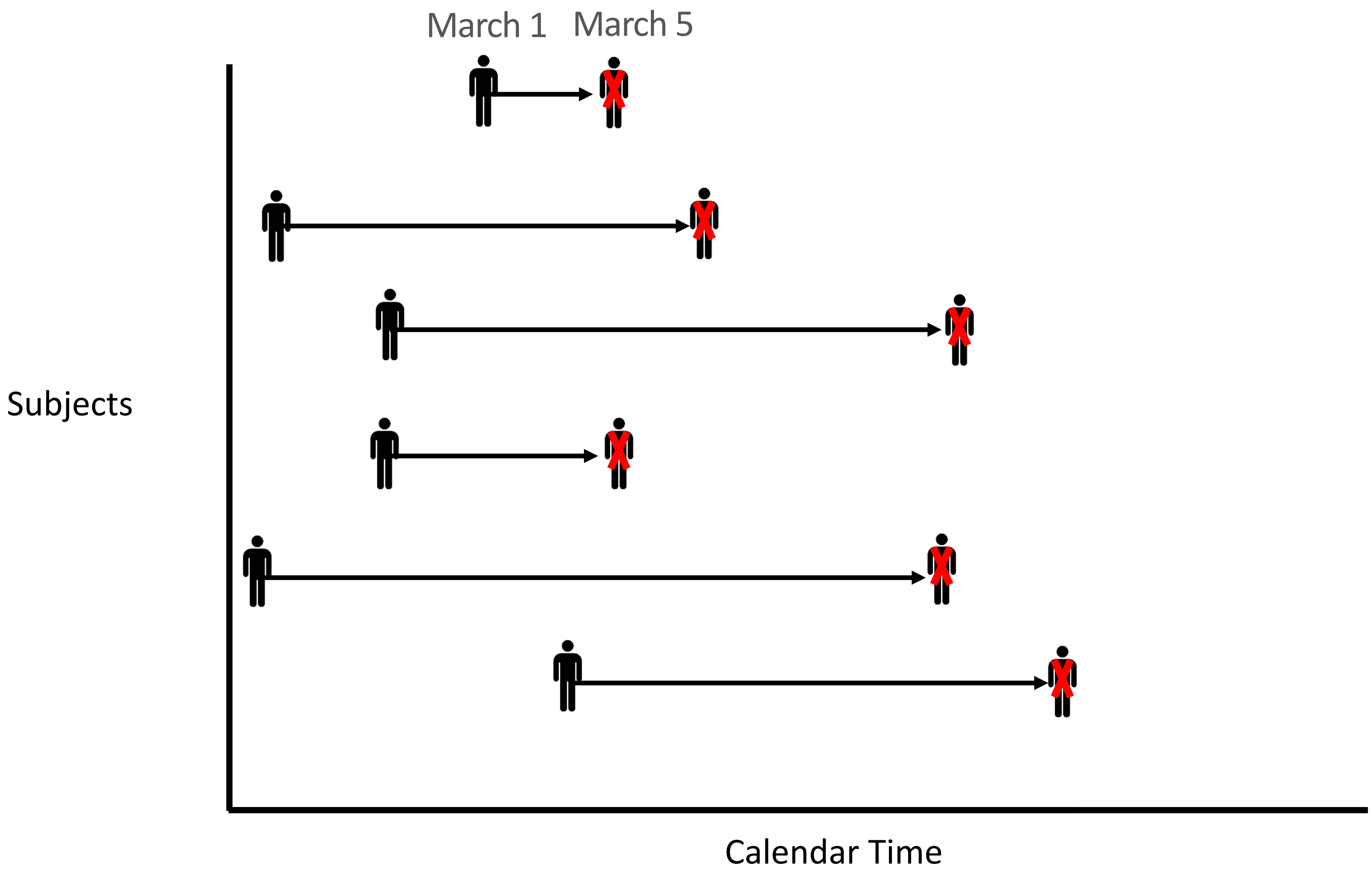
	Treatment A	Treatment B
Time to Recurrence (months)	18.1 ± 2.1	8.5 ± 3.4

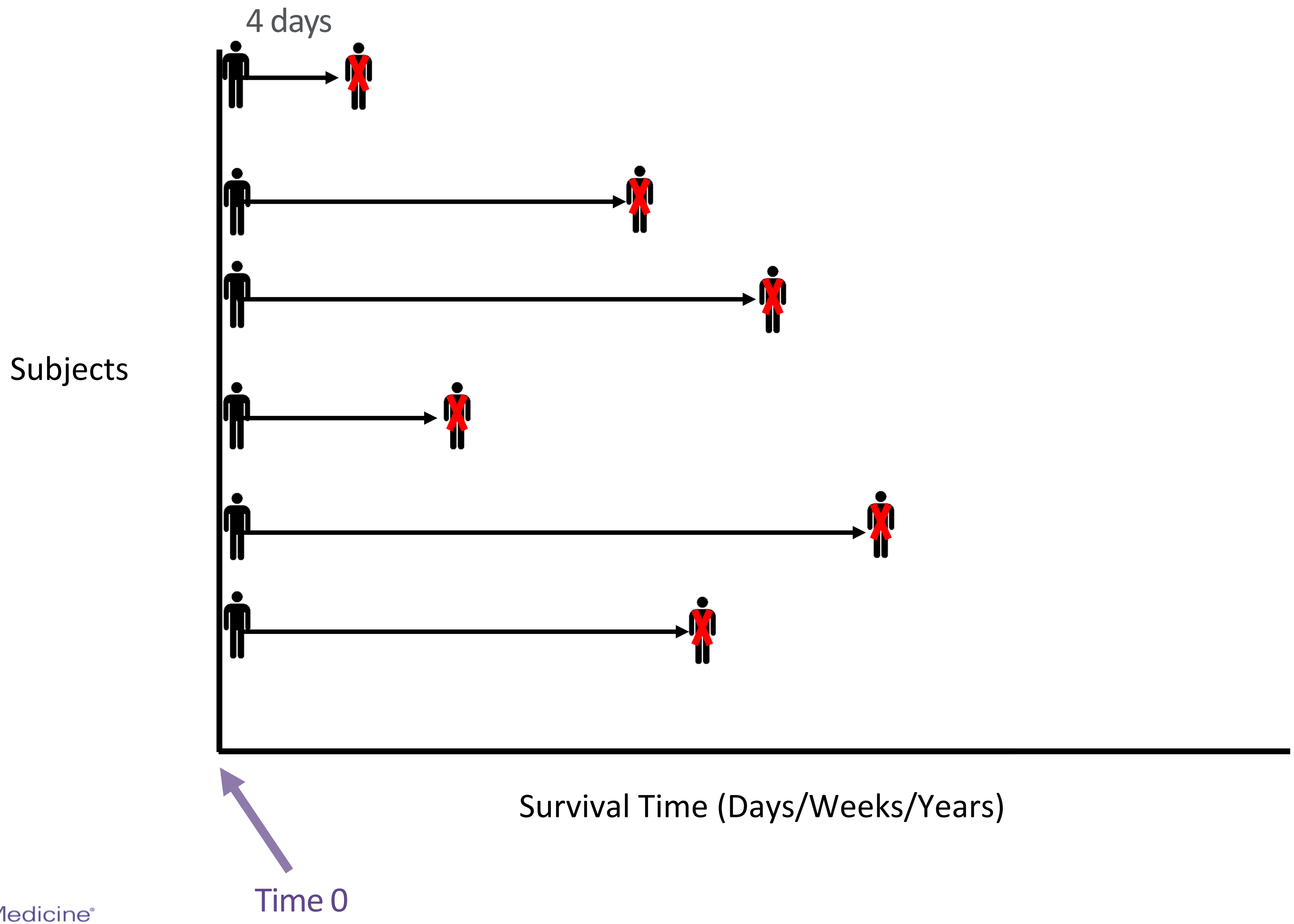


Why not traditional methods for time-to-event data?

- Compare proportion of events between groups
  - Chi-square test, logistic regression?
  - Ignores time

- Compare mean time between groups
  - T-test, linear regression?
  - Not normally distributed
  - Ignores subjects without events

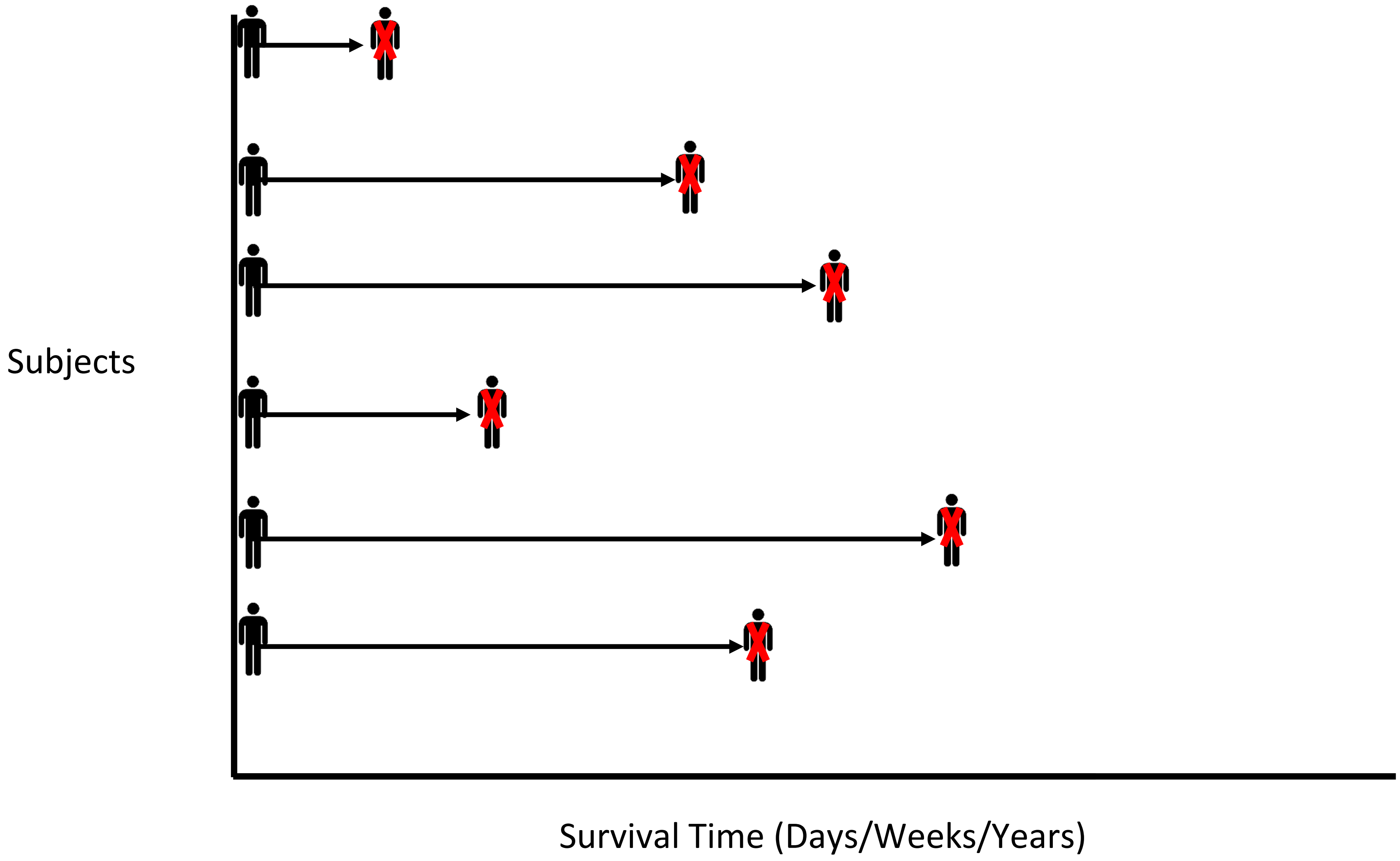

March 1
March 5
Subjects
Calendar Time

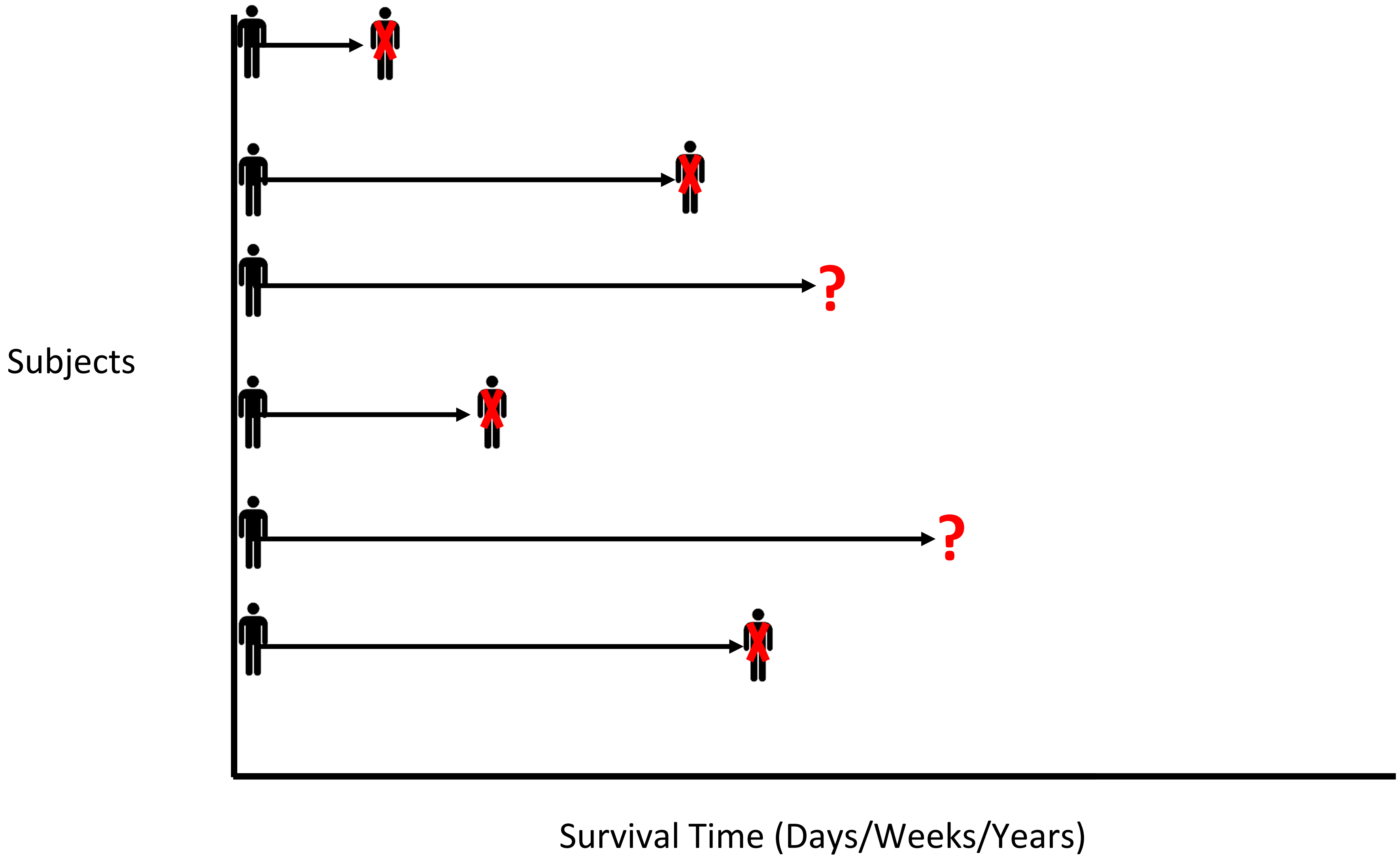

4 days
Subjects
Survival Time (Days/Weeks/Years)
Time 0

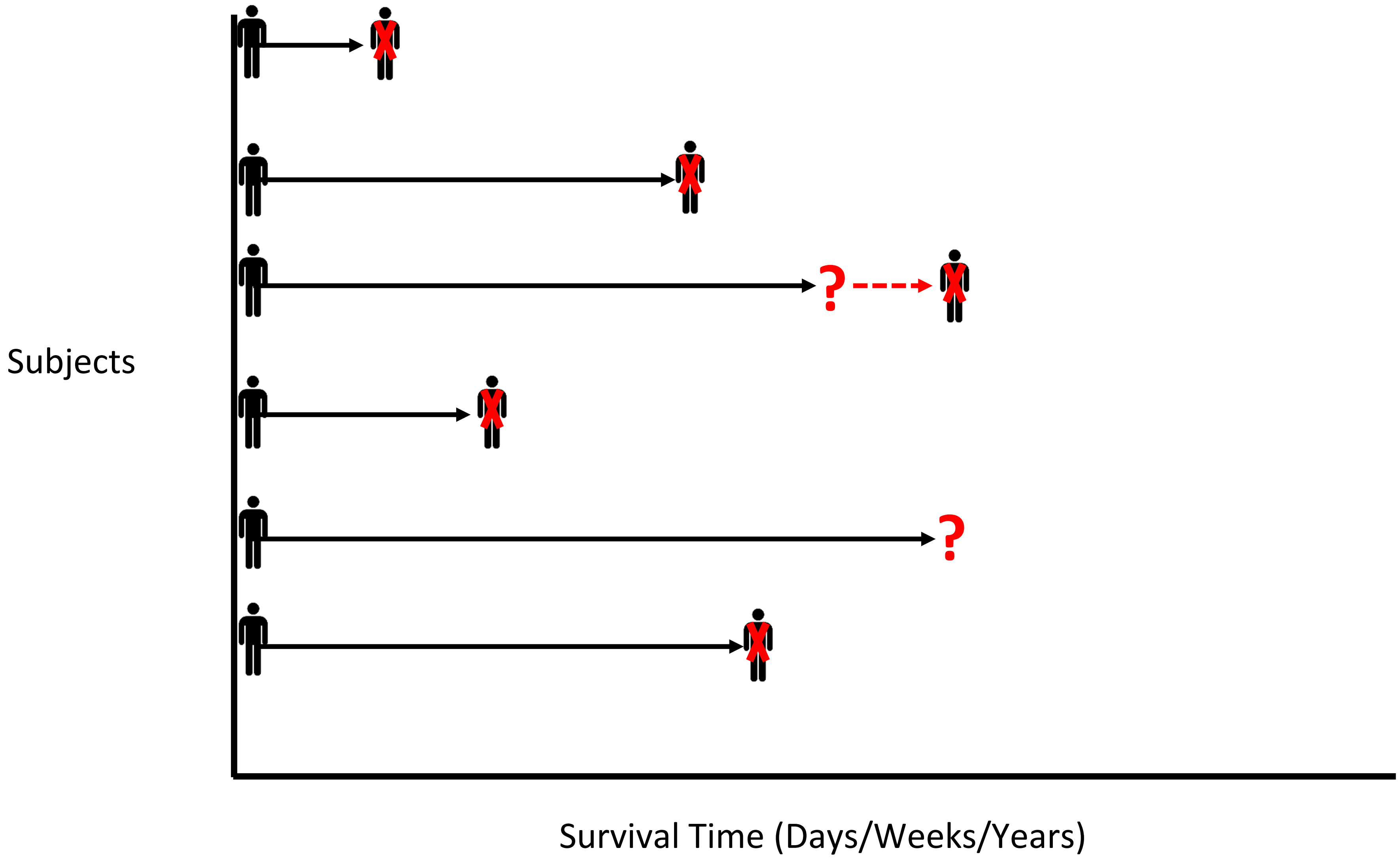
Follow-up Time

- Defining time zero
  - Time at which participants are considered at risk
  - Enrollment into study
  - Time of randomization

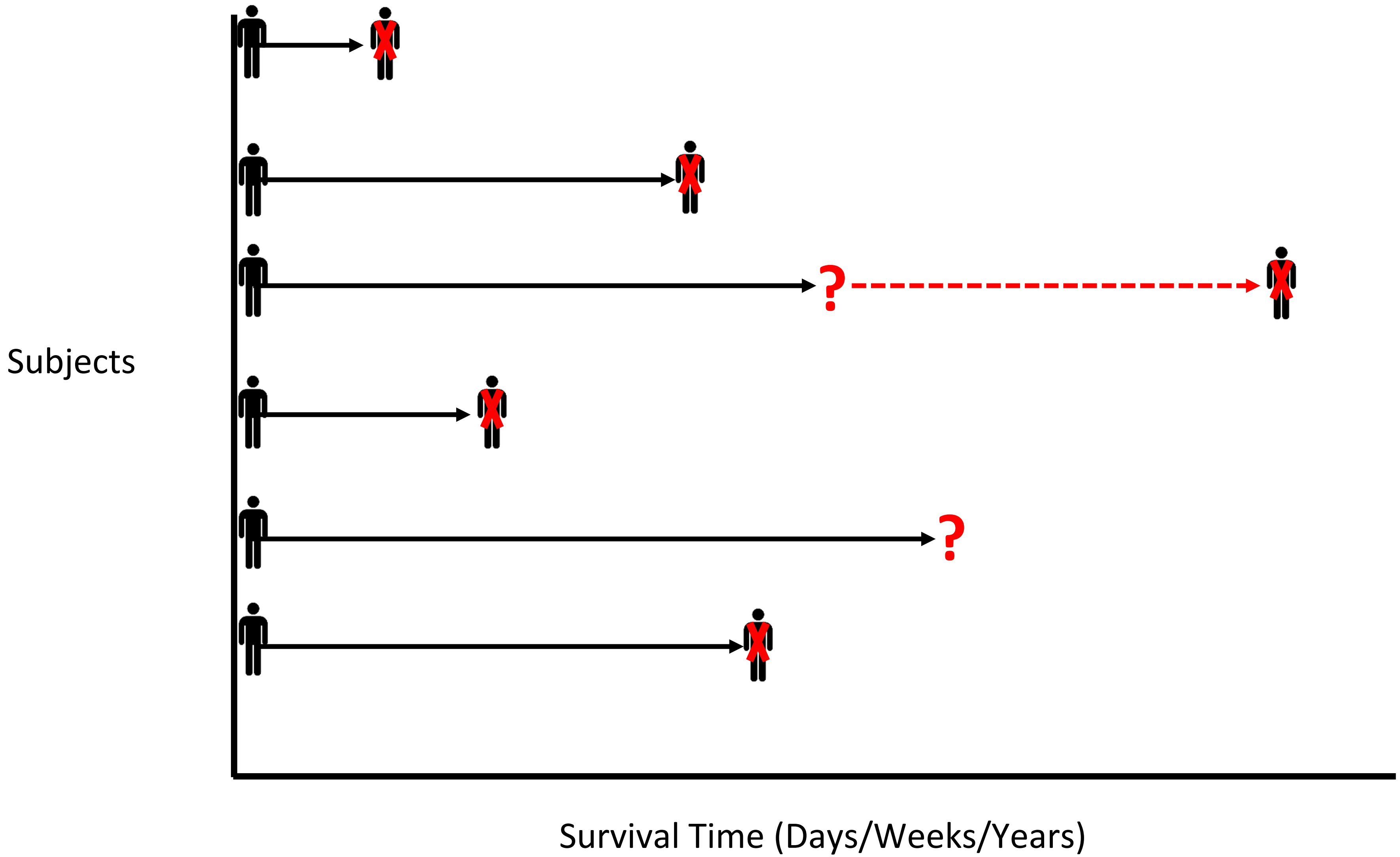
- Followed until
  - Event occurs
  - Study ends
  - Participant is lost


Subjects
Survival Time (Days/Weeks/Years)


Subjects
?
?
Survival Time (Days/Weeks/Years)



Subjects
Survival Time (Days/Weeks/Years)

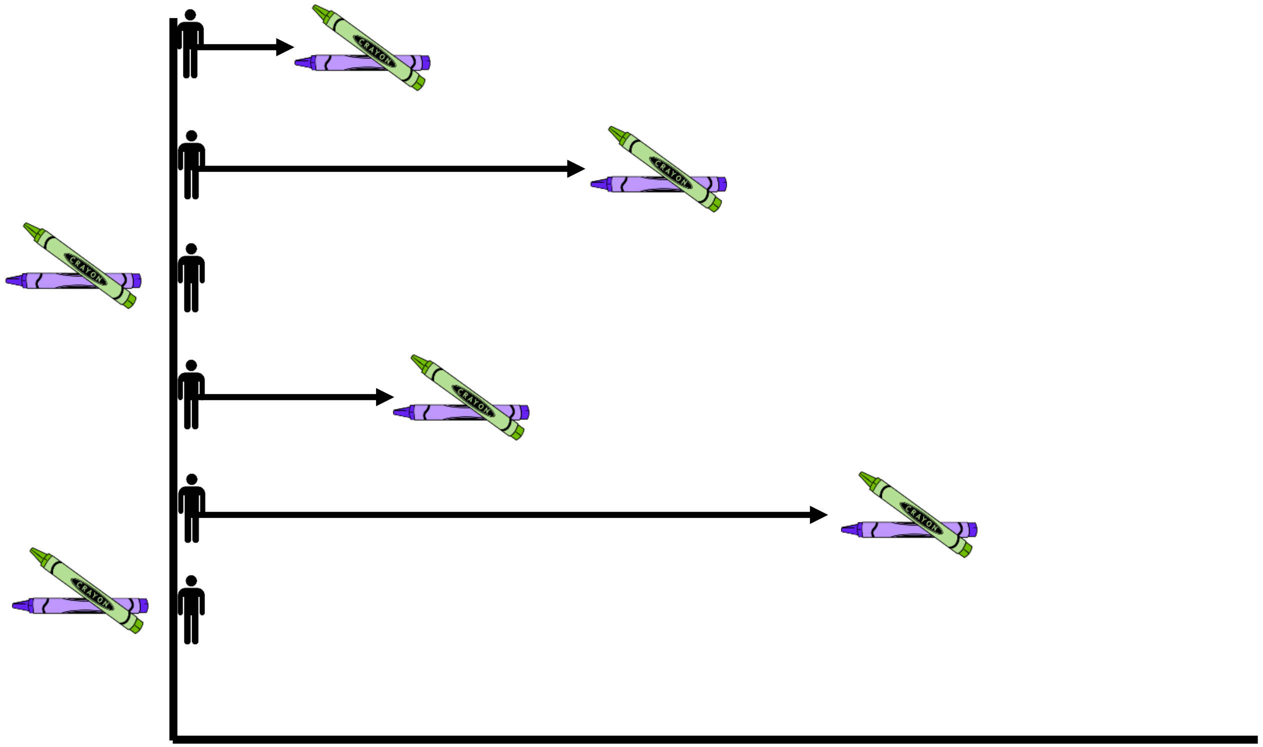

Subjects
Survival Time (Days/Weeks/Years)

Censoring

- Right censoring (most common)
  - Event occurs after a certain time point, but unknown how long after
  - Study ends
  - Lost to follow-up
  - Subject withdraws

Censoring

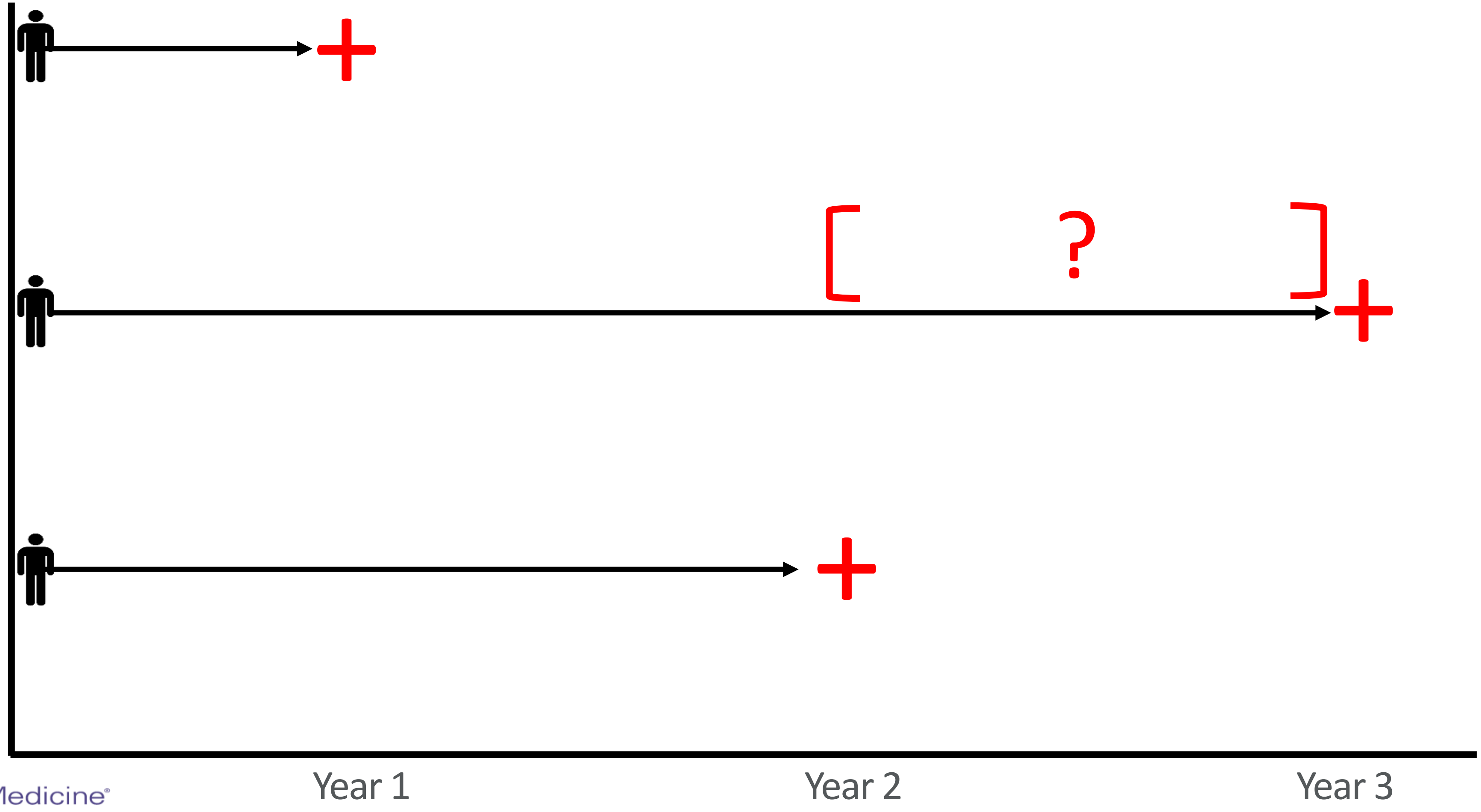
- Left censoring
  - Event occurs before a certain time point, but unknown how much earlier



Survival Time (Days/Weeks/Years)

Censoring

- Interval censoring
  - Only know that the event occurred within a certain interval of time



Censoring

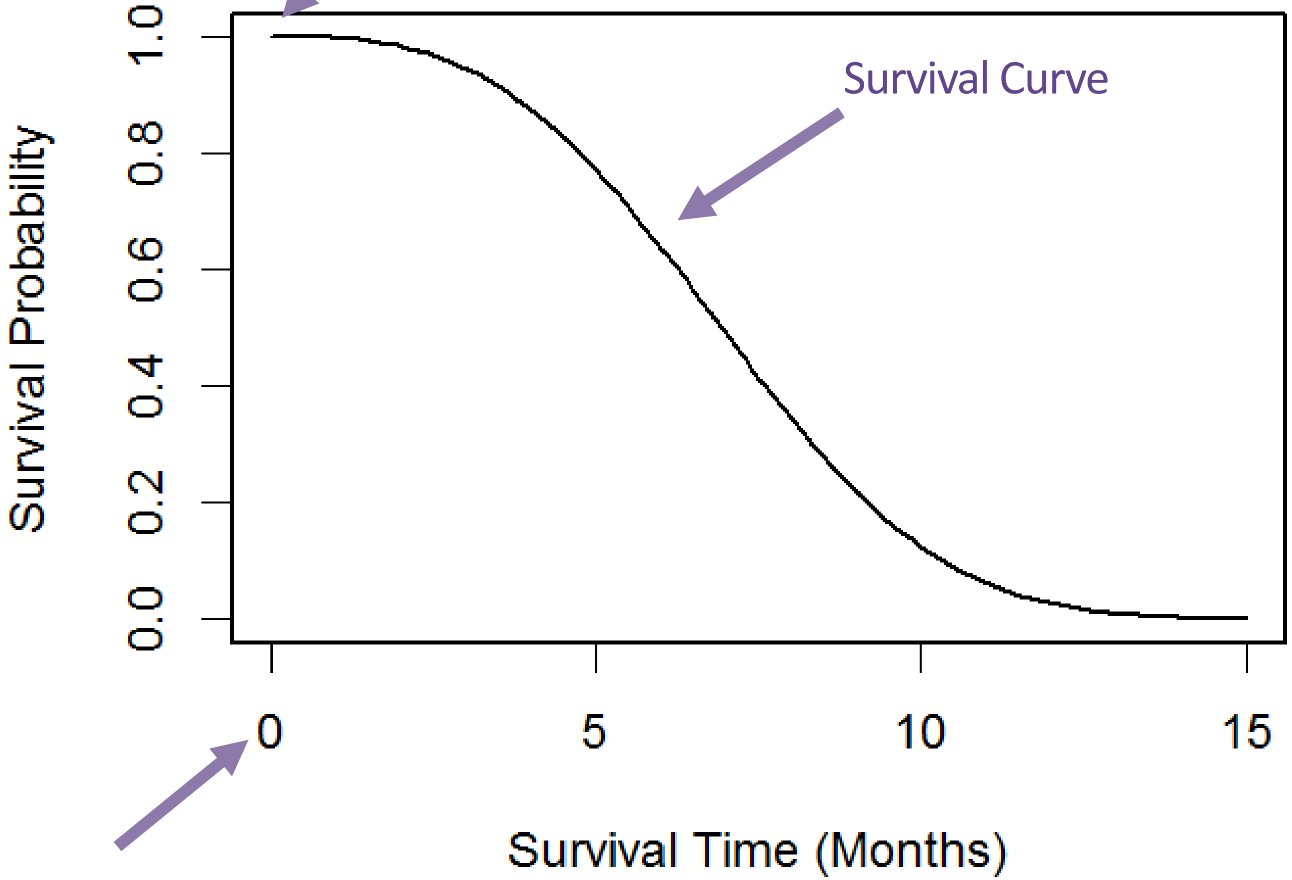
- Methods require assumption that censoring is independent of event process
  - Patients censored representative of patients still at risk
  - Knowledge of censoring provides no information of survival at future time

- Not independent?
  - Follow participants until death from lung cancer
  - Subject dies from another cancer

Basic Quantities

Survival Function

Survival probability at time 0 = 1



Time 0: Randomization of treatment

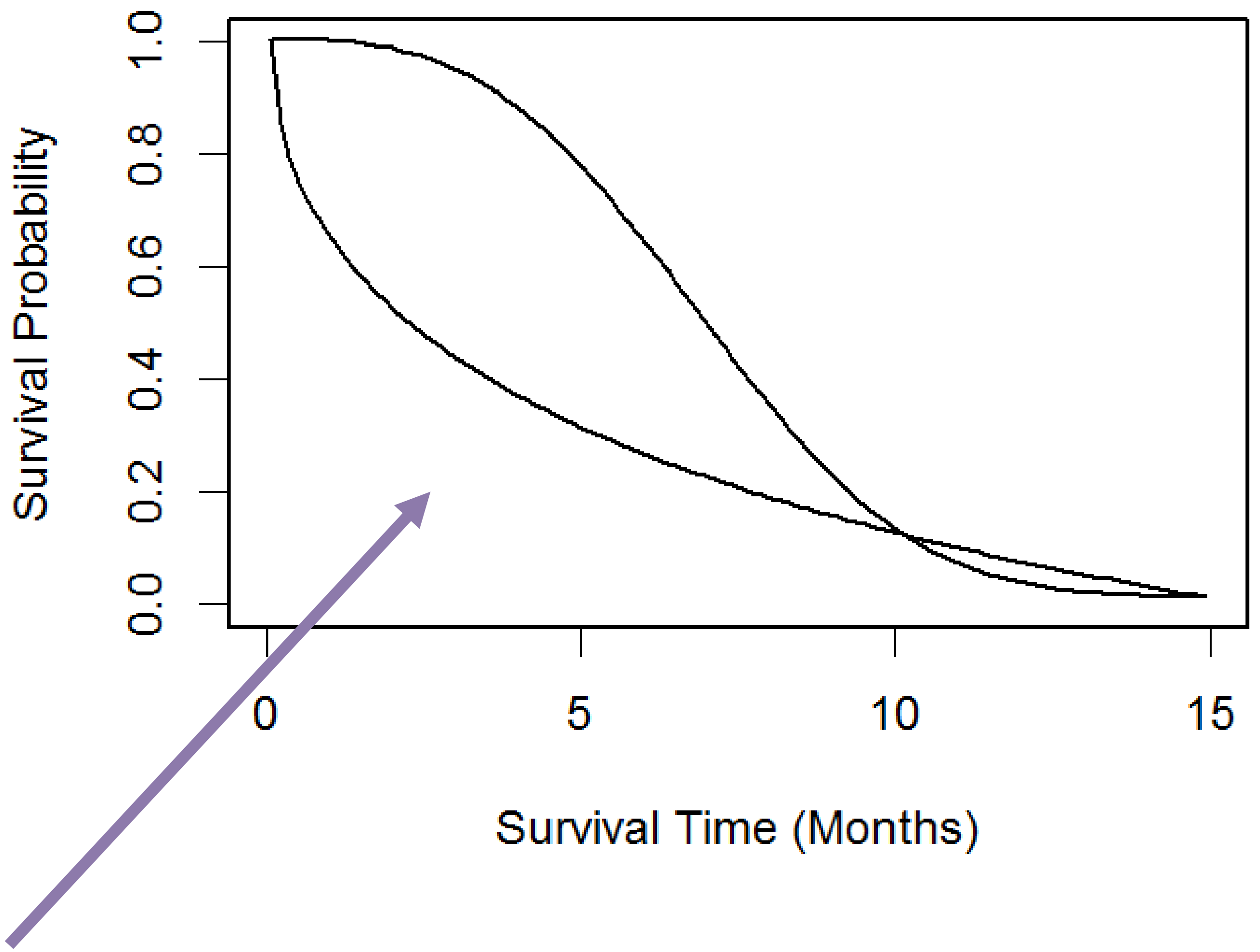
Basic Quantities

Survival Function

- Probability of an individual surviving beyond a specified time

- Never increases

- Defined up to the largest event time



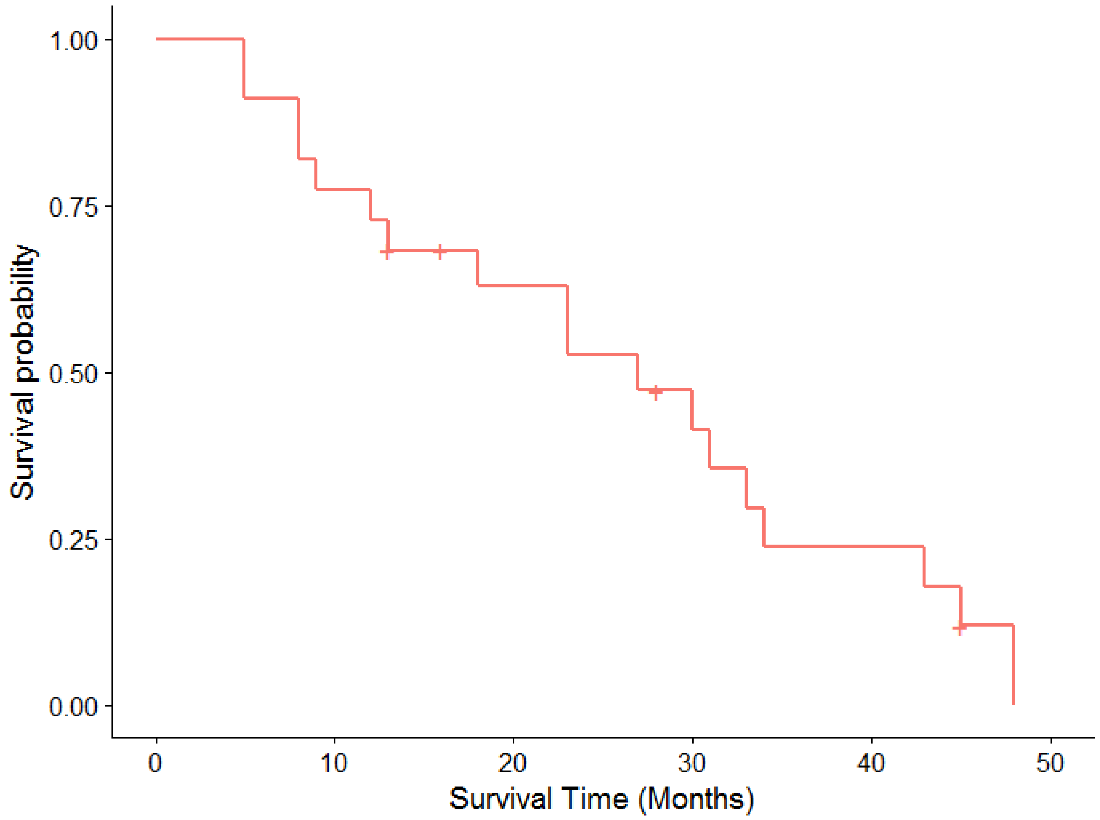
Rate of decline varies according to risk of experiencing the event

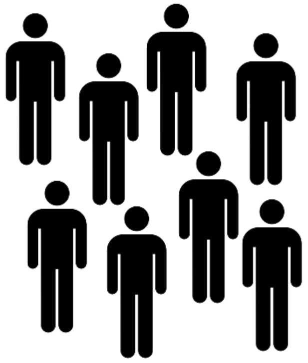
Methods – Estimation

Estimating survival probability

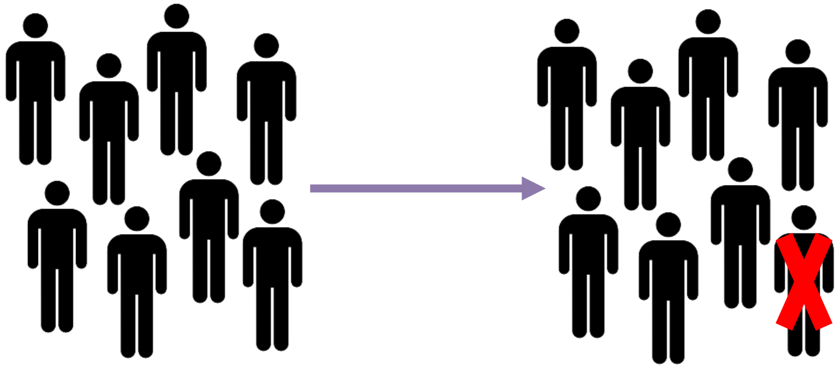
- Kaplan-Meier (Product Limit Estimator)
  - No assumptions about shape
  - Takes censored observations into account
  - Common for medical studies
  - Estimated for each unique failure time

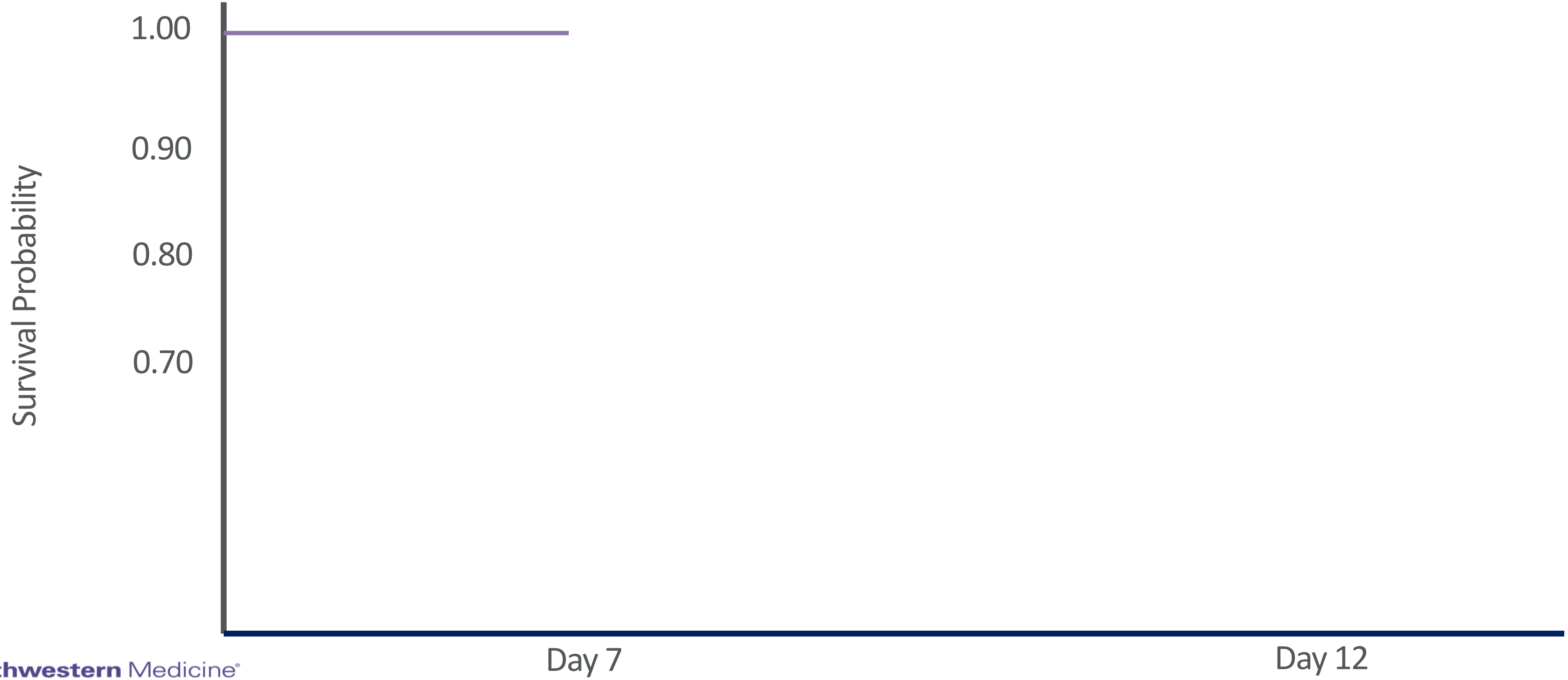
Survival in patients with Acute Myelogenous Leukemia



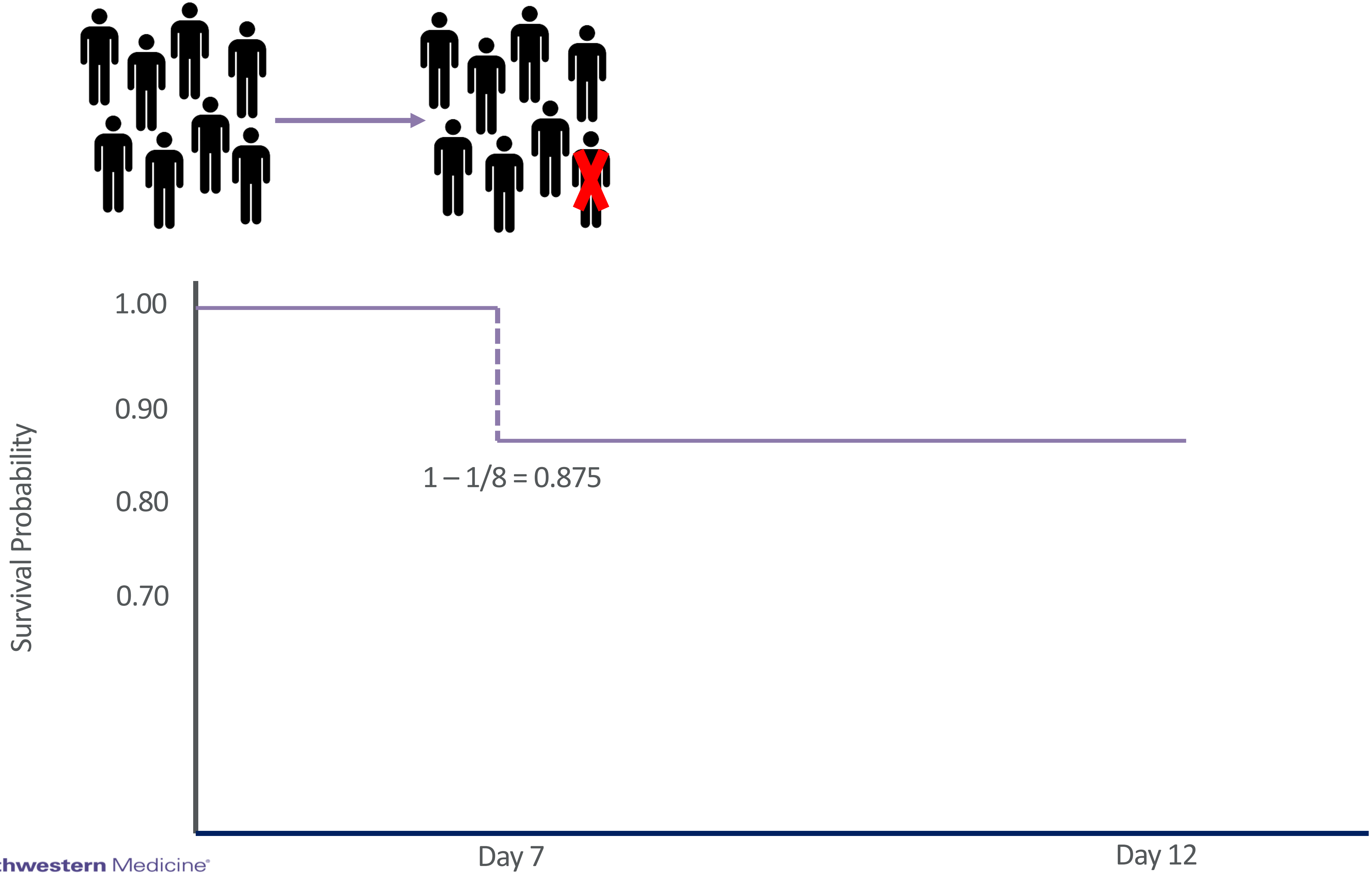


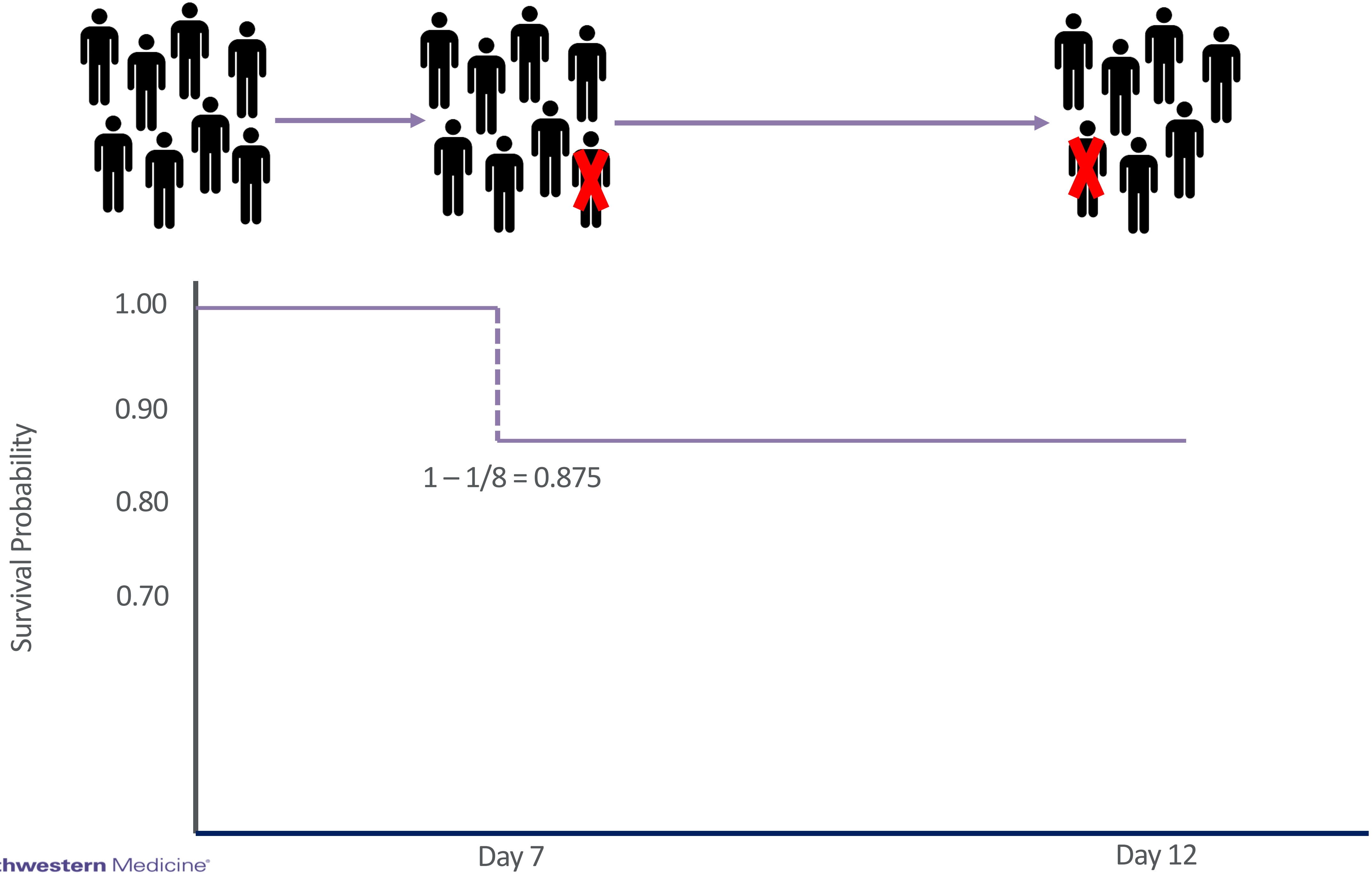

1.00
0.90
0.80
0.70
Survival Probability
Day 7
Day 12

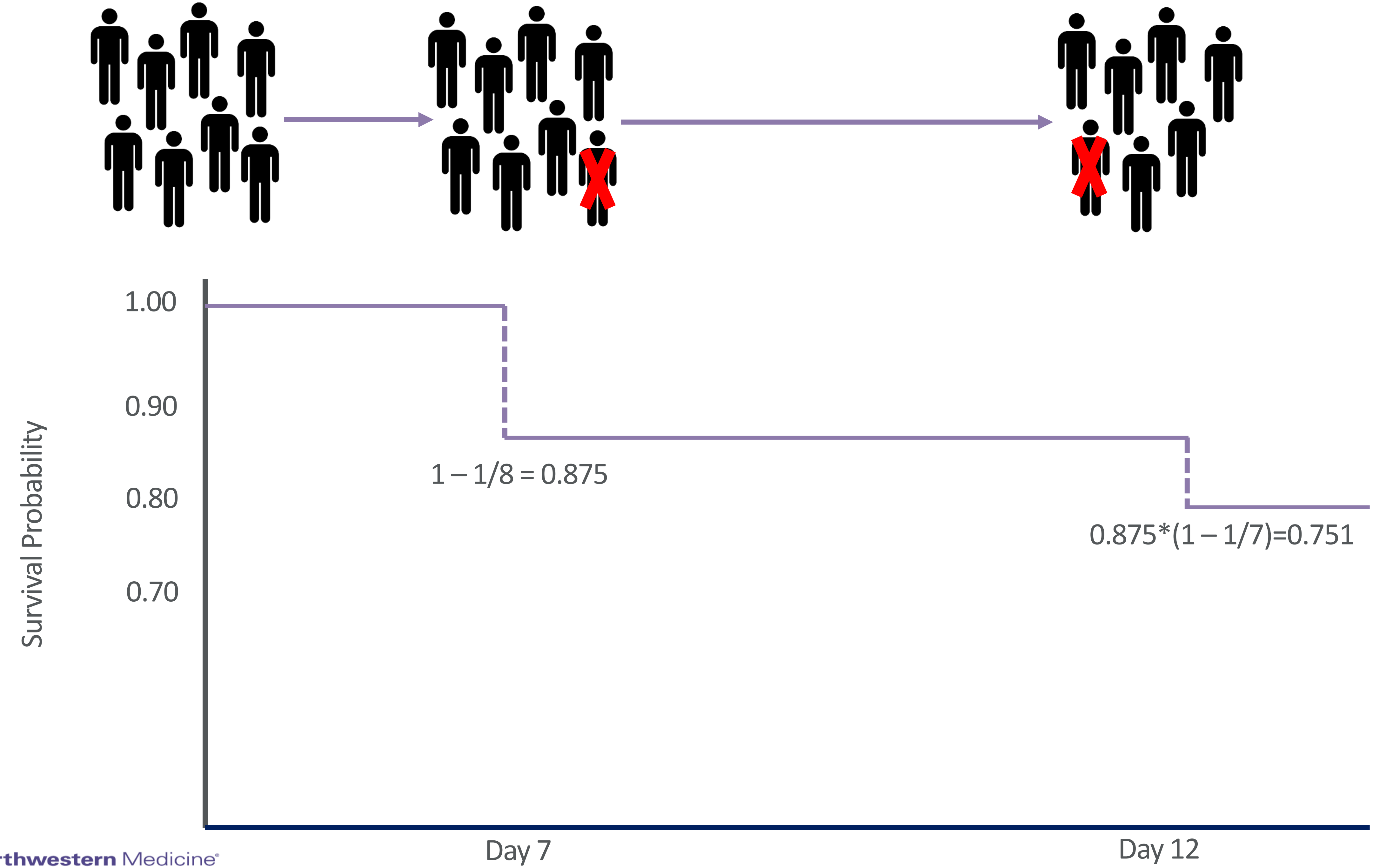


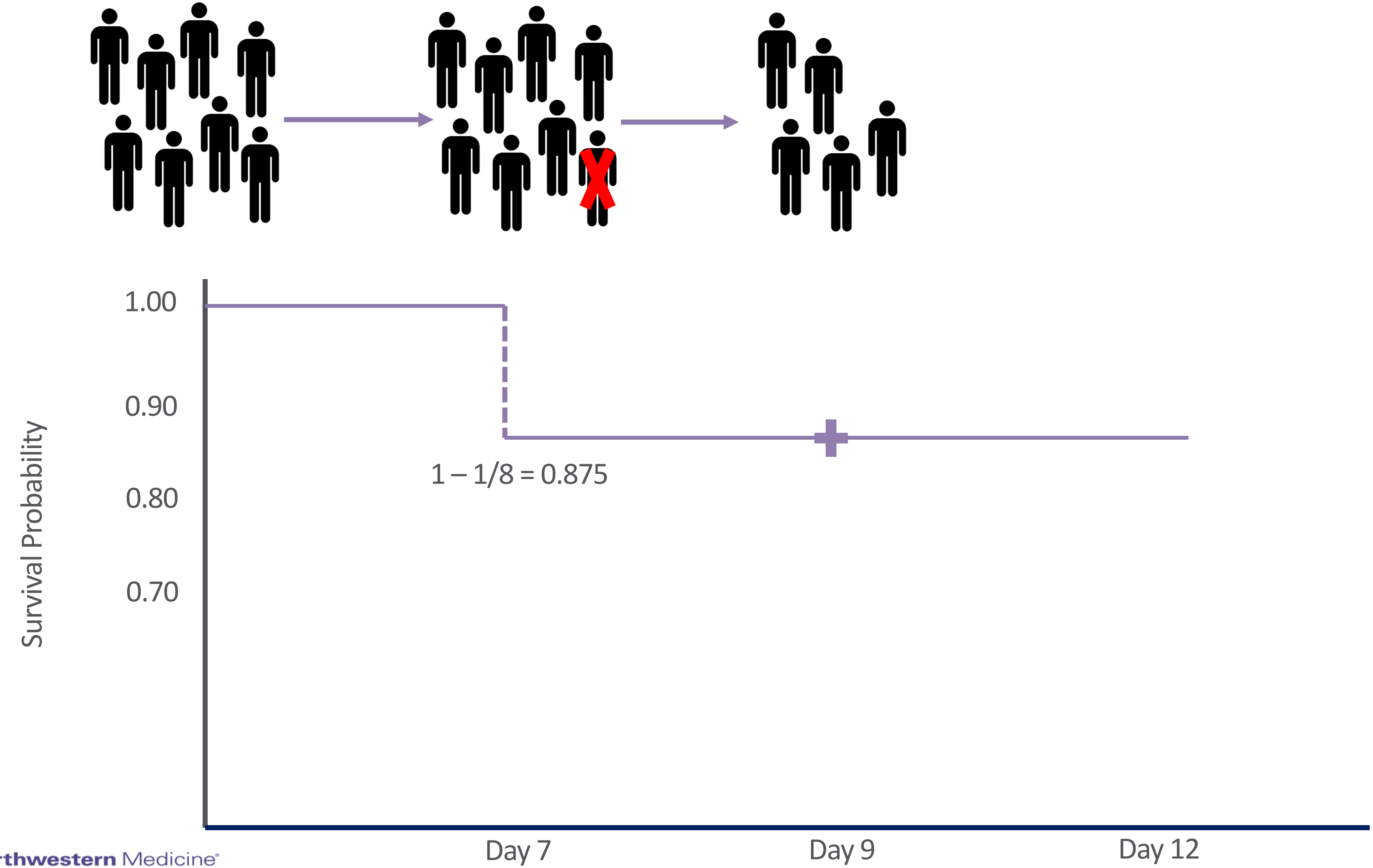


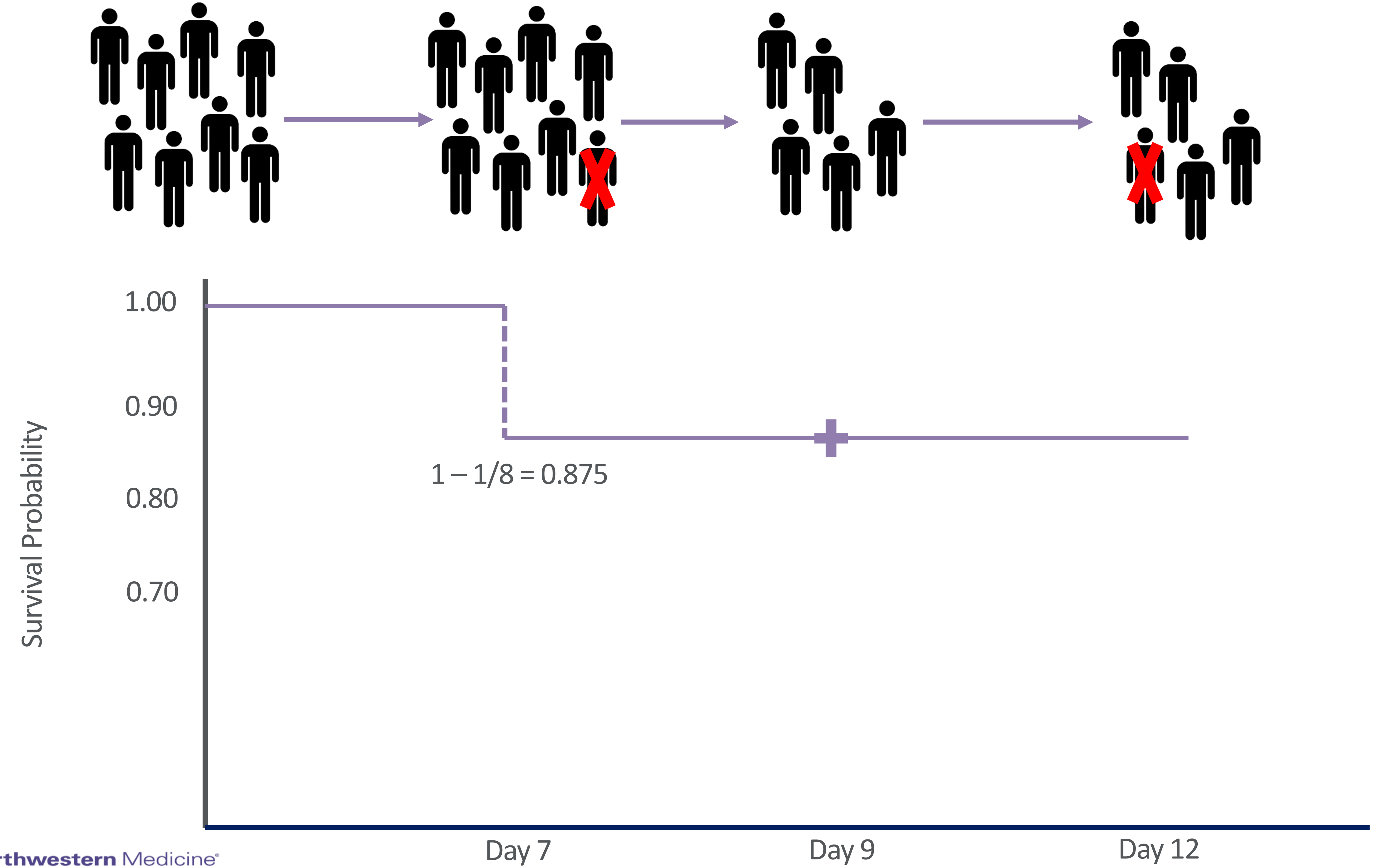
1.00
0.90
0.80
0.70
Survival Probability
Day 7
Day 12

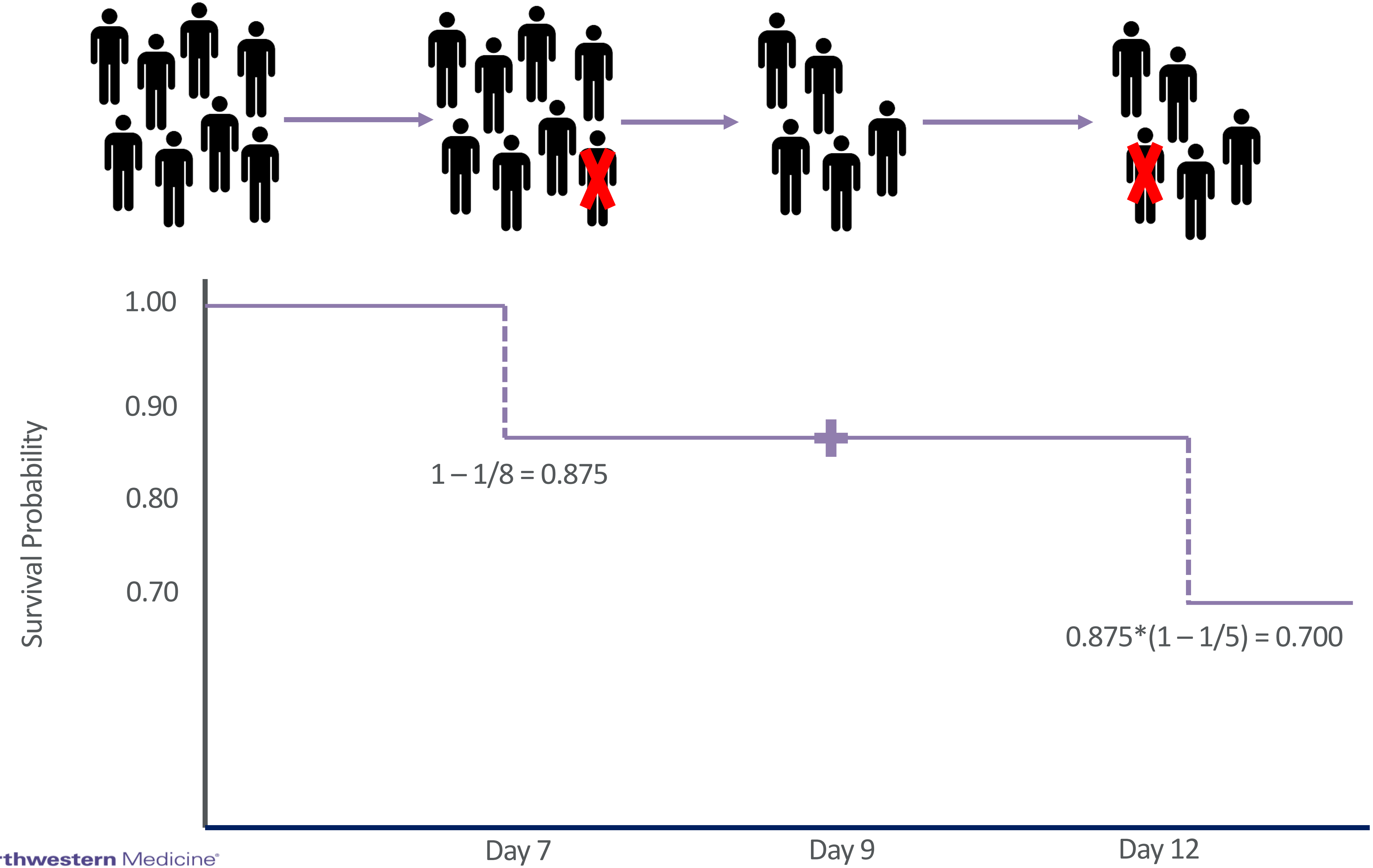

1.00
0.90
0.80
0.70
Survival Probability
1 – 1/8 = 0.875
Day 7
Day 12

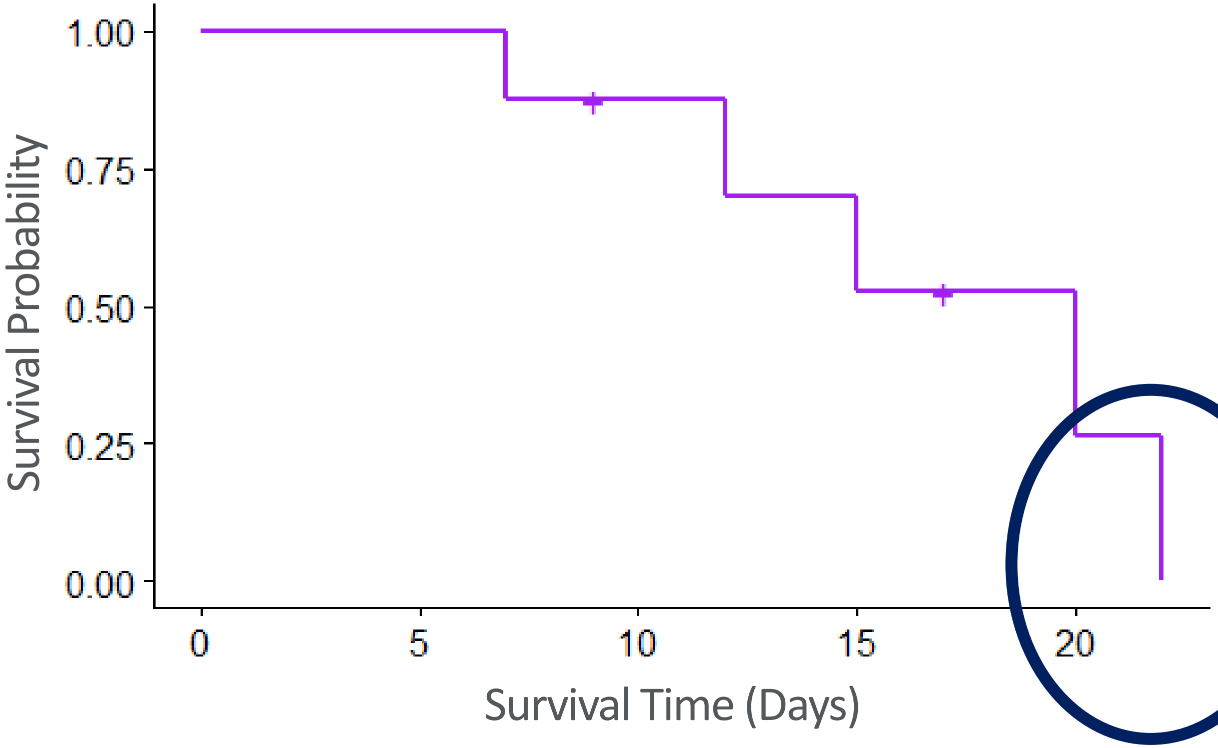

1.00
0.90
0.80
0.70
Survival Probability
1 – 1/8 = 0.875
Day 7
Day 12


1.00
0.90
0.80
0.70
Survival Probability
1 – 1/8 = 0.875
0.875*(1 – 1/7)=0.751
Day 7
Day 12

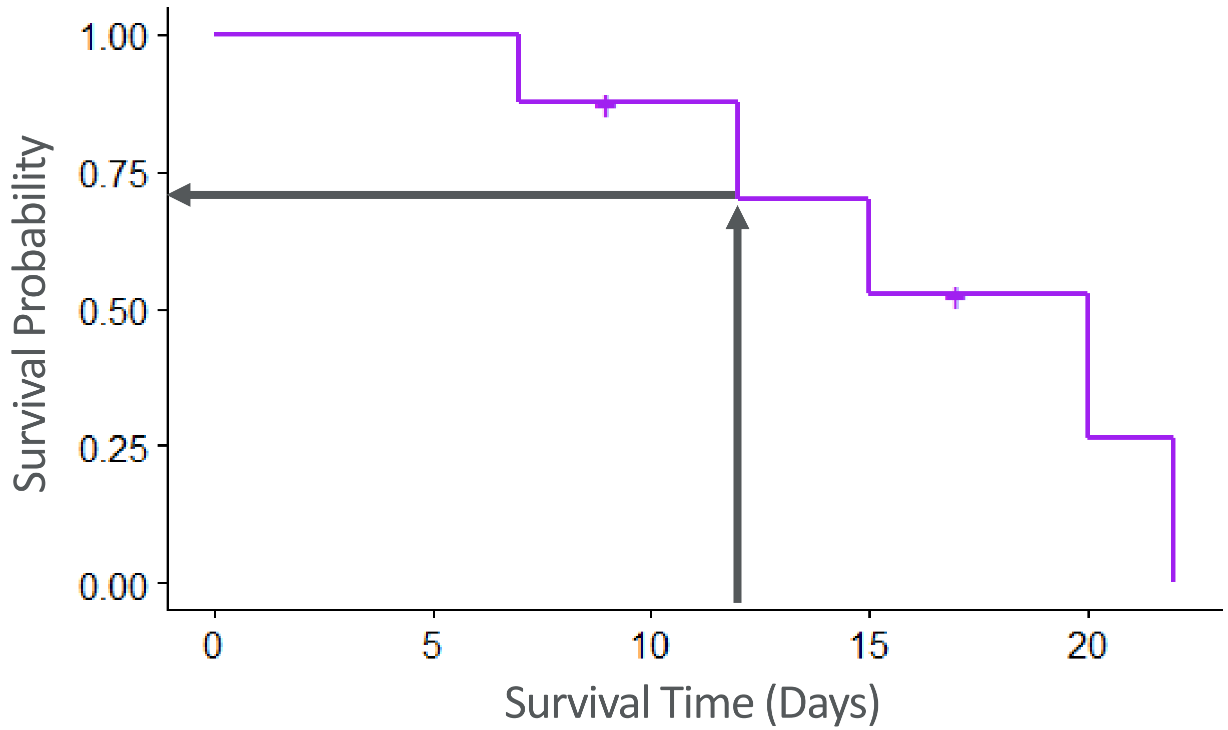

1.00
0.90
0.80
0.70
Survival Probability
1 – 1/8 = 0.875
Day 7
Day 9
Day 12


1.00
0.90
0.80
0.70
Survival Probability
1 – 1/8 = 0.875
Day 7
Day 9
Day 12


1.00
0.90
0.80
0.70
Survival Probability
1 – 1/8 = 0.875
0.875*(1 – 1/5) = 0.700
Day 7
Day 9
Day 12



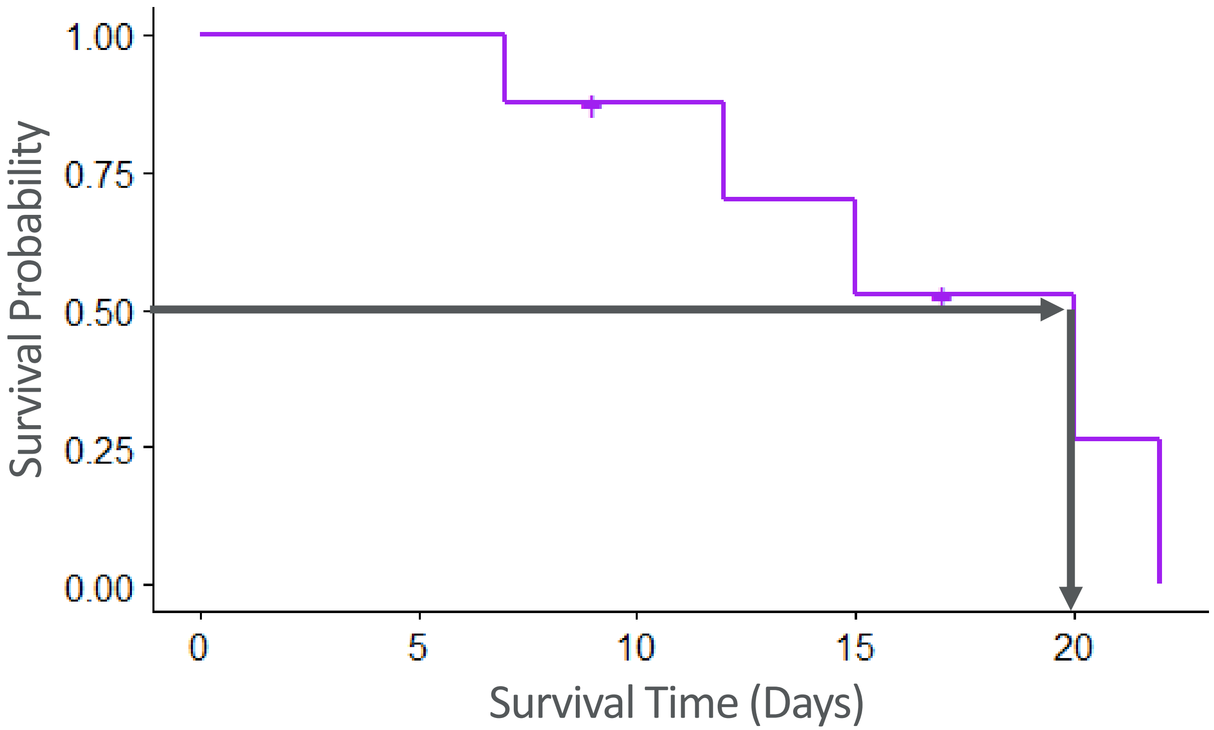
Day	At risk	Events	Estimate
7	8	1	0.875
12	5	1	0.700
15	4	1	0.525
20	2	1	0.263
22	1	1	0.000



Day	At risk	Events	Estimate
7	8	1	0.875
12	5	1	0.700
15	4	1	0.525
20	2	1	0.263
22	1	1	0.000

How can we interpret?

- Estimate survival probability at specified time



Day	At risk	Events	Estimate
7	8	1	0.875
12	5	1	0.700
15	4	1	0.525
20	2	1	0.263
22	1	1	0.000

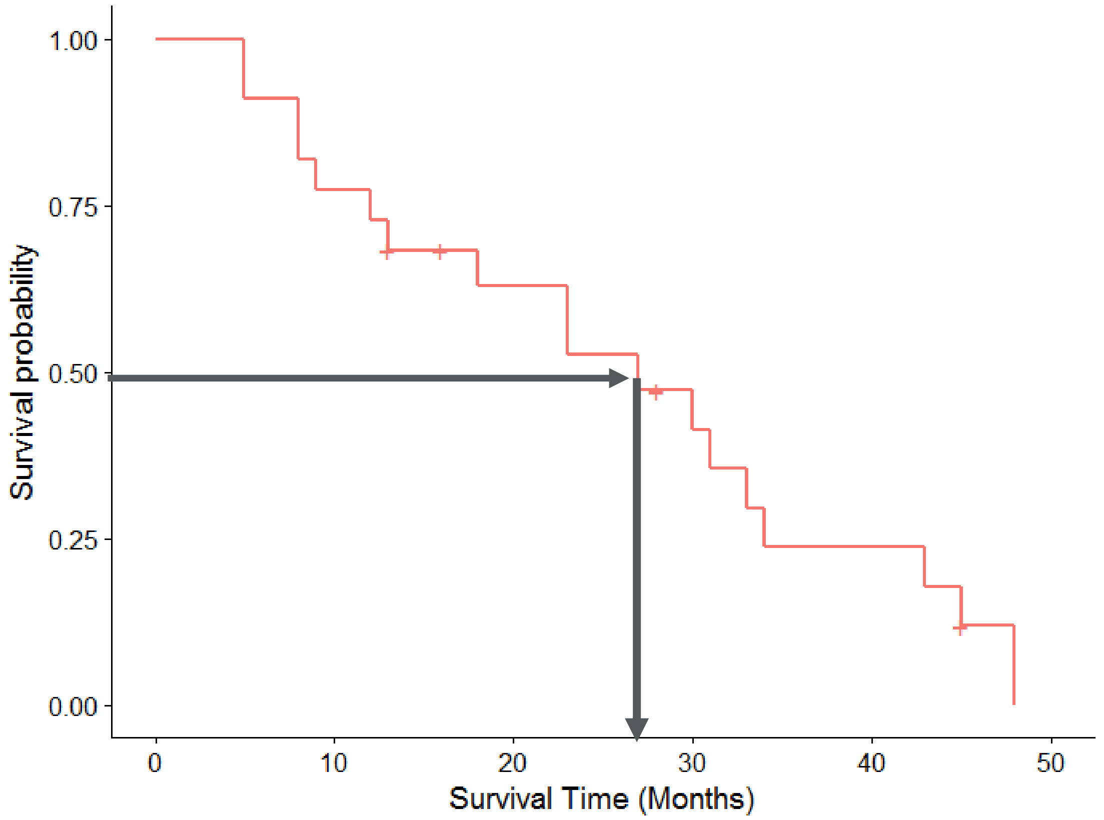
How can we interpret?

- Estimate median failure time

Example

Estimating median failure time

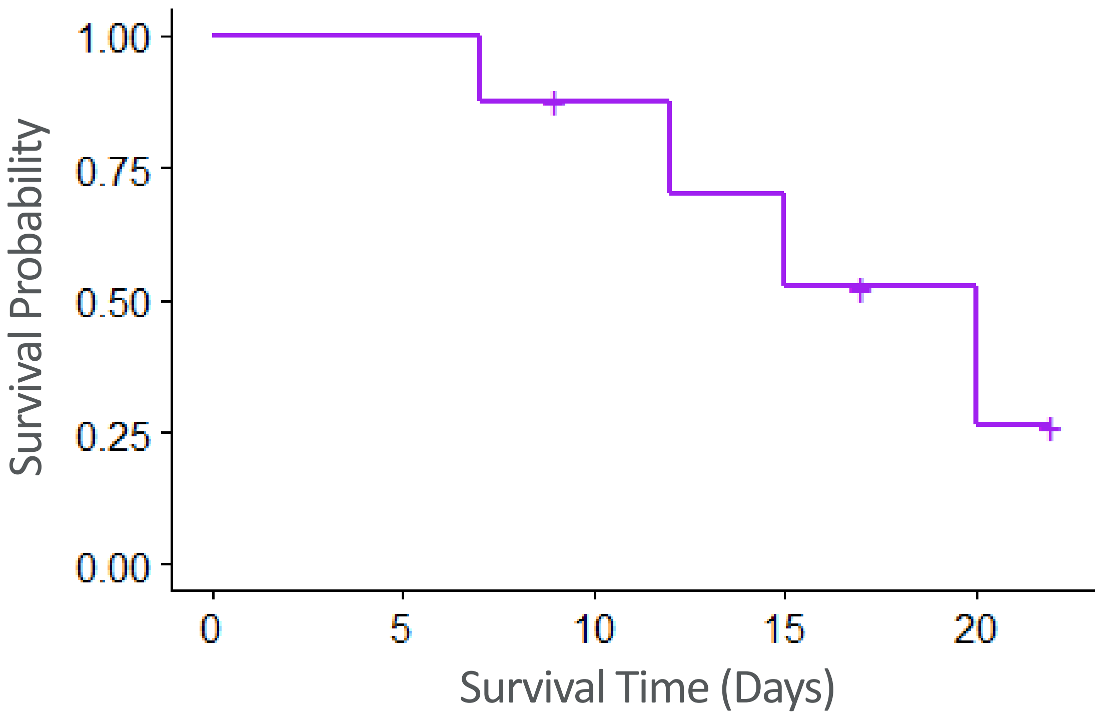
Survival in patients with Acute Myelogenous Leukemia



Day	At risk	Events	Estimate	95% CI
5	22	2	0.909	0.68-0.98
8	20	2	0.818	0.59-0.93
⋮				
18	13	1	0.629	0.39-0.80
23	12	2	0.524	0.29-0.71
27	10	1	0.472	0.25-0.67
30	8	1	0.413	0.20-0.62
⋮				

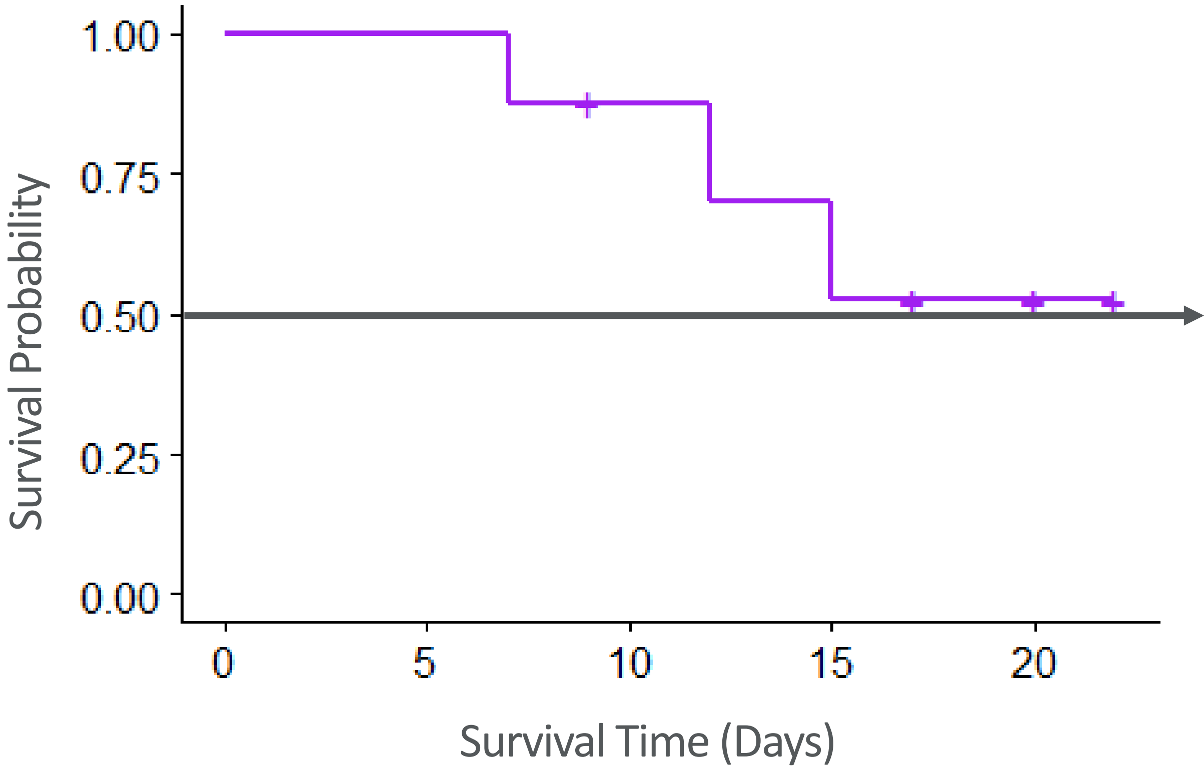
What if last observation is censored?

Day	At risk	Events	Estimate
7	8	1	0.875
12	5	1	0.700
15	4	1	0.525
20	2	1	0.263
22	1	0	--



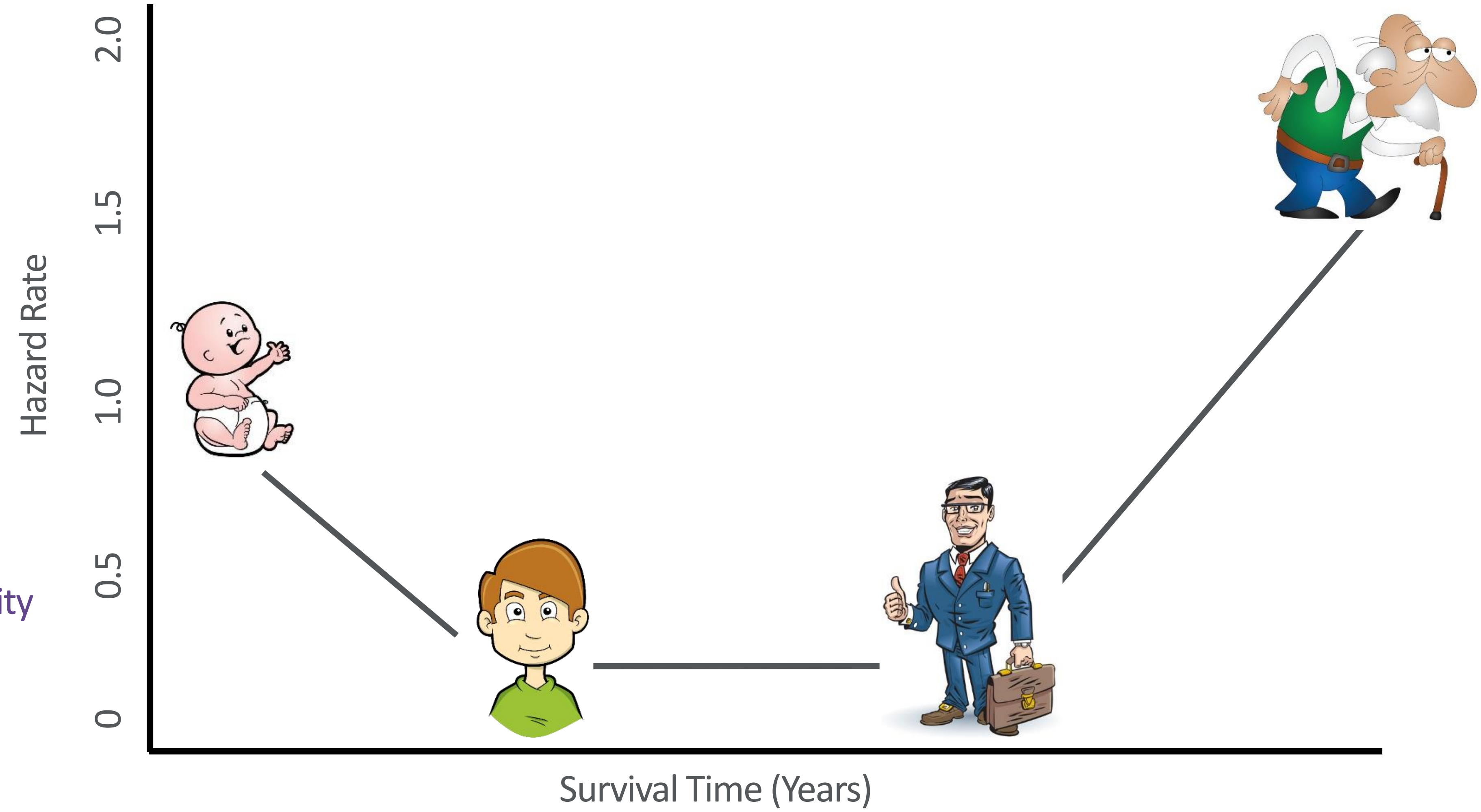
Median failure time not always estimable

Day	At risk	Events	Estimate
7	8	1	0.875
12	5	1	0.700
15	4	1	0.525
20	2	0	--
22	1	0	--



Basic Quantities

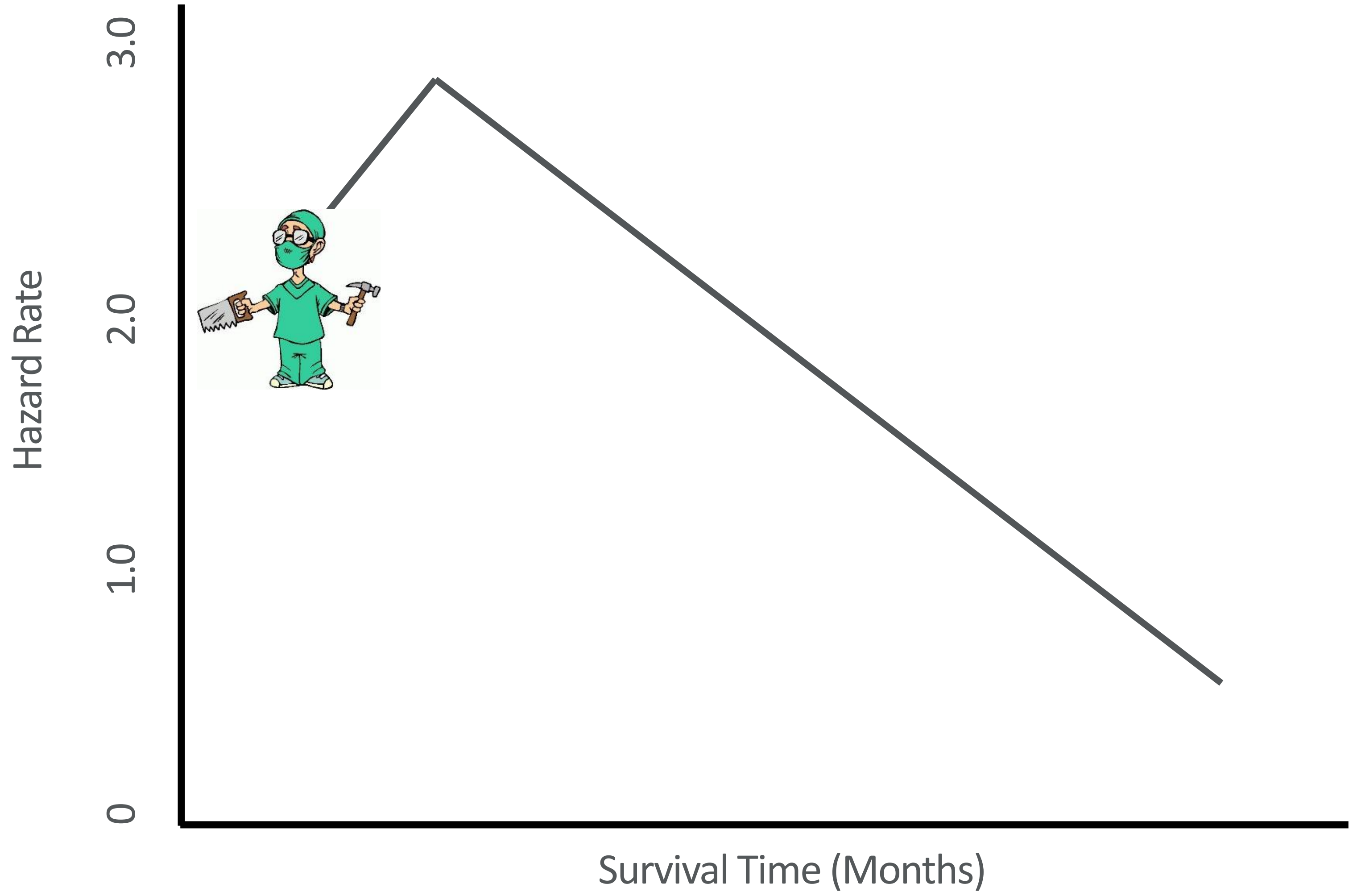
Hazard Function



Not a probability

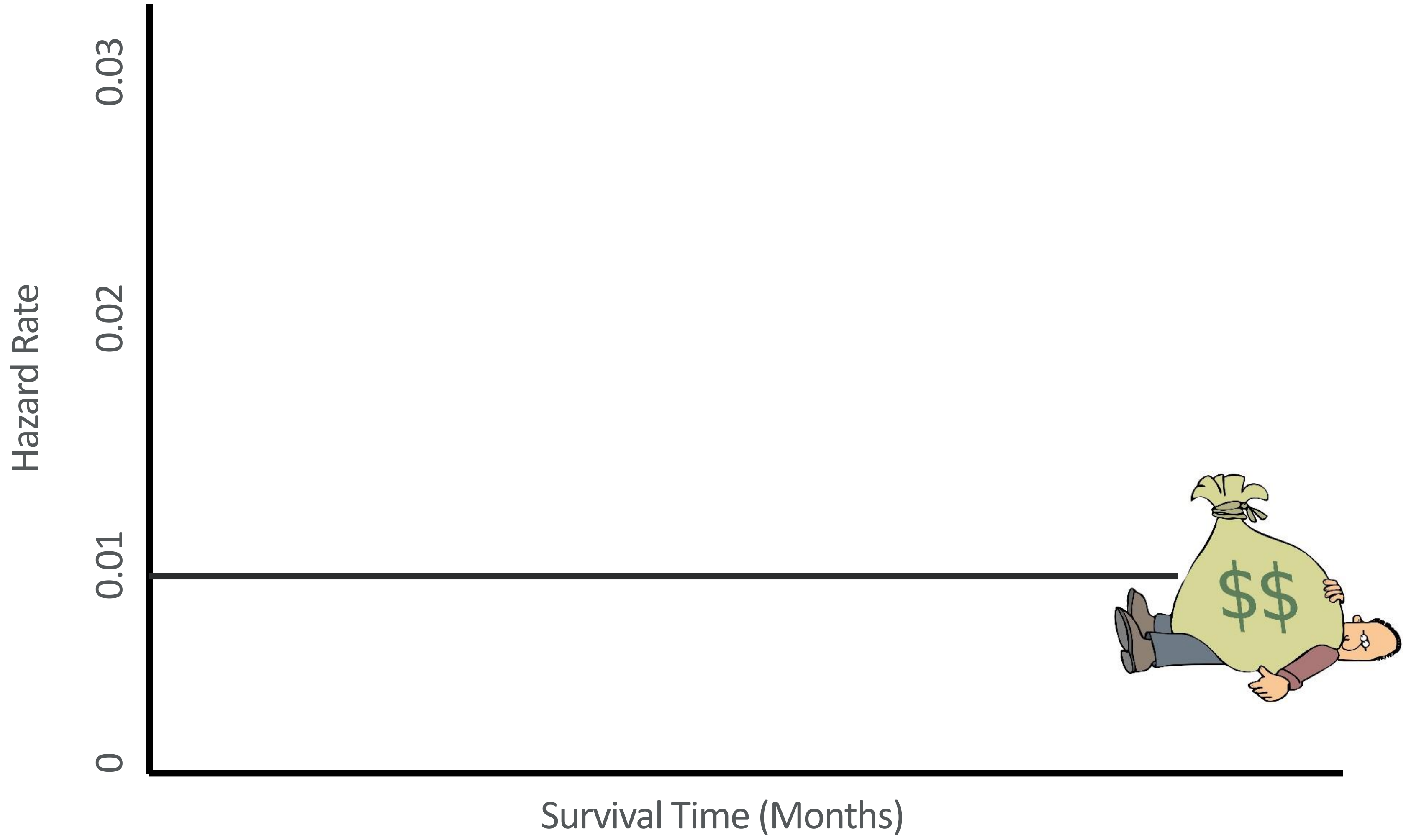
Basic Quantities

Hazard Function



Basic Quantities

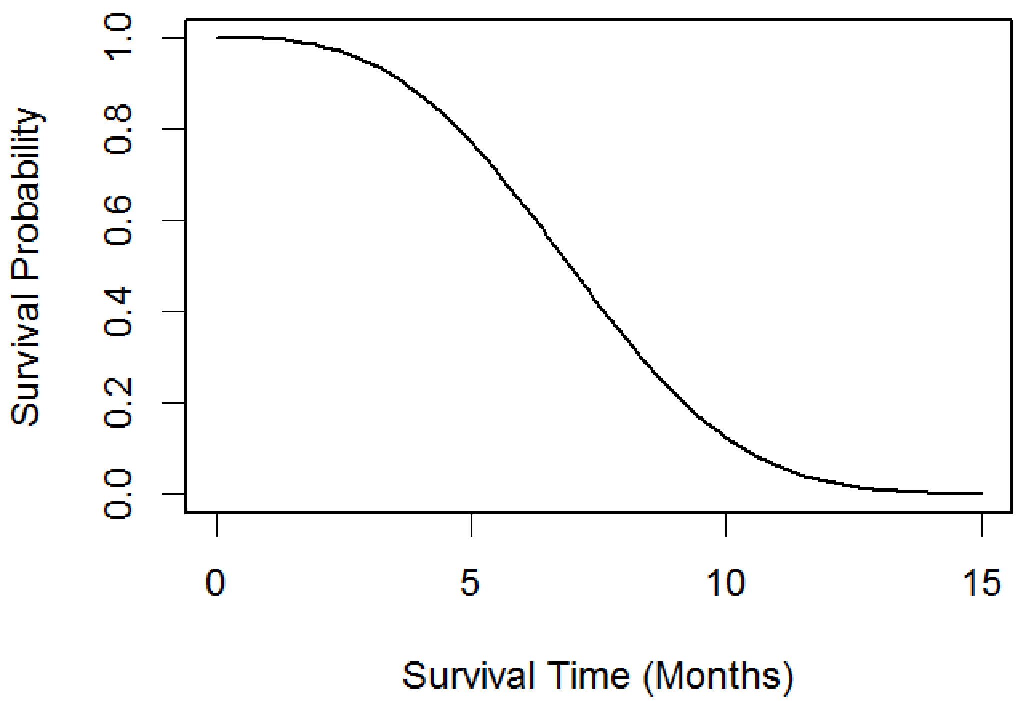
Hazard Function



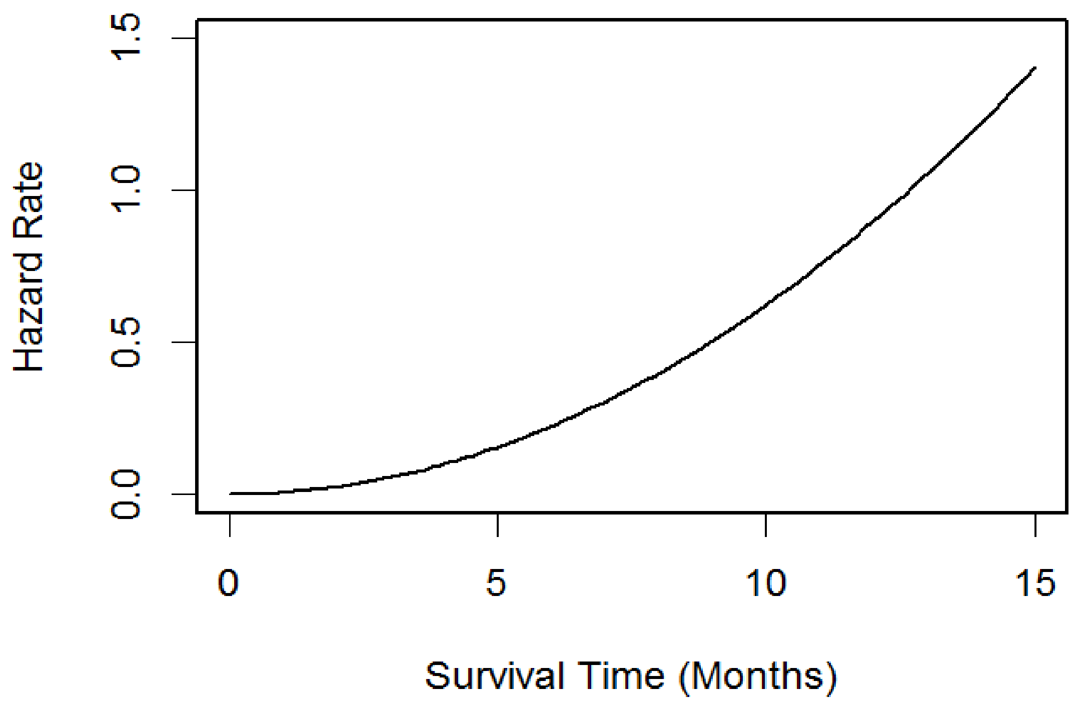
Basic Quantities

Hazard Function

Survival Function

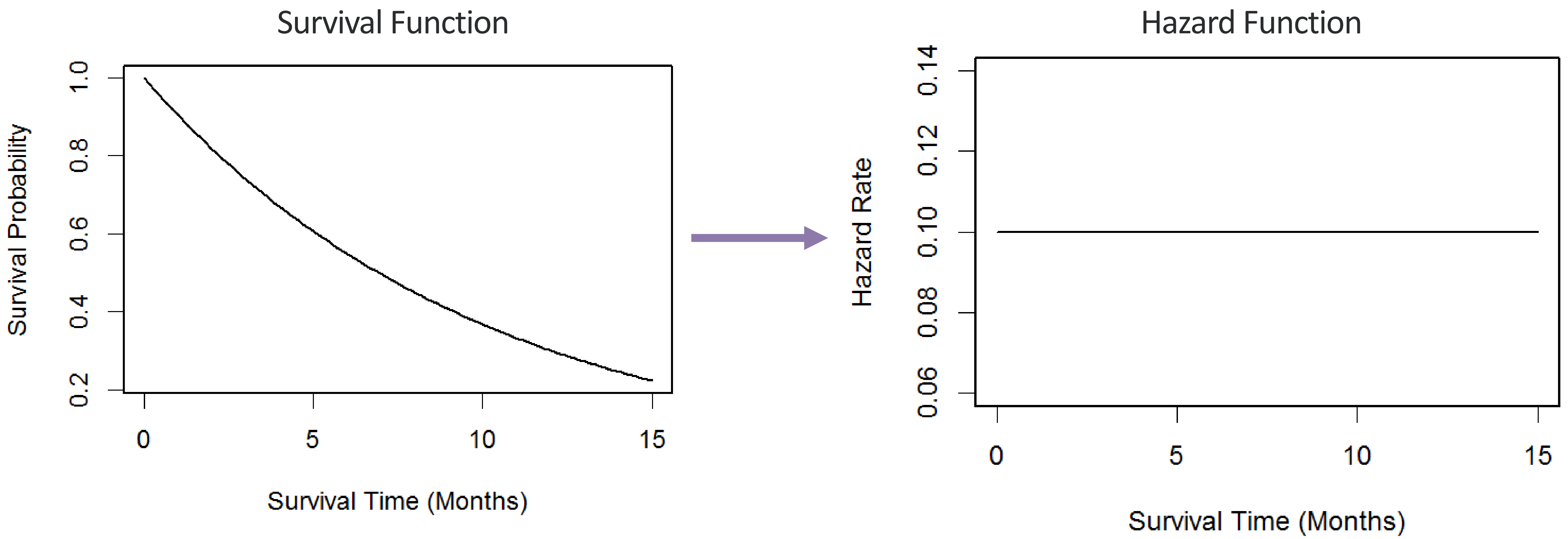


Hazard Function



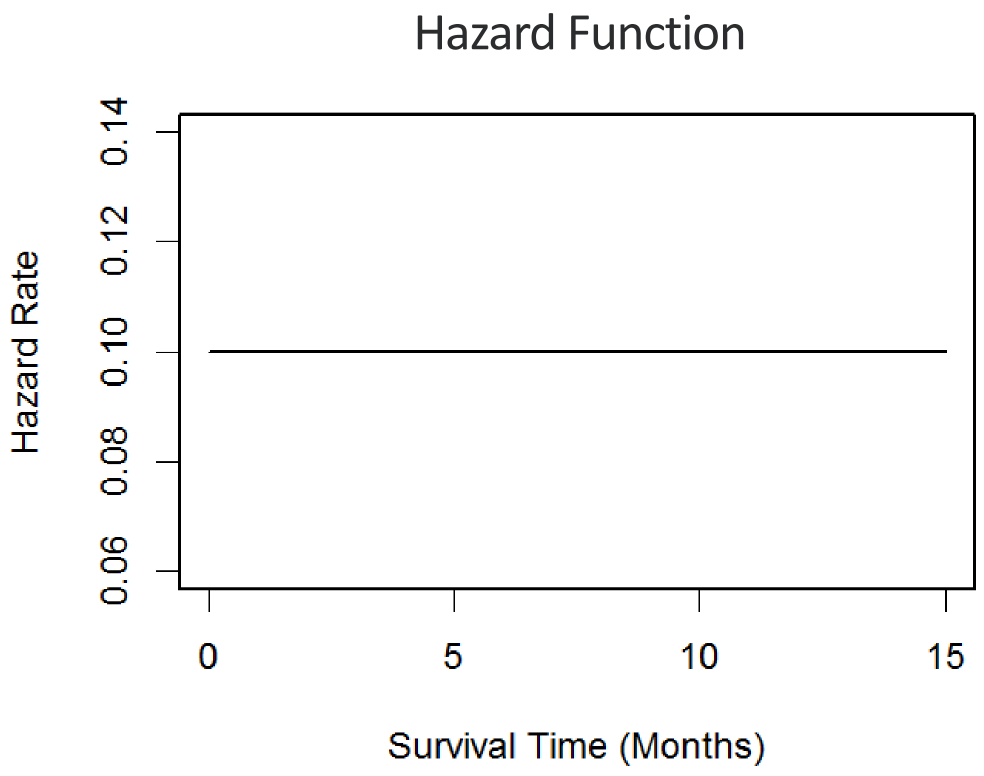
Basic Quantities

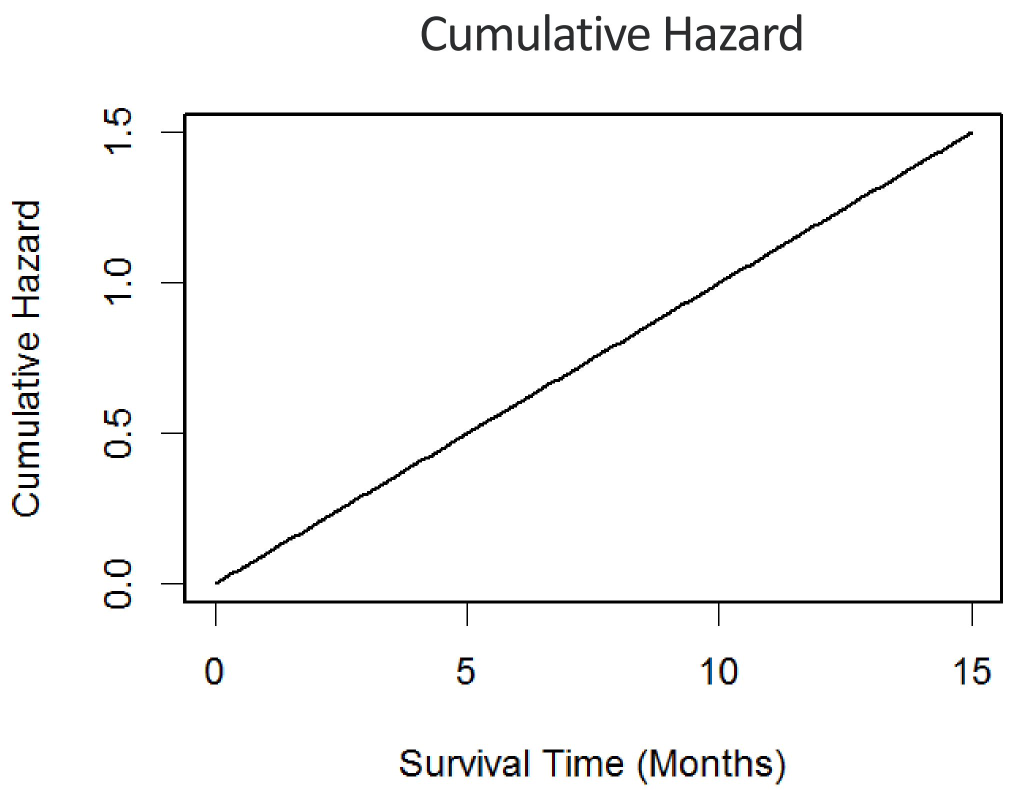
Hazard Function



Basic Quantities

Cumulative Hazard Function





Basic Quantities

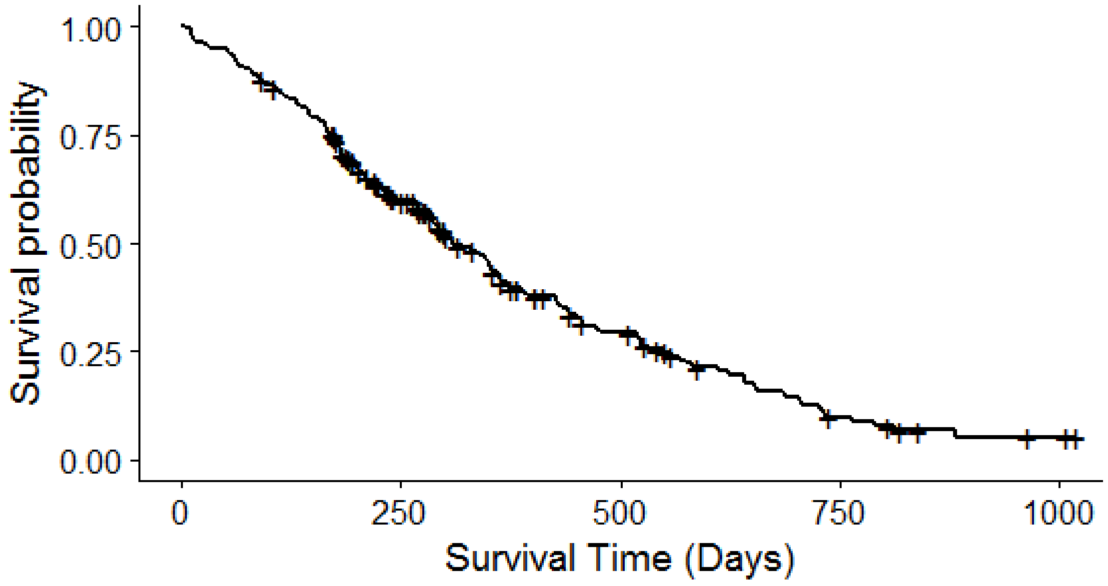
Hazard Function

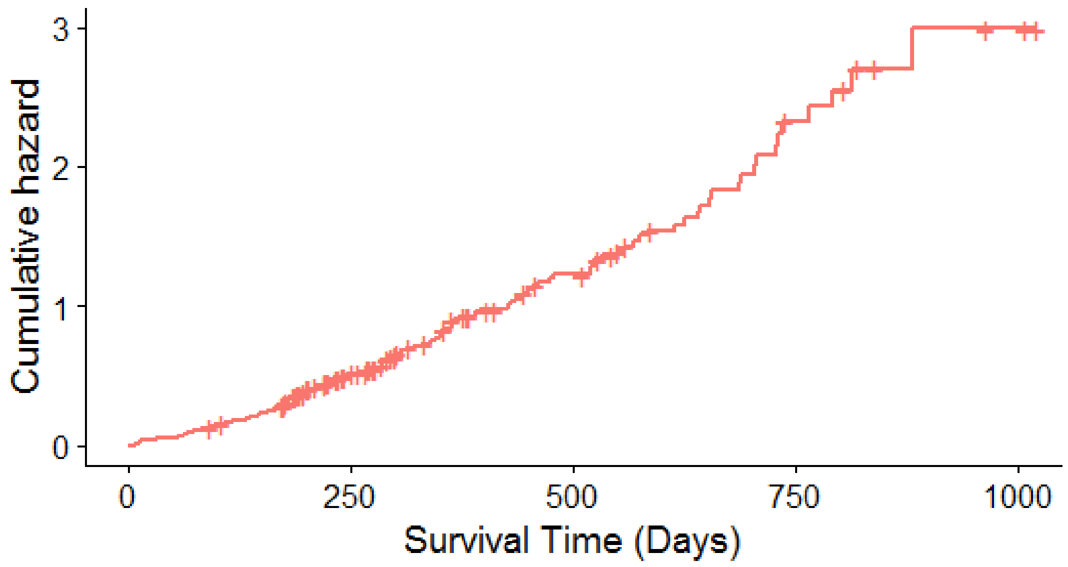
- Hazard Function
  - Instantaneous failure rate at a specified time
  - Measure of risk
  - Non-negative
  - Increasing, decreasing, or constant
- Cumulative Hazard
  - Accumulation of risk up until a specified time
  - Increasing or constant

Methods – Estimation

Cumulative Hazard function

Survival in patients with advanced lung cancer

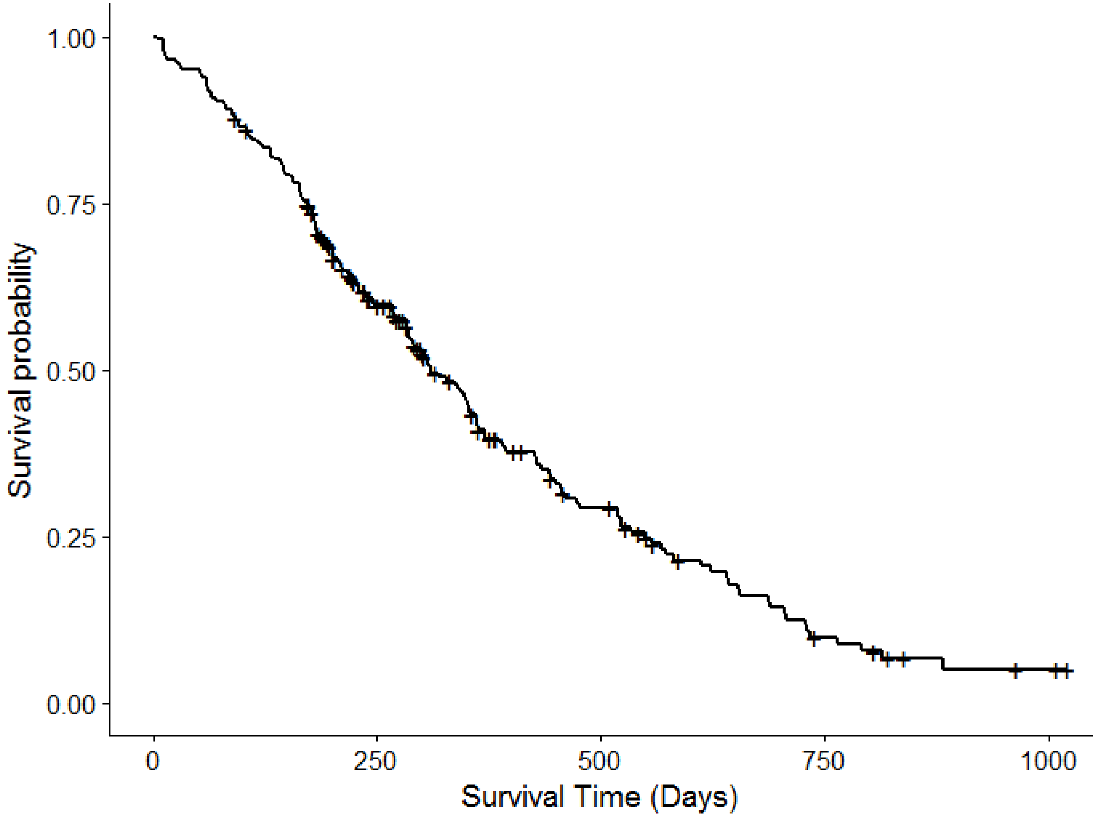


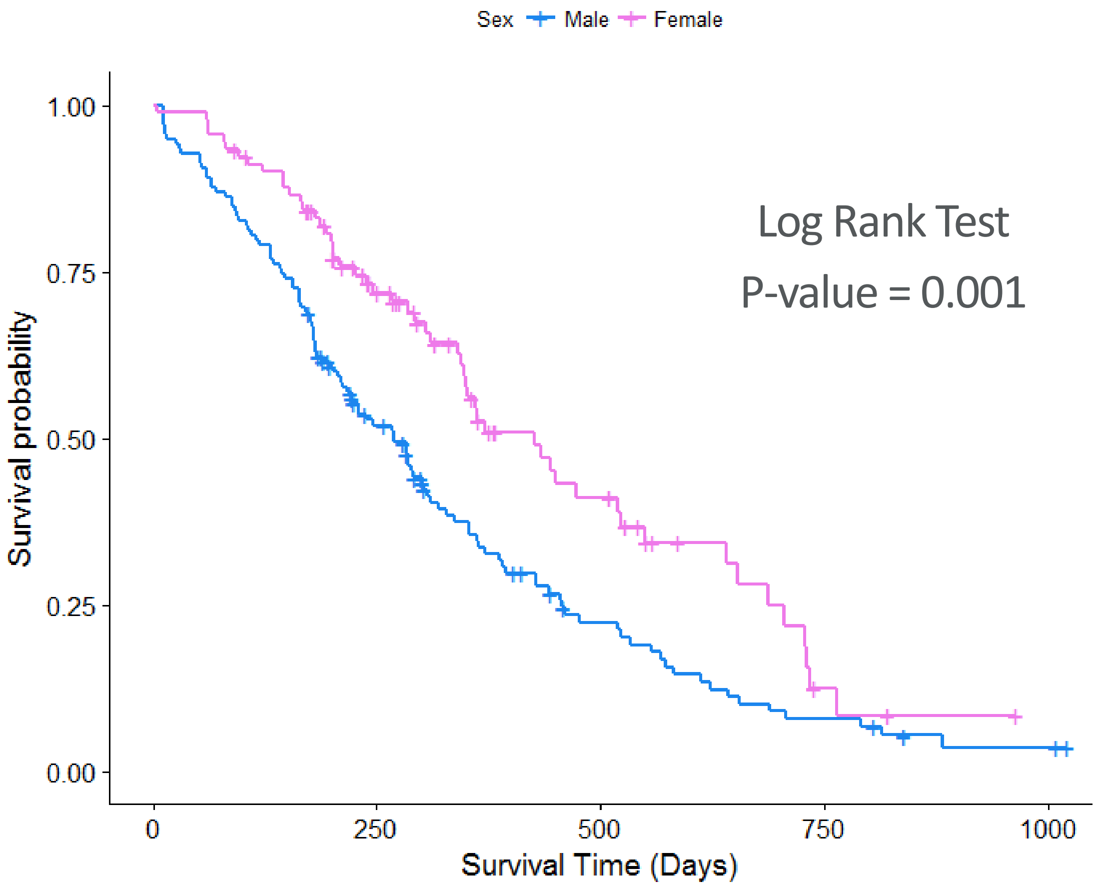


Methods - Inference

Comparing time-to-event between groups

Survival in patients with advanced lung cancer

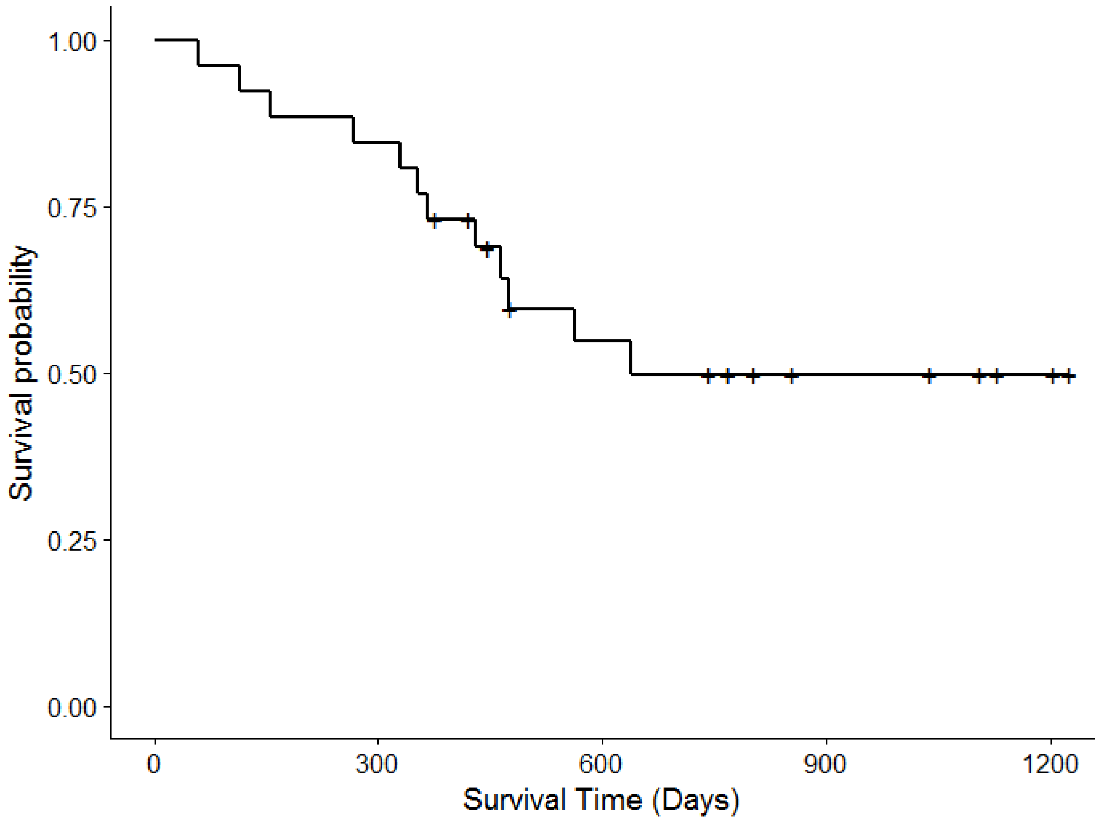


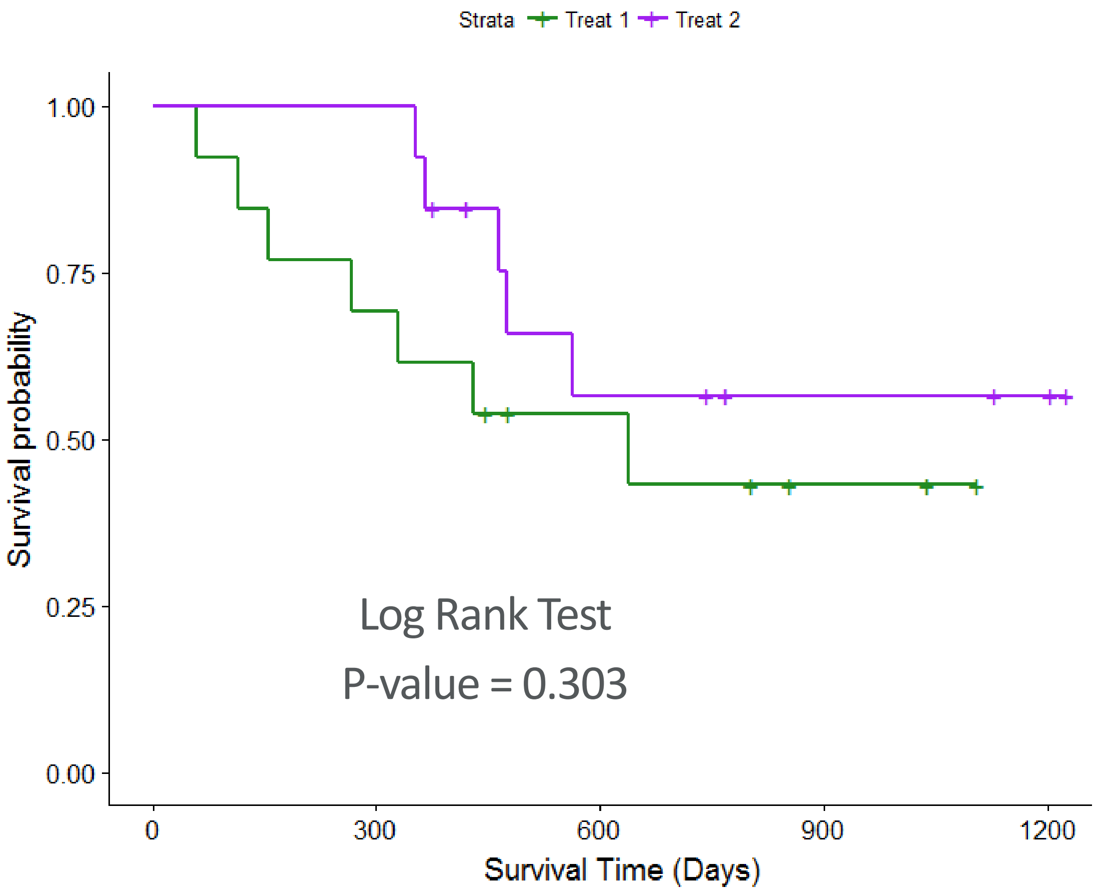


Methods – Inference

Comparing time-to-event between groups

Survival in randomized trial comparing treatments for ovarian cancer



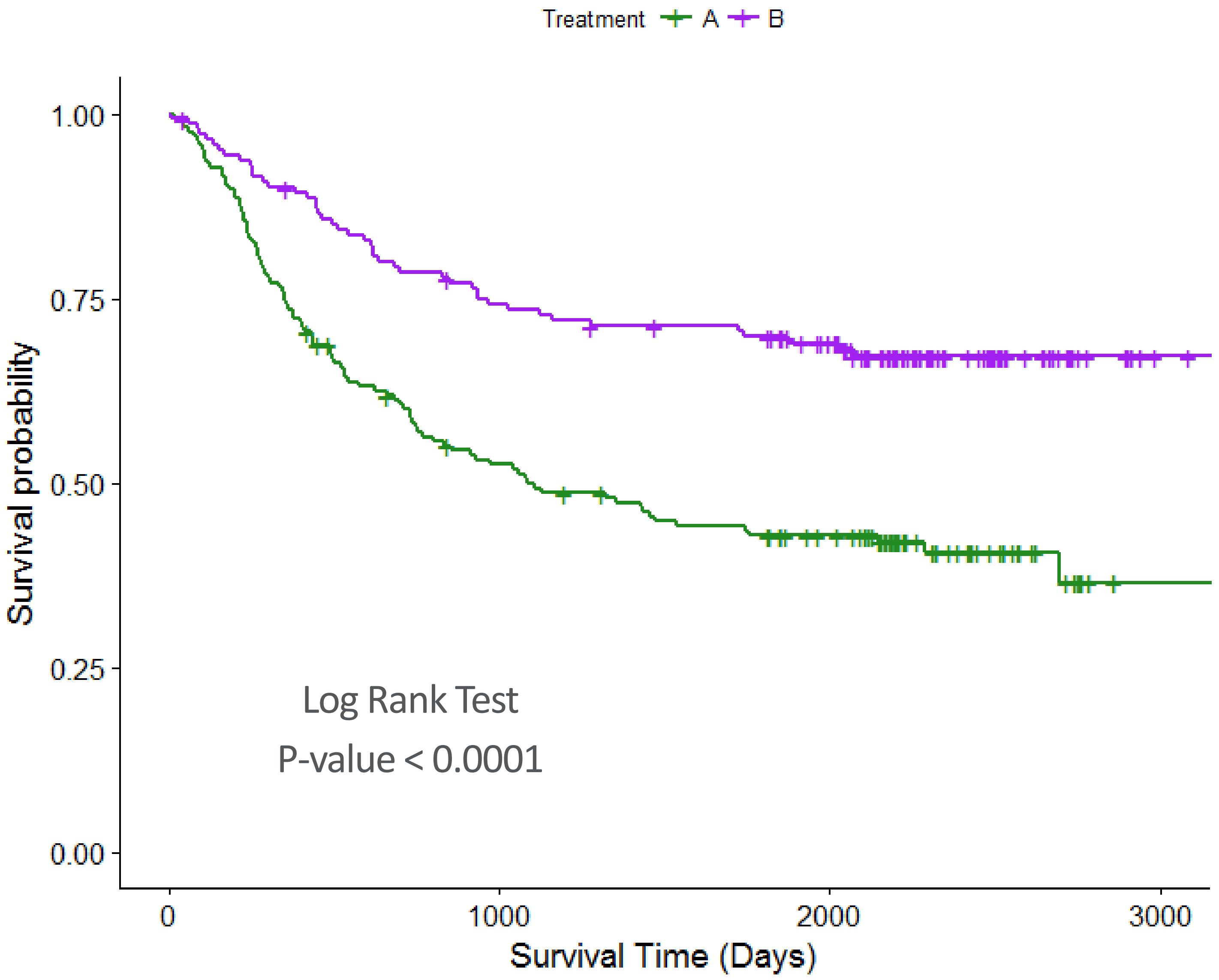


Methods - Inference

Stratified Tests

- Adjust for another factor
- Few levels of factor
- Alternative to regression setting

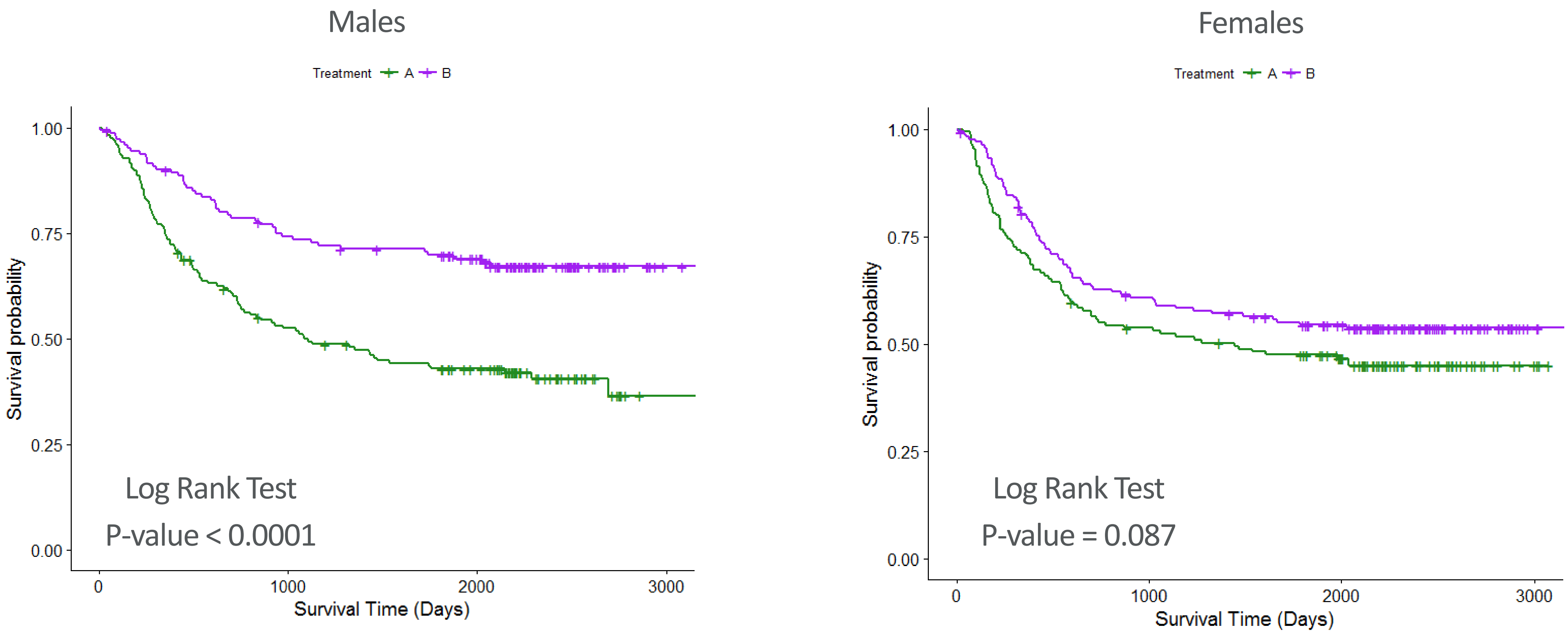
Time to recurrence of colon cancer



Methods - Inference

Stratified Tests

Stratify by Sex



Methods

Assessing relationship of covariates on time-to-event

- Regression Models
- Cox Proportional Hazards Model

  - Exponential(coefficient) = hazard ratio
    - Hazard Ratio < 1: Reduction in hazard (risk of event) relative to reference group
    - Hazard Ratio > 1: Increase in hazard (risk of event) relative to reference group

Interpretation of Hazard Ratio depends on how you code your variables!

Cox Proportional Hazards Model

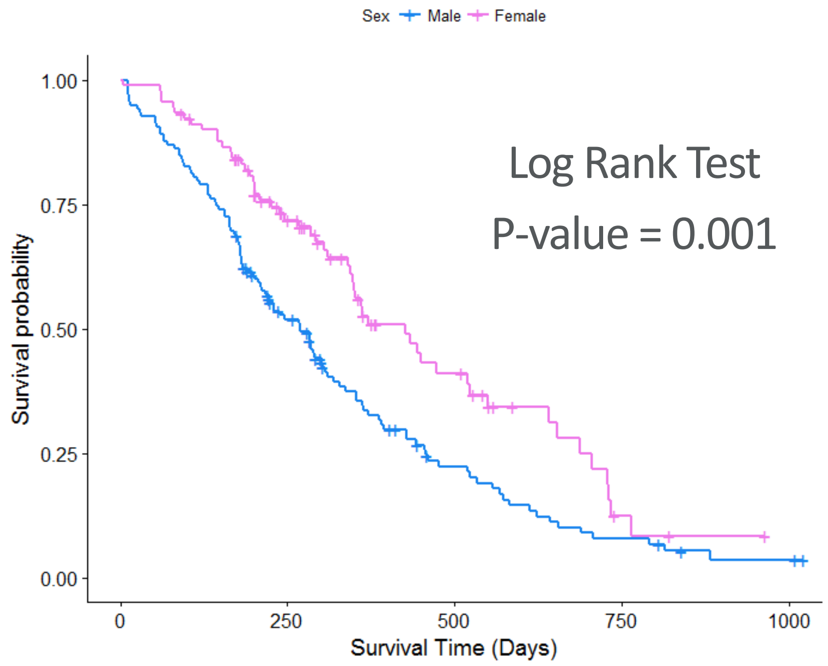
Example

Survival in patients with advanced lung cancer

- Proportional hazards model

	Coefficient	Hazard Ratio	P-value
Male	0.531	1.701	0.002

- Males have an increased risk of death
- There is a 70.1% increase in the expected hazard for males compared to females
- The expected hazard is 1.701 times higher in males compared to females



Cox Proportional Hazards Model

Example

	Coefficient	Hazard Ratio	P-value
Male	0.513	1.671	0.002
Age (years)	0.017	1.017	0.065

- Holding age constant, being male increases the expected hazard by 67%
- Holding sex constant, a one year increase in age is associated with a 2% increase in the expected hazard

	Coefficient	Hazard Ratio	P-value
Age (10 years)	0.170	1.186	0.065

- A ten year increase in age is associated with a 20% increase in the expected hazard

Cox Proportional Hazards Model

Example

- Proportional hazards assumption
  - Hazard functions are proportional over time

	Coefficient	Hazard Ratio	P-value
Male	0.531	1.701	0.002

  - Risk of death for males compared to females is constant over time

- Test for proportional hazards assumption
  - Assess graphically
  - Assess with interaction between variable and time
  - Assess with test of proportionality (available in some statistical packages)

Cox Proportional Hazards Model

Example

	Coefficient	Hazard Ratio	P-value
Male	0.531	1.701	0.002

- Test for proportional hazards

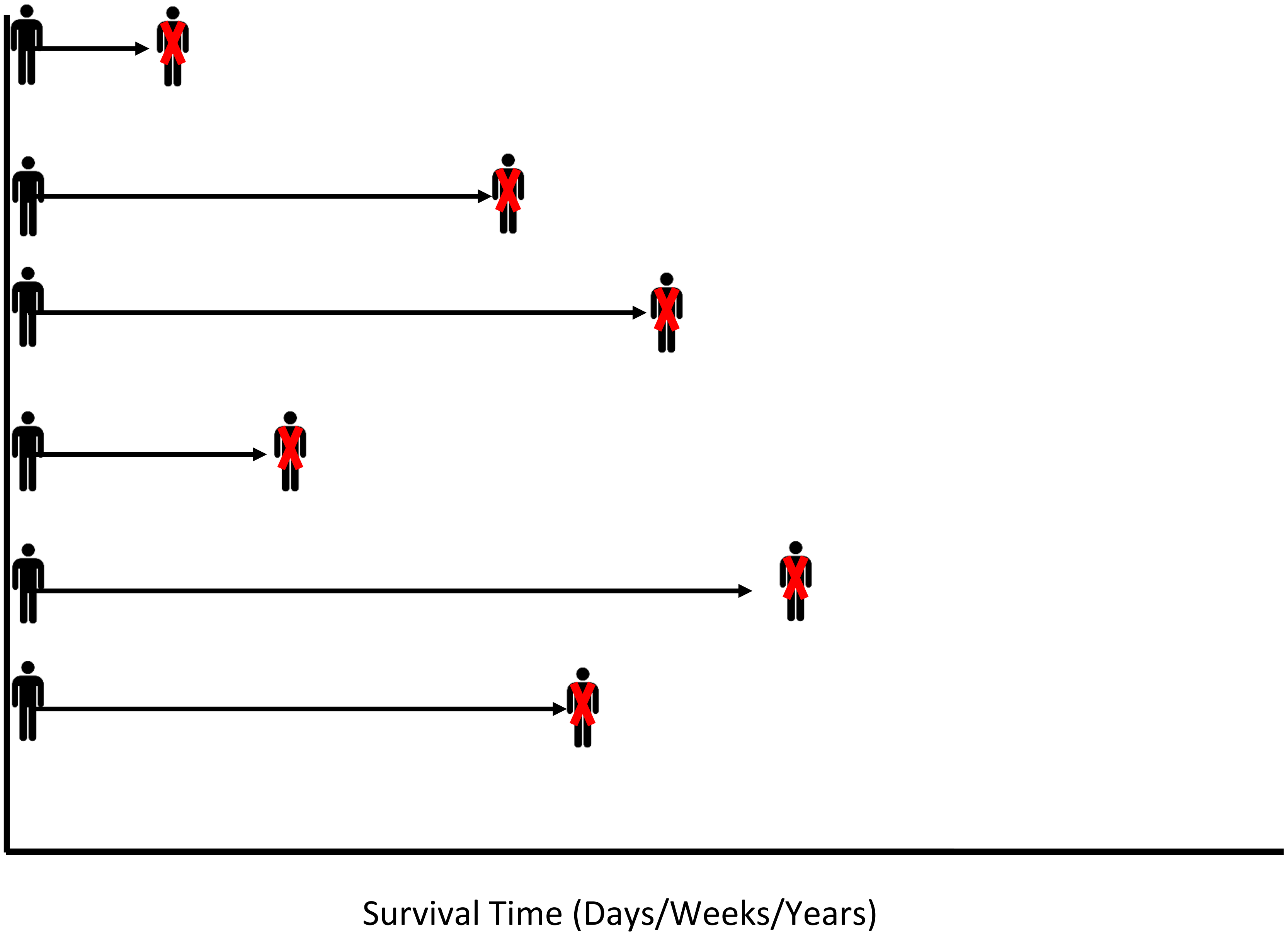
	P-value
Male	0.117

- Does not violate proportional hazards assumption
- What if assumption is violated?
  - Stratified analyses
  - Interaction with time

Other Topics

Competing Risks

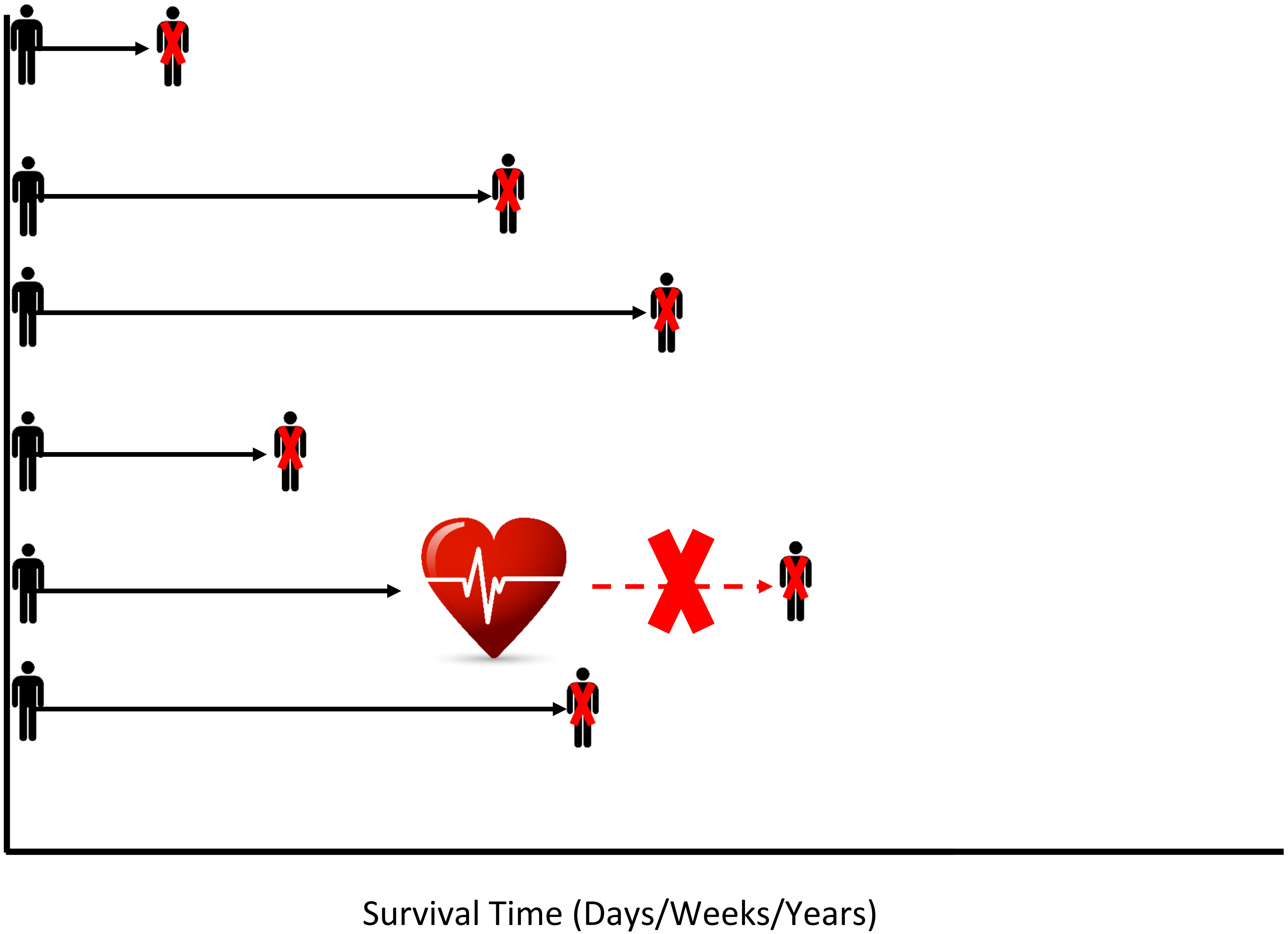
- Subjects can ‘fail’ from more than one cause
- Prevent observation of event of interest
- Alter probability of an event of interest



Other Topics

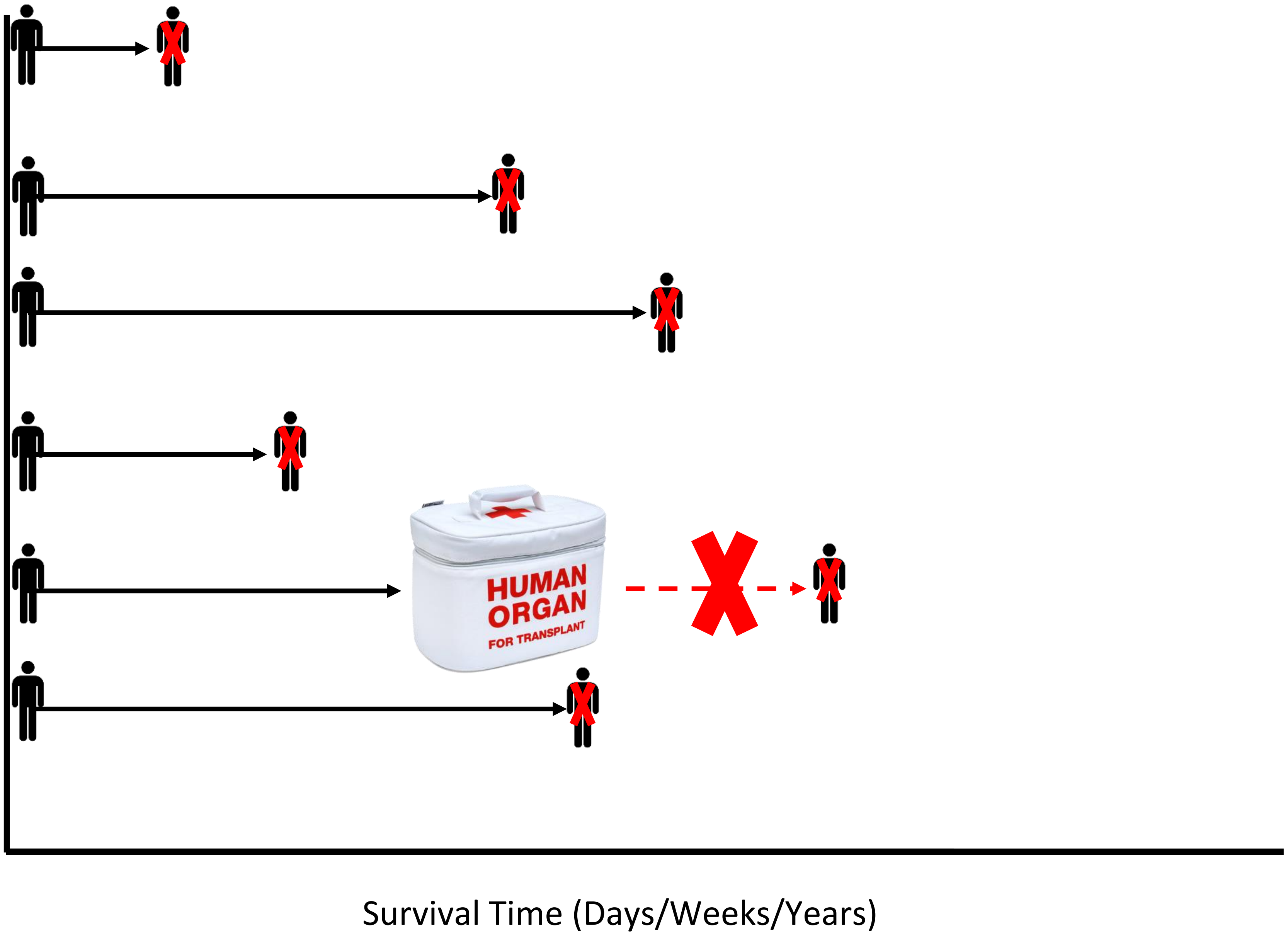
Competing Risks

- Subjects can ‘fail’ from more than one cause
- Prevent observation of event of interest
- Alter probability of an event of interest



Other Topics
Competing Risks

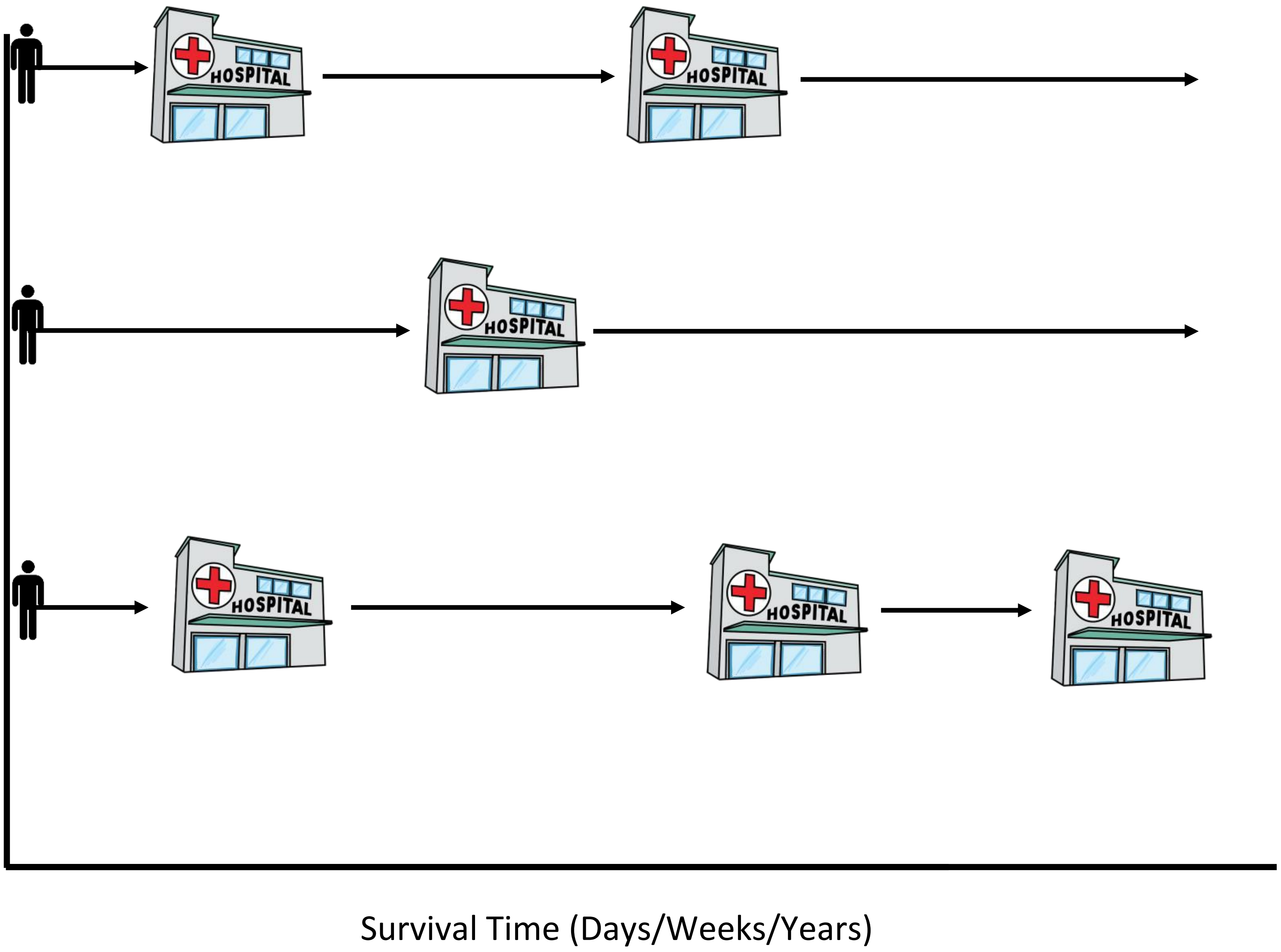
- Example:
  - Investigating death on dialysis
  - Competing risk: receiving a kidney transplant



Other Topics

Recurrent Events

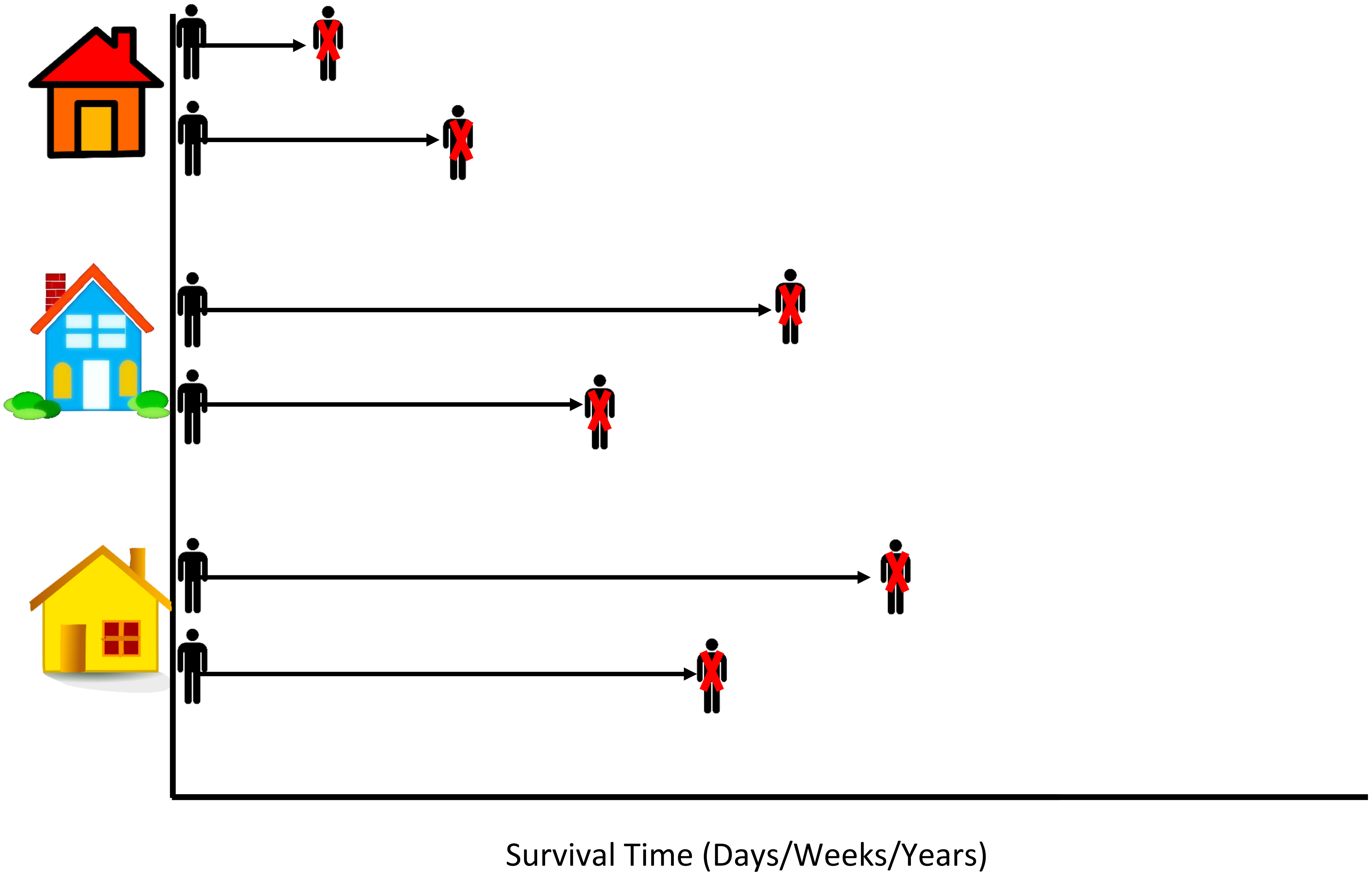
- Multiple events occurring for one subject
- Examples:
  - Recurrent tumors
  - Recurrent episodes of disease



Other Topics

Frailty Models

- When survival outcomes are correlated among clustered individuals
- Model correlations between event times of same cluster
- Introduce random effects



References

- Klein, JP and Moeschberger, ML. *Survival Analysis: Techniques for Censored and Truncated Data*. Second Edition. Springer, New York; 2003.

- R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

- Other Survival Analysis Textbooks:
  - Kleinbaum, DG. And Klein, M. *Survival Analysis: A Self-Learning Text*. Third Edition. Springer, New York; 2011.
  - Moore, DF. *Applied Survival Analysis Using R*. Springer, New York; 2016.

BCC: Biostatistics Collaboration Center

Contact Us

- Request an Appointment
  - http://www.feinberg.northwestern.edu/sites/bcc/contact-us/request-form.html

- General Inquiries
  - bcc@northwestern.edu
  - 312.503.2288

- Visit Our Website
  - http://www.feinberg.northwestern.edu/sites/bcc/index.html

Biostatistics Collaboration Center |680 N. Lake Shore Drive, Suite 1400 |Chicago, IL 60611

Your feedback is important to us! (And helps us plan future lectures).

Complete the evaluation survey to be entered in to a drawing to win 2 free hours of biostatistics consultation.

Northwestern Medicine
Feinberg School of Medicine

Thank you for your participation in the BCC Statistically Speaking Lecture Series