Session 3.1

Grace periods and treatment timing

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Today's examples

We'll walk through two clone-censor-weighting examples:

1. **Grace period example**: Treatment vs. no treatment within first trimester
2. **Treatment timing example**: Comparing three strategies specifying gestational age at treatment

Both illustrate how to handle situations where treatment assignment and initiation are not instantaneous

Example 1: grace period

Research question: Does first-trimester treatment (started by week 14) vs. no treatment affect risk of pregnancy loss?

- **Time zero:** 6 weeks gestation
- **Grace period:** 8 weeks (until week 14)
- **Strategies:**
  - Strategy 0: Don’t start treatment within first trimester
  - Strategy 1: Start treatment by week 14

The data

ID	Week treatment started	Gestational week at end of pregnancy
1	1000	18
2	36	40
3	1000	19
4	10	11
5	12	39
6	16	41
7	8	17
8	1000	36
9	13	38
10	1000	16
11	15	40
12	11	39

Create clones

ID	Treatment strategy	Time zero	Week treatment started	Gestational week at end of pregnancy
1	0	6	1000	18
1	1	6	1000	18
2	0	6	36	40
2	1	6	36	40
3	0	6	1000	19
3	1	6	1000	19
4	0	6	10	11
4	1	6	10	11
5	0	6	12	39
5	1	6	12	39
6	0	6	16	41

ID	Treatment strategy	Time zero	Week treatment started	Gestational week at end of pregnancy
6	1	6	16	41
7	0	6	8	17
7	1	6	8	17
8	0	6	1000	36
8	1	6	1000	36
9	0	6	13	38
9	1	6	13	38
10	0	6	1000	16
10	1	6	1000	16
11	0	6	15	40
11	1	6	15	40
12	0	6	11	39
12	1	6	11	39

Each person gets cloned into both treatment strategies at time zero

Clone 0 censoring rules

Clone 0 (never treat strategy): censored if they start treatment during grace period

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
1	1000	18	0	14	1	18
2	36	40	0	14	1	40
3	1000	19	0	14	1	19
4	10	11	1	10	0	10
5	12	39	1	12	0	12
6	16	41	0	14	1	41
7	8	17	1	8	0	8
8	1000	36	0	14	1	36
9	13	38	1	13	0	13

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
10	1000	16	0	14	1	16
11	15	40	0	14	1	40
12	11	39	1	11	0	11

Clone 1 censoring rules

Clone 1 (treat by week 14 strategy): censored if they don't start treatment by end of grace period

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
1	1000	18	1	14	0	14
2	36	40	1	14	0	14
3	1000	19	1	14	0	14
4	10	11	0	11	1	11
5	12	39	0	12	1	39
6	16	41	1	14	0	14
7	8	17	0	8	1	17
8	1000	36	1	14	0	14
9	13	38	0	13	1	38

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
10	1000	16	1	14	0	14
11	15	40	1	14	0	14
12	11	39	0	11	1	39

Combined results

ID	Treatment	Week treatment started	Censoring time	Censored	Outcome time	Outcome
1	0	1000	14	0	18	1
1	1	1000	14	1	14	0
2	0	36	14	0	40	1
2	1	36	14	1	14	0
3	0	1000	14	0	19	1
3	1	1000	14	1	14	0
4	0	10	10	1	10	0
4	1	10	11	0	11	1
5	0	12	12	1	12	0
5	1	12	12	0	39	1

ID	Treatment	Week treatment started	Censoring time	Censored	Outcome time	Outcome
6	0	16	14	0	41	1
6	1	16	14	1	14	0
7	0	8	8	1	8	0
7	1	8	8	0	17	1
8	0	1000	14	0	36	1
8	1	1000	14	1	14	0
9	0	13	13	1	13	0
9	1	13	13	0	38	1
10	0	1000	14	0	16	1
10	1	1000	14	1	14	0
11	0	15	14	0	40	1
11	1	15	14	1	14	0
12	0	11	11	1	11	0

Looking only at people who adhered through follow-up

ID	Treatment	Week treatment started	Censoring time	Censored	Outcome time	Outcome
1	0	1000	14	0	18	1
2	0	36	14	0	40	1
3	0	1000	14	0	19	1
4	1	10	11	0	11	1
5	1	12	12	0	39	1
6	0	16	14	0	41	1
7	1	8	8	0	17	1
8	0	1000	14	0	36	1
9	1	13	13	0	38	1

ID	Treatment	Week treatment started	Censoring time	Censored	Outcome time	Outcome
10	0	1000	14	0	16	1
11	0	15	14	0	40	1
12	1	11	11	0	39	1

Grace periods handle uncertainty

During weeks 6-14, we don't know who will ultimately be "treated" or "untreated"

- Each person contributes to both strategies until their status is determined
- Early pregnancy losses are properly attributed to both groups
- Eliminates immortal time bias

Example 2: treatment timing

Research question: What is the optimal timing for treatment initiation?

- **Time zero:** 8 weeks gestation
- **Strategies:**
  - Strategy 1: Start treatment at week 12
  - Strategy 2: Start treatment at week 14
  - Strategy 3: Start treatment at week 16

Treatment timing data

ID	Week treatment started	Gestational week at end of pregnancy
1	12	40
2	1000	11
3	10	11
4	14	39
5	18	41
6	8	17
7	1000	36
8	16	38
9	12	13
10	15	39
11	17	42
12	1000	15

Create three clones

Each person gets cloned into all three treatment timing strategies

ID	Planned week treatment started	Time zero	Week treatment started	Gestational week at end of pregnancy
1	12	8	12	40
1	14	8	12	40
1	16	8	12	40
2	12	8	1000	11
2	14	8	1000	11
2	16	8	1000	11
3	12	8	10	11
3	14	8	10	11
3	16	8	10	11

ID	Planned week treatment started	Time zero	Week treatment started	Gestational week at end of pregnancy
4	12	8	14	39
4	14	8	14	39
4	16	8	14	39
5	12	8	18	41
5	14	8	18	41
5	16	8	18	41
6	12	8	8	17
6	14	8	8	17
6	16	8	8	17
7	12	8	1000	36
7	14	8	1000	36
7	16	8	1000	36
8	12	8	16	38

ID	Planned week treatment started	Time zero	Week treatment started	Gestational week at end of pregnancy
8	14	8	16	38
8	16	8	16	38
9	12	8	12	13
9	14	8	12	13
9	16	8	12	13
10	12	8	15	39
10	14	8	15	39
10	16	8	15	39
11	12	8	17	42
11	14	8	17	42
11	16	8	17	42
12	12	8	1000	15
12	14	8	1000	15

Clone 1: treat at week 12

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
1	12	40	0	12	1	40
2	1000	11	0	11	1	11
3	10	11	1	10	0	10
4	14	39	1	12	0	12
5	18	41	1	12	0	12
6	8	17	1	8	0	8
7	1000	36	1	12	0	12
8	16	38	1	12	0	12
9	12	13	0	12	1	13
10	15	39	1	12	0	12

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
11	17	42	1	12	0	12
12	1000	15	1	12	0	12

Clone 2: treat at week 14

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
1	12	40	1	12	0	12
2	1000	11	0	11	1	11
3	10	11	1	10	0	10
4	14	39	0	14	1	39
5	18	41	1	14	0	14
6	8	17	1	8	0	8
7	1000	36	1	14	0	14
8	16	38	1	14	0	14
9	12	13	1	12	0	12
10	15	39	1	14	0	14

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
11	17	42	1	14	0	14
12	1000	15	1	14	0	14

Clone 3: treat at week 16

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
1	12	40	1	12	0	12
2	1000	11	0	11	1	11
3	10	11	1	10	0	10
4	14	39	1	14	0	14
5	18	41	1	16	0	16
6	8	17	1	8	0	8
7	1000	36	1	16	0	16
8	16	38	0	16	1	38
9	12	13	1	12	0	12
10	15	39	1	15	0	15

ID	Week treatment started	Gestational week at end of pregnancy	Censored	Censoring time	Outcome	Outcome time
11	17	42	1	16	0	16
12	1000	15	0	15	1	15

All clones who followed their assigned strategy

ID	Planned week treatment started	Week treatment started	Outcome time
1	12	12	40
2	12	1000	11
2	14	1000	11
2	16	1000	11
4	14	14	39
8	16	16	38
9	12	12	13
12	16	1000	15

Cloning-censoring-weighting tips

- Descriptive analysis beforehand will help tell you what treatment strategies you have *positivity* for
  - i.e., anyone has a chance of following
- It's really easy to mess up – start with a few examples to develop your code
  - Be sure they cover all different posssibilities
- Time-to-event outcomes are nice because you get to use clones' data until they're censored
  - Same with outcomes that you can estimate with time-to-event models, like pregnancy loss by 20 weeks or preterm birth by 37 weeks
  - If looking at a continuous outcome (e.g., birthweight), you only get to use data for people who followed a strategy through the end of follow-up