Conditional Logistic Modelling for Adaptive Trials

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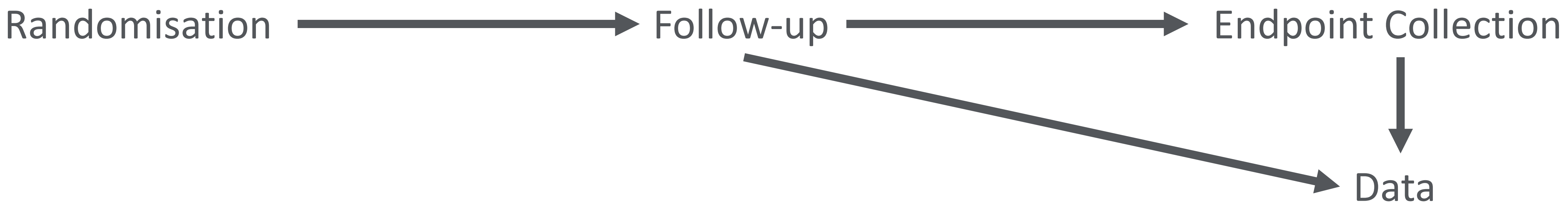
Where don't adaptive trials work?

– When the **time to endpoint** is long relative to the **recruitment period**
– If most participants have been recruited before an interim analysis, then there is minimal future recruitment to inform
– Example: vaccine efficacy trials
  - high recruitment rate
  - long time to endpoint
  - long follow up period
– For these trials adaptive designs are typically avoided

But what if it was different?

– How could an adaptive design be used in this context?
– If participants have follow-up **observations before endpoint** collection, could we model their endpoint **conditional** on these prior observations?



Set the scene

– Consider a two arm (control + intervention) trial with a binary endpoint (states 0/1 e.g., infection status)
– Assume the binary endpoint to be absorbing (in state 1)
– Participants have follow-up observations **before the endpoint** is collected
– We are interested in the probability that an individual will be in state 1 at the time of endpoint collection

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Notation

- Arm $j \in \{1,2\}$ for control and intervention
- Participant $i \in \{1, \dots, n_j\}$ on arm j
- Follow-up time $t \in \{0,1, \dots, T\}$ (T is endpoint collection time)
- Binary observation $y_{ijt} \in \{0,1\}$ ($y_{ijT} \in \{0,1\}$ is the endpoint)

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Model

- We model the endpoint: $Y_{ijT} \sim \text{Bern}(\pi_j)$
- Parameters of interest: $\pi_j = \text{P}(Y_{ijT} = 1)$
- Instead of estimating directly we will instead model the **incremental** probabilities:

$$\pi_{jt} = \text{P}(Y_{ijt} = 1 | Y_{ij(t-1)} = 0, \ldots, Y_{ij0} = 0)$$

- Probability that a participant transitions from state 0 to state 1 between follow-up observations $t - 1$ and t
- Incremental model: $Y_{ijt} = 1 | Y_{ij(t-1)} = 0, \ldots, Y_{ij0} = 0 \sim \text{Bern}(\pi_{jt})$

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Why?

- To reduce the time to decision making
- Potential to save resources in collection of follow-up data, unless entire cohort required full follow-up for safety data
- Gains come from incorporation of information at earlier follow-up observations
- We use this information to estimate the incremental parameters π_{jt}
- There is a **deterministic relationship** between the incremental parameters π_{jt} and the parameters of interest π_j
- These parameters can then **recover the parameters of interest**

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Deriving the relationship

1) $\mathrm{P}(Y_{ijt'} = 0 | Y_{ijt} = 1) = 0 \quad \forall t' > t$ (absorbing state)

2) $\pi_{jt} = \mathrm{P}(Y_{ijt} = 1 | Y_{ij(t-1)} = 0)$ (incremental parameters)

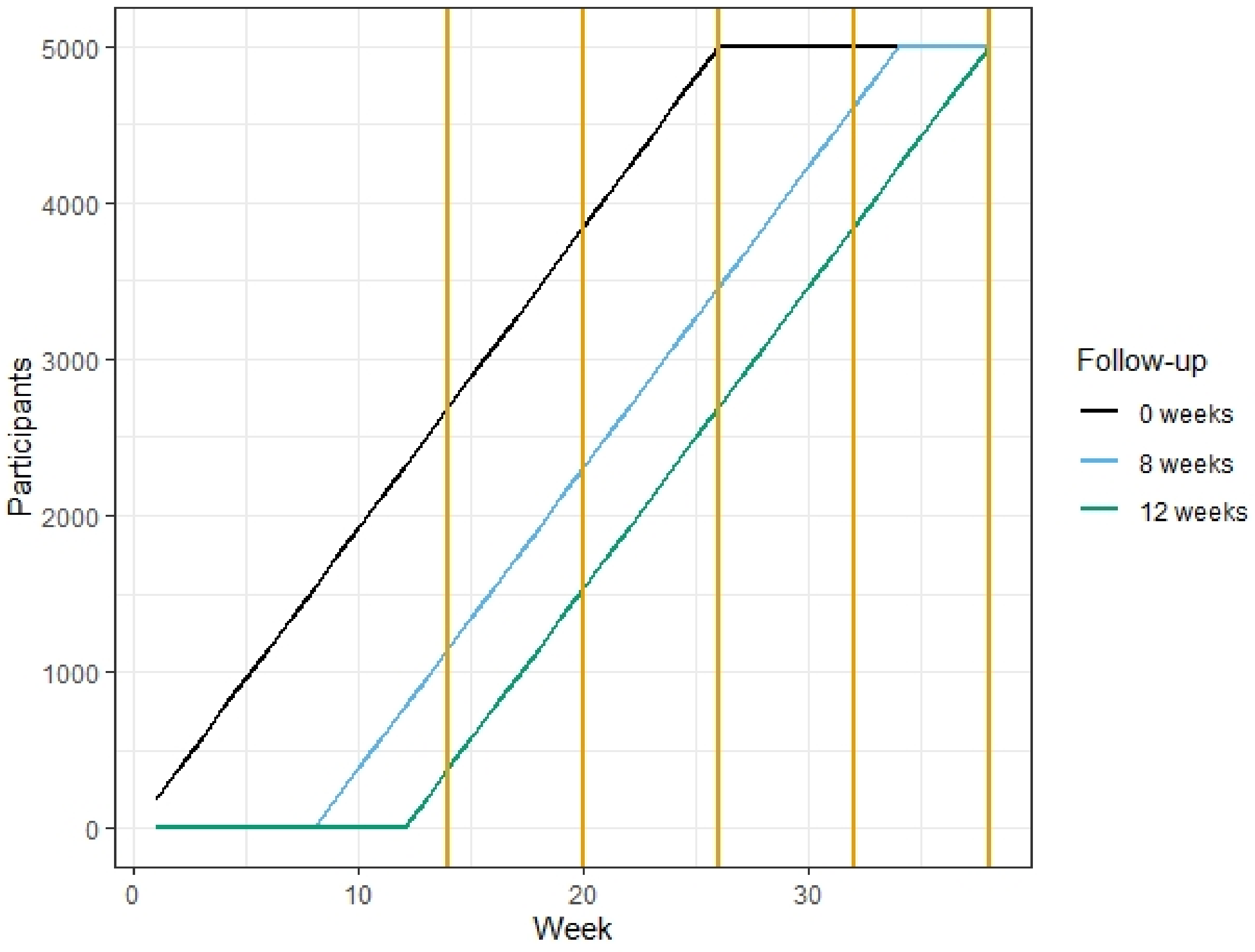
3) $\gamma_{jt} = \mathrm{P}(Y_{ijt} = 0) = \prod_{\tau=0}^{t}(1 - \pi_{j\tau})$ (intermediate derivation)

4) $\pi_j = \sum_{t=1}^{T} \pi_{jt} \prod_{\tau=0}^{t-1}(1 - \pi_{j\tau})$ (deterministic relationship)

Ta Da!

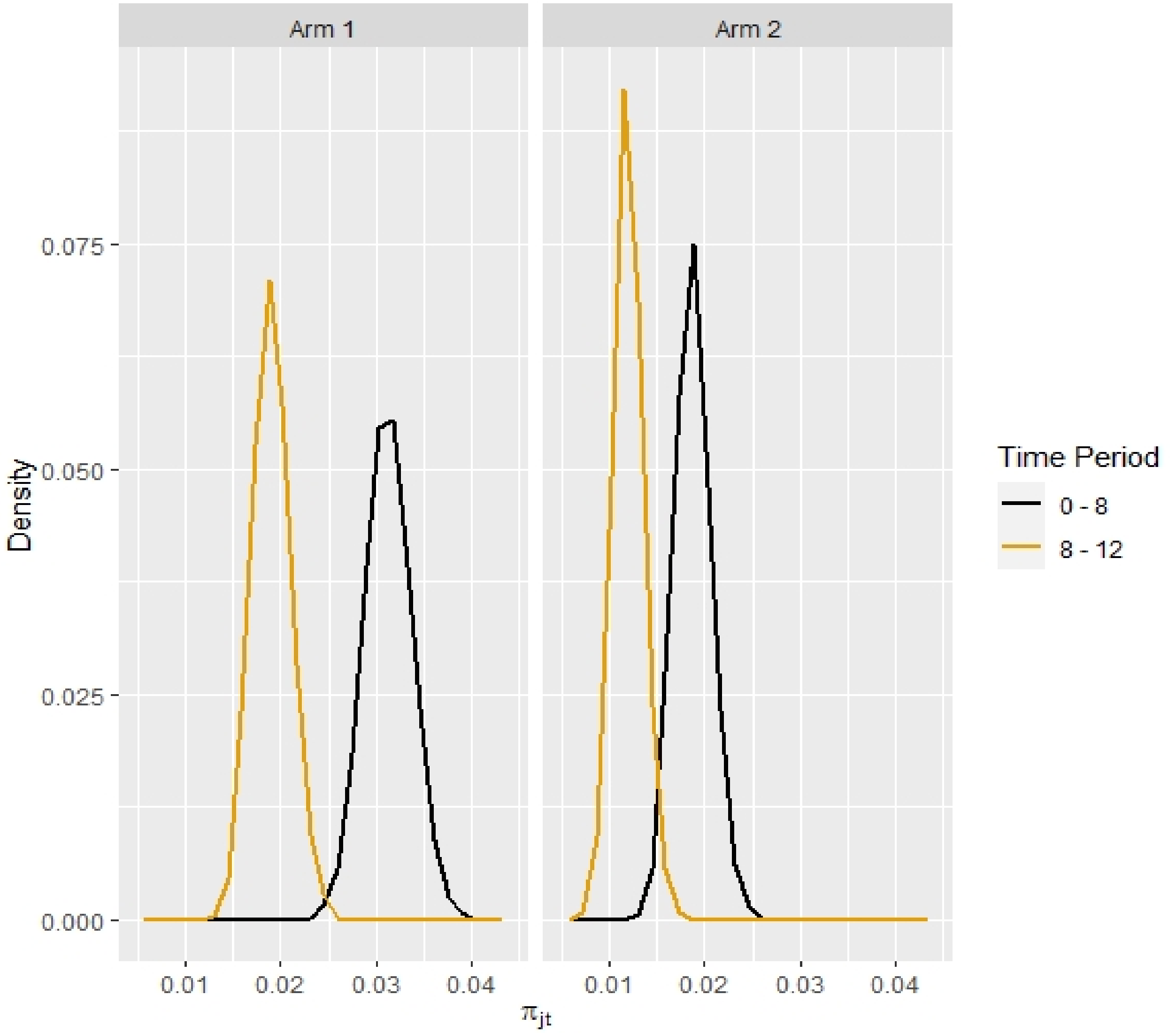
Vaccine trial example

- 5000 participants allocated 1:1 to two arms ($j \in \{1,2\}$)
- Infection status measured at 8 weeks and **12 weeks** ($t \in \{0, 8, 12\}$)
- Uniform recruitment over 26 weeks
- True probabilities $\pi_1 = 0.05$ and $\pi_2 = 0.03$
- Planned analyses at 14, 20, 26, 32 and 38 weeks



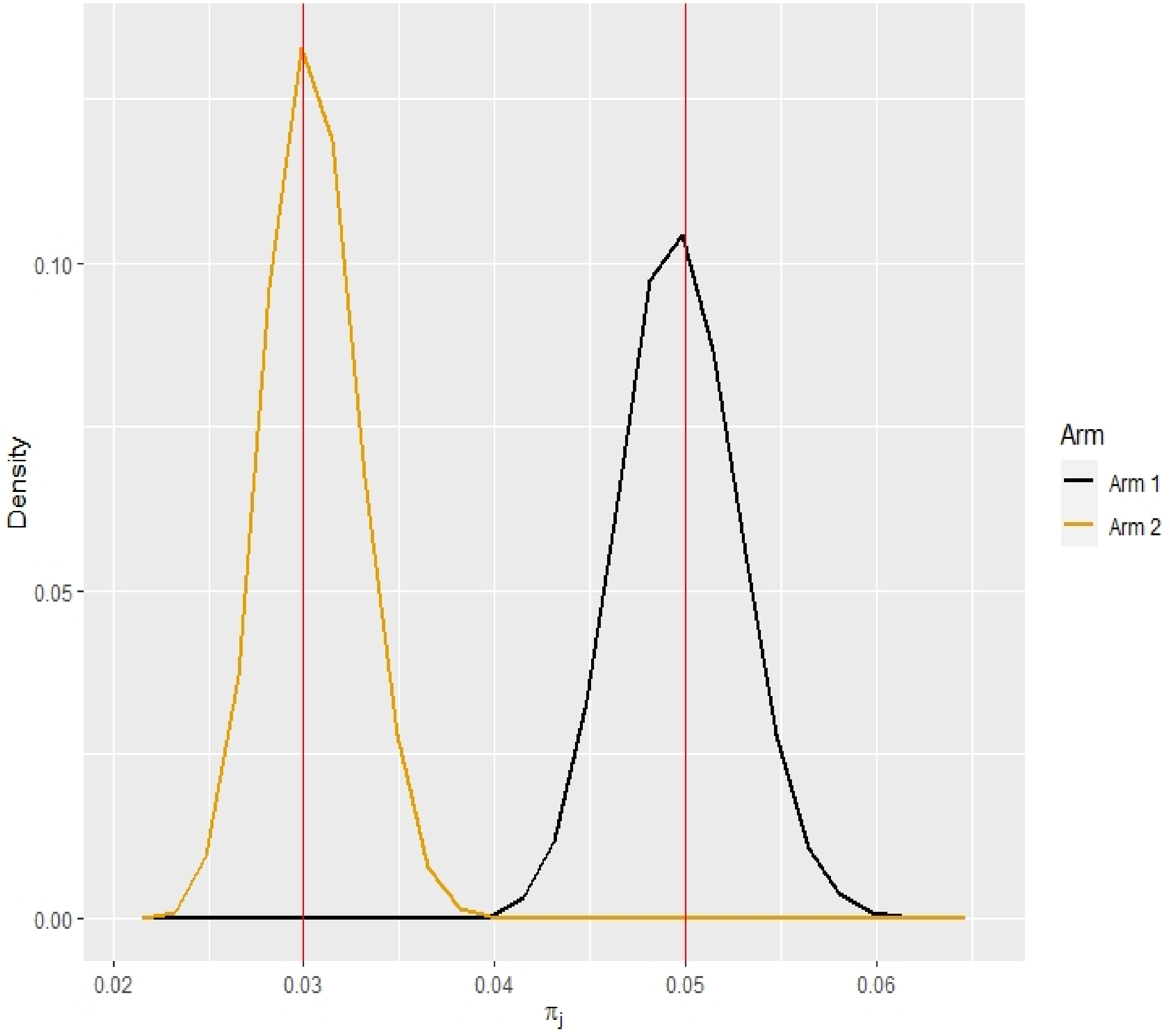
Incremental parameter posteriors

Parameter	Mean	5%	95%
$\hat{\pi}_{11}$	0.0312	0.0273	0.0353
$\hat{\pi}_{12}$	0.0187	0.0157	0.0219
$\hat{\pi}_{21}$	0.0190	0.0159	0.0224
$\hat{\pi}_{22}$	0.0119	0.0096	0.0146



Parameters of interest posteriors

Parameter	Mean	5%	95%
$\hat{\pi}_1$	0.0497	0.0446	0.0549
$\hat{\pi}_2$	0.0304	0.0266	0.0346



Simulation Study – No effect

Arm 1 Prob. = Arm 2 Prob. = 0.05

Model	Prop. Success*	Mean Sample Size
Standard	0.049	4901
Conditional	0.051	4899

	Standard	Conditional
Interim 1	0.017	0.016
Interim 2	0.011	0.012
Interim 3	0.009	0.010
Interim 4	0.007	0.009
Interim 5	0.005	0.004

*proportion of trials that declared Arm 2 superior to Arm 1 –type I error controlled at 5%

Simulation Study – Small effect

Arm 1 Prob. = 0.05, Arm 2 Prob. = 0.03

Model	Prop. Success*	Mean Sample Size
Standard	0.942	3268
Conditional	0.950	3021

	Standard	Conditional
Interim 1	0.123	0.205
Interim 2	0.351	0.384
Interim 3	0.252	0.215
Interim 4	0.143	0.106
Interim 5	0.073	0.040

*proportion of trials that declared Arm 2 superior to Arm 1 – power

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Summary

- Adaptive trials struggle when the time to endpoint is long **relative** to the length of recruitment
- We can incorporate information from follow-up observations **prior** to the endpoint
- Model probability of state transition **conditional** on prior follow-ups
- Ability to **stop earlier** compared to standard methodology

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Appendix - Proof Derivation 3

$$
\begin{aligned}
\gamma_{jt} &= \mathrm{P}(Y_{it} = 0) \\
&= \mathrm{P}\left(Y_{ijt} = 0 \middle| Y_{ij(t-1)} = 0\right)\mathrm{P}\left(Y_{ij(t-1)} = 0\right) + \mathrm{P}\left(Y_{ijt} = 0 \middle| Y_{ij(t-1)} = 1\right)\mathrm{P}\left(Y_{ij(t-1)} = 1\right) \\
&= (1 - \pi_{jt})\mathrm{P}(Y_{ij(t-1)} = 0) + (0)\mathrm{P}(Y_{ij(t-1)} = 1) \\
&= (1 - \pi_{jt})\mathrm{P}(Y_{ij(t-1)} = 0) \\
&= (1 - \pi_{jt})(1 - \pi_{j(t-1)})\mathrm{P}(Y_{ij(t-2)} = 0) \\
&= \ \dots \\
&= (1 - \pi_{jt})(1 - \pi_{j(t-1)})(1 - \pi_{j(t-2)}) \dots \mathrm{P}(Y_{ij0} = 0) \\
&= (1 - \pi_{jt})(1 - \pi_{j(t-1)})(1 - \pi_{j(t-2)}) \dots (1 - \pi_{j0}) \\
&= \prod_{\tau=0}^{t}(1 - \pi_{j\tau})
\end{aligned}
$$

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Appendix - Proof Derivation 4

$$
\begin{aligned}
\pi_{jt} &= \mathrm{P}(Y_{ijT} = 1) \\
&= \mathrm{P}(Y_{ijT} = 1 | Y_{ij(T-1)} = 0)\mathrm{P}(Y_{ij(T-1)} = 0) + \mathrm{P}(Y_{ijT} = 1 | Y_{ij(T-1)} = 1)\mathrm{P}(Y_{ij(T-1)} = 1) \\
&= \pi_{jT}\gamma_{j(T-1)} + (1)\mathrm{P}\left(Y_{ij(T-1)} = 1\right) \\
&= \pi_{jT}\gamma_{j(T-1)} + \pi_{j(T-1)}\gamma_{j(T-2)} + (1)\mathrm{P}\left(Y_{ij(T-2)} = 1\right) \\
&= \ \ldots \\
&= \pi_{jT}\gamma_{j(T-1)} + \pi_{j(T-1)}\gamma_{j(T-2)} + \pi_{j(T-2)}\gamma_{j(T-3)} + \cdots + \pi_{j1}\gamma_{j0} + (1)\mathrm{P}(Y_{ij0} = 1) \\
&= \sum_{t=1}^{T} \pi_{jt}\, \gamma_{j(t-1)} \\
&= \textstyle\sum_{t=1}^{T} \pi_{jt} \prod_{\tau=0}^{t-1}(1 - \pi_{j\tau})
\end{aligned}
$$

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