Modeling longitudinal count data with dropouts

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* Views expressed in this presentation are those of the presenter and do not reflect those of the FDA

Outline

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II. Motivating example (clinical trial for actinic keratosis lesions & dropouts)

III. Generalized Linear Model for repeated measurements count data

   a. Marginal model, GEE and WGEE for handling missing data (moments based)

   b. Transition models

IV. Generalized Poisson Integer-valued AR(1) model (likelihood based)

   a. Simulation study

   b. Application to AK clinical trial data

V. Overall comments

I. Background: Repeated measurements clinical trials

- Although clinical trials often involve repeated evaluations of the endpoints during the course of the trial, frequently the analysis focuses on the final assessment.
- Final assessment might be acceptable if the final status is all that is relevant for evaluating treatment effect or AE (e.g., clear / not clear of the disease; death/alive, etc..)
- In general the patient response profile (PRF) based on the repeated measurements over the course of the trial should be more informative for interpretation of study findings as it reflects status trajectory (disease severity) before final status.
- In addition, PRF might provide insight on the nature of missingness and consequently suggest approaches for handling missing data.

I. Background: Repeated measurements clinical trials

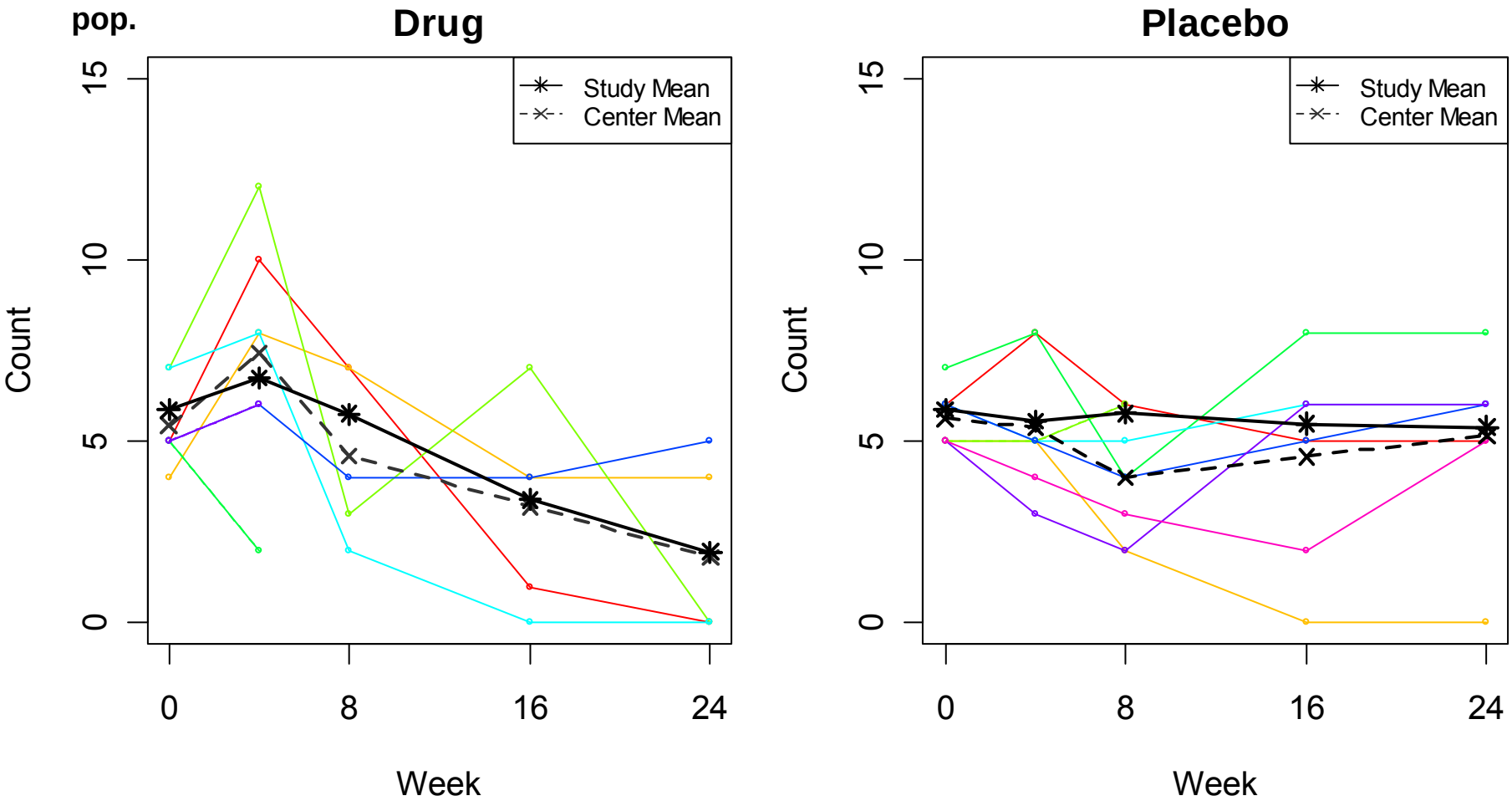
- We will focus on repeated measurements clinical trials with counts being the primary endpoint.
- Such trials are encountered in many clinical areas including dermatology (e.g., treatment of basal and squamous cell carcinomas (BCC, SCC), actinic keratosis (AK), genital warts, and acne among others).
- We consider an example of a clinical trial for treatment of AK and summarize some features of this data set and their impact on the statistical modeling strategy.

II. Motivating example: Actinic keratosis trial

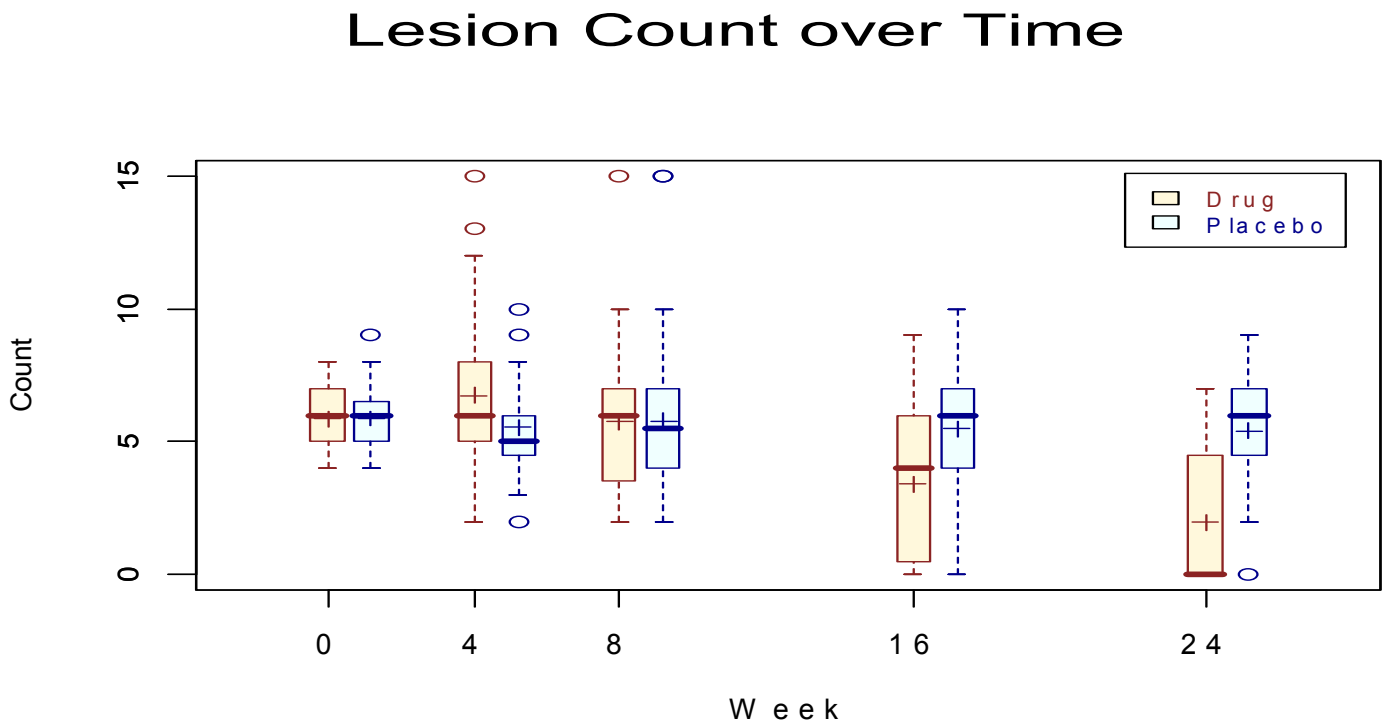
- Data from a multi-center, placebo-controlled, clinical trial for treatment of AK lesions on the face and balding scalp.
- For enrollment a subject should have 4-8 AK lesions.
- Treatment is for 16 weeks with efficacy evaluation at week 24. Visits at weeks: 0, 4, 8, 16 and 24.
- The objective of the trial is to establish the efficacy of the test drug using change in lesion counts (or disease clearance) as the primary endpoint.

II. Motivating example: Actinic keratosis trial

Subject Lesion Count profile (Center A), mean change for center A and mean for the overall study pop.



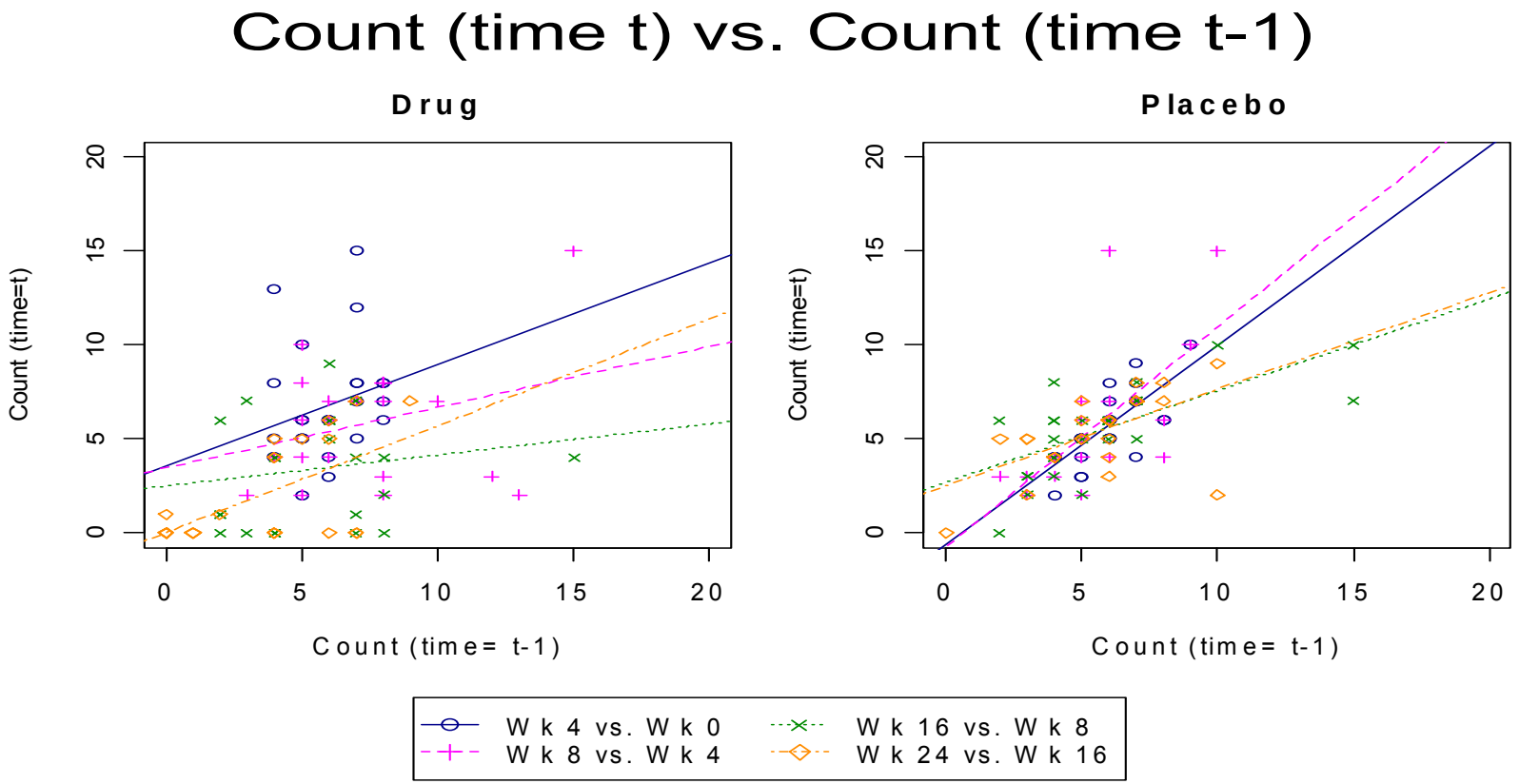
II. Motivating example: Actinic keratosis trial



Visit (n1,n2)	0 (30,31)	4 (27,31)	8 (24,30)	16 (23,29)	24 (23,28)
Overall	5.87 (1.65)	6.10 (6.02)	5.76 (9.09)	4.56 (7.51)	3.84 (8.21)
active	5.87 (1.84)	6.74 (8.89)	5.75 (9.15)	3.39 (8.34)	1.96 (7.04)
vehicle	5.87 (1.52)	5.55 (3.06)	5.77 (9.36)	5.48 (5.12)	5.39 (3.95)

II. Motivating example: Actinic keratosis trial

Scatter plot for number of AK (per subject and slope) at time t vs. AK at time (t-1)



II. Motivating example: Actinic keratosis trial

This data has several features, likely shared with data from similar trials:

- Unevenly spaced time of measurements.
- Slight decrease in # of AK over time for vehicle with relatively constant variability to the mean over time. In contrast,
- Substantial reduction in # of AK for the active after week 8, with over time greater variability in response (might be typical for active drugs).
- The impact of subject's AK counts on subsequent time counts, if any, might vary by treatment arm.

In light of the differences between the two groups: What is a reasonable model for such data?

We will discuss alternative models for analyzing such data, both standard as well as briefly discussing new methodologies.

III. GLM for repeated measurements count data:

a. Marginal models

For count data typically we consider a model for the mean count of the form:

$$\log(\, E(Y_{ij})\,) = \beta_0 + \beta_1\, time_{ij} + \beta_2\, (time_{ij} * trt_i) \qquad (1)$$

Alternatively, as response pattern change for subjects on the active treatment change by Week 4 (likely due AE), one might consider piecewise linear model, i.e:

$$\log(E(Y_{ij})) = \beta_0 + \beta_1\, time_{ij} + \beta_2\, (time_{ij} - 4)_+ + \beta_4\, (time_{ij} * trt_i) + \beta_5\, trt * (t_{ij} - 4)_+ \qquad (2)$$

- Marginal models consider change in mean counts over time. In contrast, a conditional (transition) model considers the response at next visit given the response at current visit. Whether a marginal model is appropriate depends on the scientific question, however, this model does not consider the mechanism generating the data:

- Modeling the log mean response is considered for mathematical convenience.

- The marginal model is semi-parametric fitted using the Generalized Estimation Equation (GEE), which assumes that any dropout are completely random (MCAR).

III. GLM for repeated measurements count data:

a. Marginal models

Table 1 presents the results of fitting model (1) to the AK data

Parameter	Estimate	SE(emp.)	Pr > Z
Intercept	1.844	0.044	< 0.001
$Time_{ij}$	- 0.008	0.003	0.016
$Time_{ij}*trt_i$	- 0.030	0.008	< 0.001

- The underlying assumption of the GEE concerning dropouts (MCAR) might not hold for this data
- Fit model for dropouts to check whether it is MCAR. The model can be used to estimate the propensity for dropouts.
- Use WGEE, by assigning weights (inversely proportional to the propensities for dropouts) to the observed response to handle MAR.

III. GLM for analysis of count data:

a. Marginal models

- What are the relevant covariates when building model for dropouts ?
- Are dropouts related to time (visit), treatment, previous AK counts?
- What is the impact of the above questions on the modeling approach?

- Consider dropouts pattern by treatment arm and AK counts prior dropouts:

Drug	WK0	WK4	WK8	WK16	WK24
1	4	X	X	X	X
1	6	X	X	X	X
1	7	X	X	X	X
1	5	2	X	X	X
1	4	4	X	X	X
1	5	6	X	X	X
1	5	5	10	X	X
0	5	5	X	X	X
0	5	5	5	2	X
0	5	5	6	X	X

III. GLM for repeated measurements count data:
a. Marginal models - WGEE

- Note by using a narrow definition for MCAR, one might conclude if 'previous' counts are not predictive of dropouts for this data then:
- $\rightarrow$ (strictly speaking) we have MCAR
- $\rightarrow$ Complete Case Analysis ?

- For this data set dropouts might be related to treatment or time. Thus, consider other covariates, in addition to the 'previous' counts.

- The conclusion is that disregarding relevant covariates in the model, is expected to lead to the wrong conclusion (as known).

III. GLM for repeated measurements count data:

a. Marginal models-WGEE

Consider the following model for dropouts:

$$\log it\ P(D_i = j / D_i \geq j) = \psi_0 + \psi_1 y_{i.j-1} + \psi_2 trt_i \qquad (3)$$

Table 2. Estimation results for the dropouts (model 3) .

Parameter	Initial model			Final model		
	Estimate	SE	p-value	Estimate	SE	p-value
Intercept	-3.350	0.911	0.0002	-3.212	0.416	<0.0001
Y_{ij-1}	- 0.058	0.129	0.652			
Trt_i	1.030	0.705	0.144	1.504	0.474	0.0015

III. GLM for repeated measurements count data:

a. Marginal models-WGEE

Table 3. mean number of AK (n) by dropout status, visits and treatment

Visit	0	4	8	16	24
Completers	5.87 (61)	6.10 (58)	5.76 (54)	4.56 (52)	3.84 (51)
active	5.87 (30)	6.74 (27)	5.75 (24)	3.39 (23)	1.96 (23)
vehicle	5.87 (31)	5.55 (31)	5.77 (30)	5.48 (29)	5.39 (28)
Drop.(prev.)		5.66 (3)	3.50 (4)	8.00 (2)	2.00 (1)
active		5.66 (3)	3.33 (3)	10.00 (1)	NA
vehicle		NA	5.00 (1)	6.00 (1)	2.00 (1)

- Although the numbers are small for dropouts, 'previous' counts prior to dropout are similar for completers and dropouts. This might explain that 'previous' counts are not predictive to dropouts.

- There are 7 dropouts in the active vs 3 in the vehicle. Table 3 results show the propensity for dropout is higher for subjects on active treatment compared to those on placebo (1.504 on the log odds scale).

III. GLM for repeated measurements count data:

a. Marginal models-WGEE

Table 4. Estimation results for the WGEE compared with those of GEE

Parameter	WGEE		GEE	
	Estimate	SE (emp.)	Estimate	SE (emp.)
Intercept	1.771	0.041	1.844	0.044
$Time_{ij}$	-0.013	0.008	-0.008	0.003
$Time_{ij}$* Trt_i	-0.018	0.011	-0.030	0.008

Comments:

- Although SE for WGEE estimates are, in general, smaller that their analogues of the GEE, however the estimates are similar for the two approaches; that is the adjustment for dropouts (MAR) did not change the GEE findings.

- **Does the WGEE address our concerns about dropouts ?**
  Is it reasonable to handle dropouts due to irritation as treatment failure, using LOCF or other imputation methods ?

III. GLM for repeated measurements count data:

b. Autoregressive-type model:

Such models expresses the mean response as a function of previous counts in addition to other covariates (see, e.g.Diggle et al. 2002). For the AK counts consider:

$$\log(E(Y_{ij})) = \beta_0 + \beta_1 Y_{i(j-1)} + \beta_2\, trt_i + \beta_3\, (Y_{i(j-1)} * trt_i) \qquad (4)$$

Table 5. Estimation results for model (4) using GLIMMIX, with random residual statement (interaction was not sig. with p-value= 0.844):

Parameter	Estimate	SE	Pr > |t|
Intercept	1.101	0.090	< 0.001
Trt	- 0.195	0.071	0.007
$Y_{i(j-1)}$	0.103	0.012	< 0.001

- Transition models, unlike Gaussian data, do not have an explicit lag structure in the endogenous count variable.
- Some restrictions on the parameters and values of previous counts are required for the model to be meaningful.

IV. Generalized Poisson INAR(1) model

- Consider a conditional model for the actual counts instead of modeling log (μ_{ij})
- Given previous counts, scalar multiplication is not useful (unlike continuous data) since we can't speak of a fraction of lesion (count).
- Consider a probabilistic argument (thinning) operation denoted by 'o', where a lesion present at time t will be carried–out to the next time with probability α.

$$\alpha \circ x = x \text{ with probability } \alpha$$
$$= 0 \text{ with probability } (1-\alpha)$$

IV. Generalized Poisson INAR(1) model

The Poisson INAR (1) model (Al-Osh & Alzaid,1987; McKenzie,1988) is

$$Y_t = \alpha \circ Y_{t-1} + E_t$$

# counts	=	# carried out	+	# new counts
at t		from (t-1)		(t-1, t]

For clinical trials setting the probability of carry-over (α) should be related to treatment & time instead of being constant.

IV. Generalized Poisson INAR(1) model

Thus we consider extending the Poisson INAR(1) model to:

$$Y_{ij} = \alpha\,(X_{ij})\; o\; Y_{i\,(j-1)} + E_{ij} \qquad (6)$$

with:

$$\log it(\alpha\,(X_{ij})) = \beta_0 + \beta_1\, time_{ij} + \beta_2\,(time_{ij} * trt_i) \qquad (a)$$

Also, to account for the correlation between subject's lesions we extend model (a) by adding random intercept which also allows modeling variability across subjects. Thus we consider:

$$\log it(\alpha\,(X_{ij})) = \beta_0 + b_{0\,i} + \beta_1\, time_{ij} + \beta_2\,(time_{ij} * trt_i) \qquad (b)$$

The model can be fitted using, e.g., Proc NLMIXED in SAS

IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study

Generate Poisson count data (2 trt arms with 4 repeated measurements).

- Baseline counts for enrollment = 3 + $Y_{i\,j}$(2).

- $\log it(\alpha\ (X_{ij})) = \beta_0 + \beta_1\ time_{ij} + \beta_2\ (time_{ij} * trt_i)$

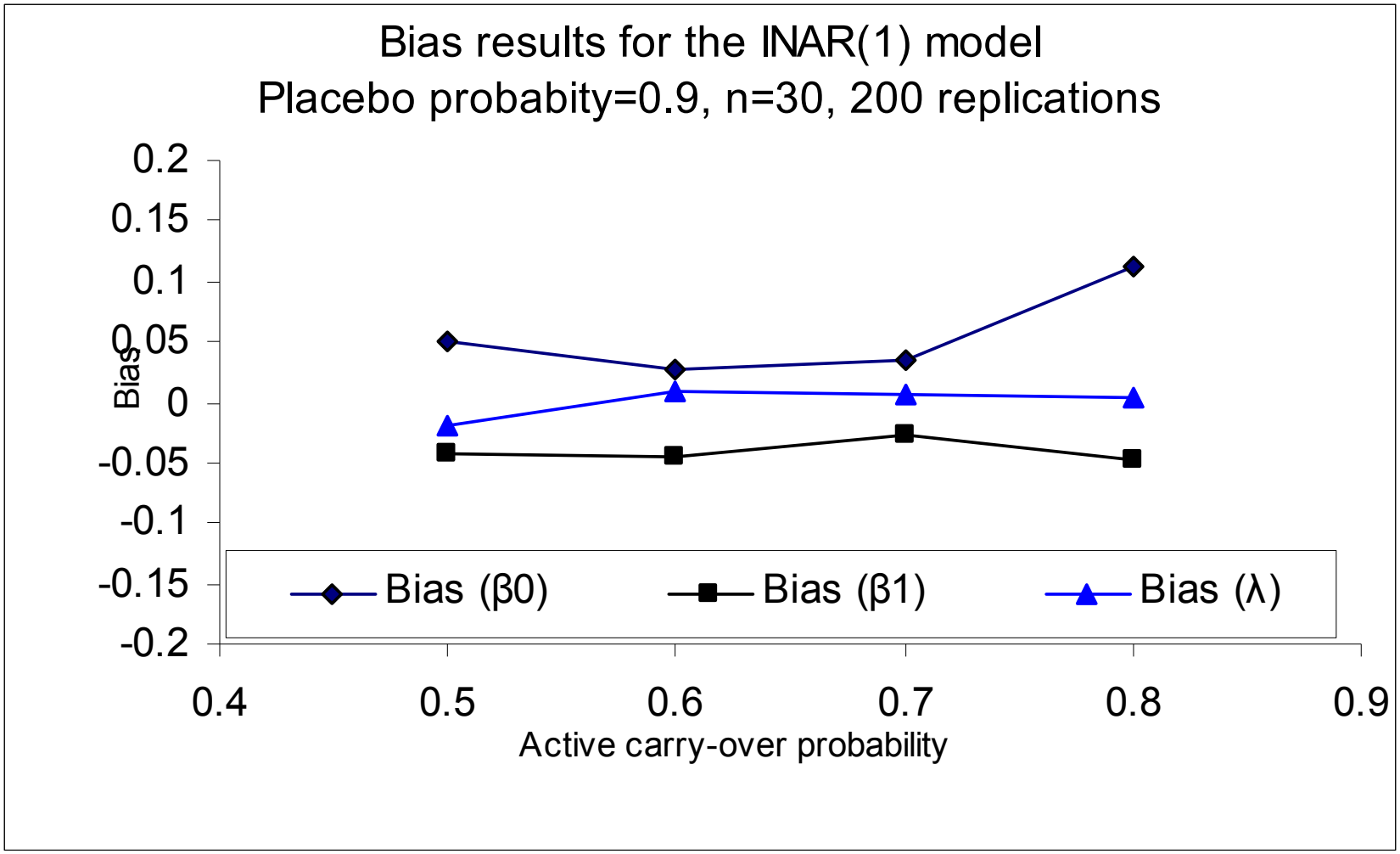
with $\alpha\ (X_{ij})$ for placebo $\geq$ that of the active (for placebo = 0.9, 0.8 and 0.7).

- $E_{i\,j}$ ~ Poisson (1).
- Per arm, n=30, 60, 120 per trt arm with 200 replications.
- Get estimate of β_0 , β_1 and λ by fitting the INAR(1) model using PROC NLMIXED in SAS.

Bias and MSE results for α_0 =0.9 (placebo) and α_1 = 0.8, 0.7, 0.6 and 0.5 (for the active) (corresponding to β_0 =-2.197, β_1 =0.811, 1.350, 1.792 and 2.197, respectively, are presented in the following figures.

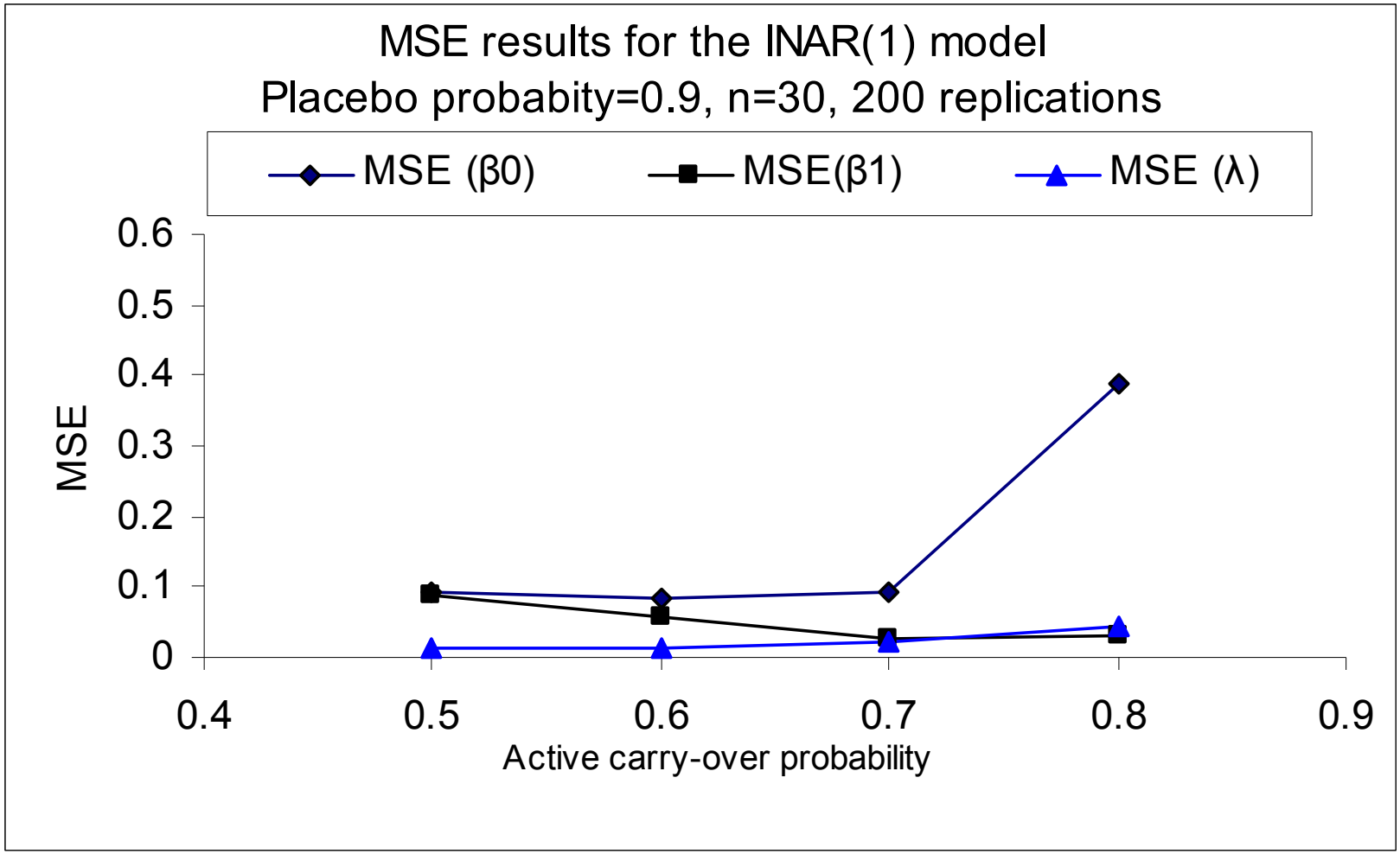
IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study



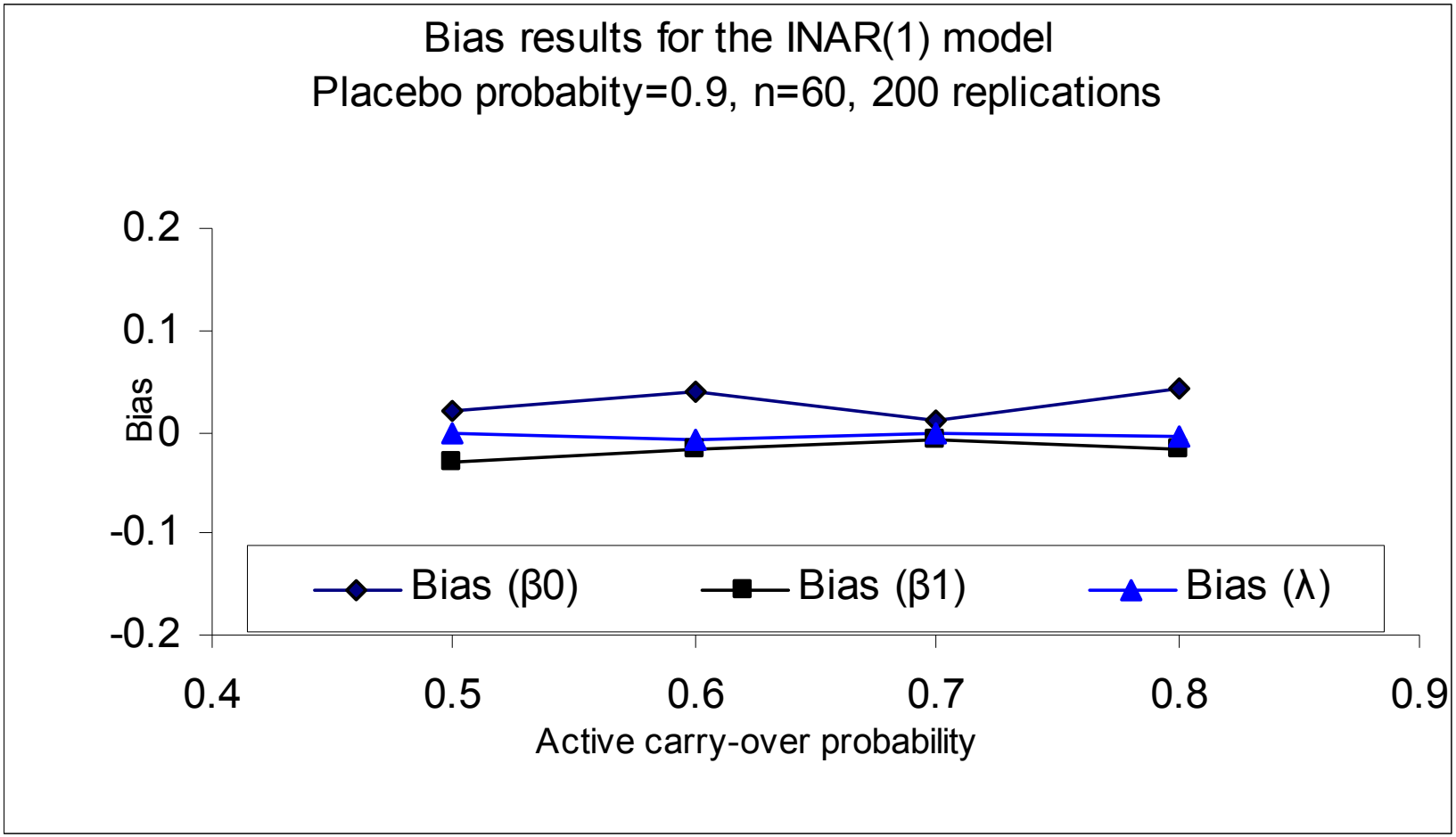
IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study



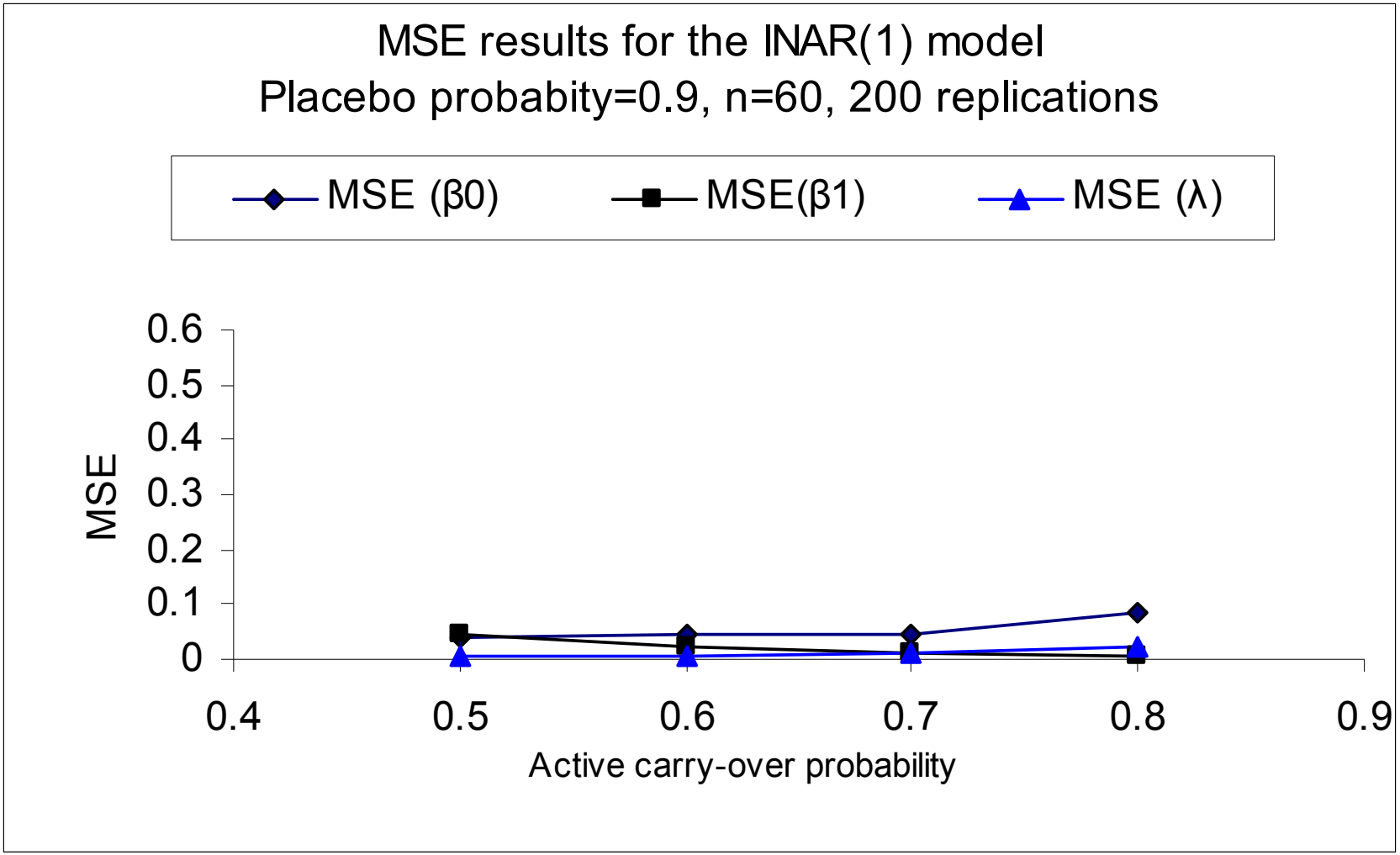
IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study



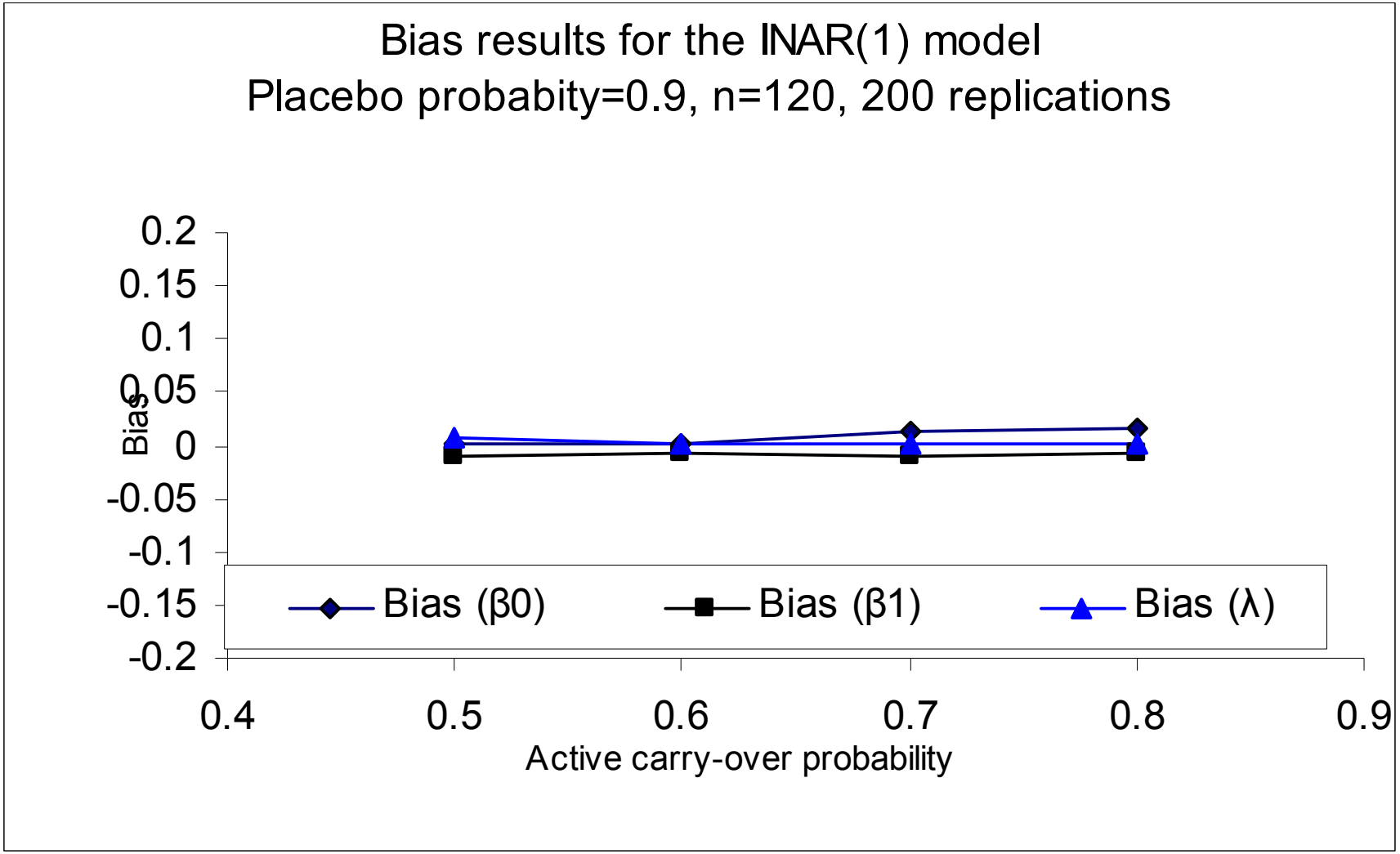
IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study



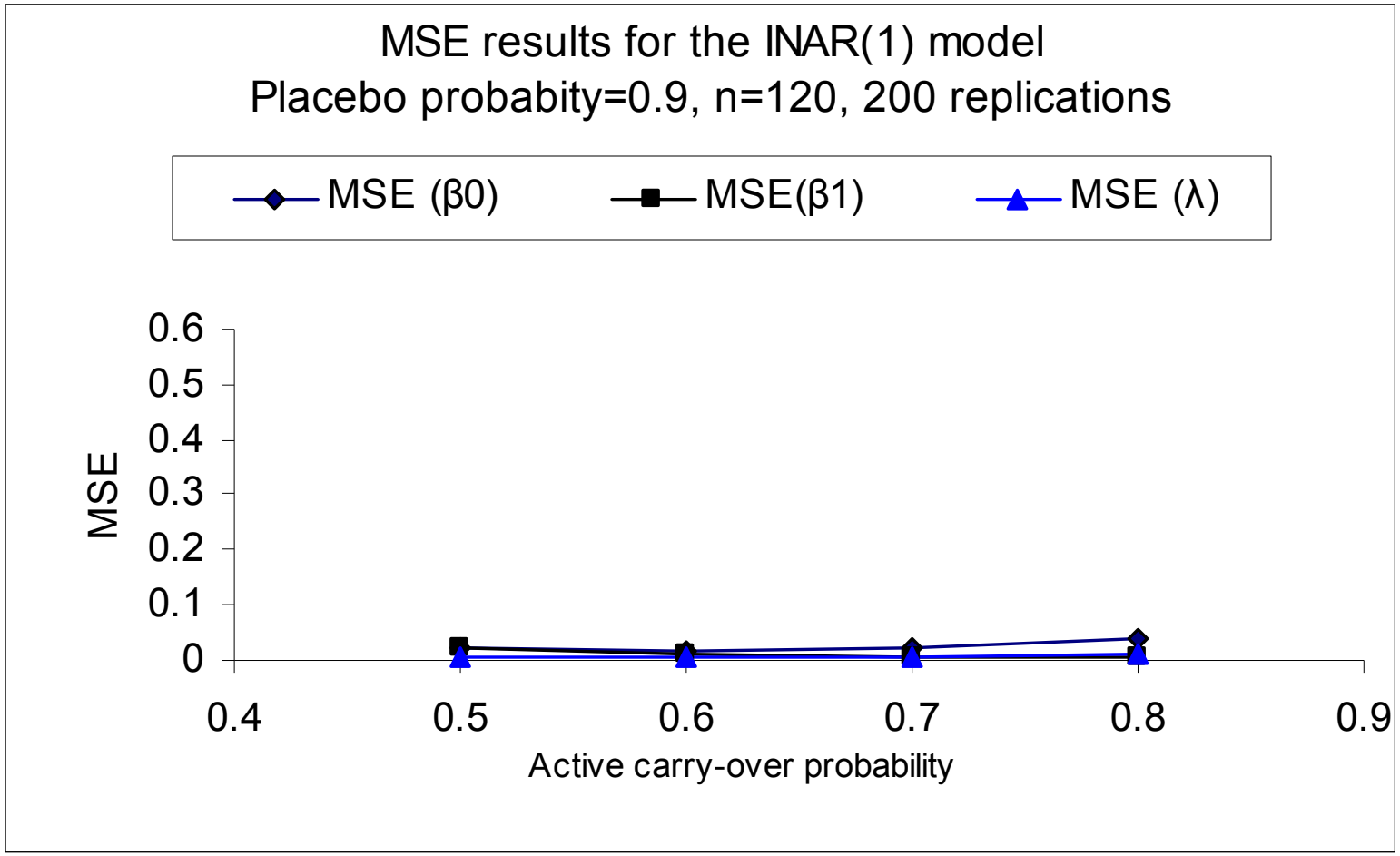
IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study



IV. Generalized Poisson INAR(1) model-cont.

a. Simulation study



IV. Generalized Poisson INAR(1) model

b. Application to the AK data

Table 6. Estimation results for models (6-a and 6-b)

Parameter	Model (a)			Model (b)		
	Estimate	SE	Pr >|t|	Estimate	SE	Pr > |t|
Intercept	2.054	0.489	< 0.001	28.076	10.634	0.009
Time	- 0.024	0.253	0.346	- 0.275	0.119	0.024
Trt	- 0.088	0.022	< 0.001	- 1.180	0.540	0.033
Error (λ)	0.740	0.329	0.026	0.190	0.093	0.047
g11= var b_{0i}				117.43	97.671	

IV. Generalized Poisson INAR(1) model

b. Application to the AK data

Comments:

- The utility of the INAR (1) is to test whether ‘α’ ‘the survival probabilities’ are related to treatment and/or time. Here both treatment and time are significant.

- The parameters of the two models (a and b) are of different magnitude and they have different interpretation (population average under (a) vs. subject specific under (b)). The magnitude of difference between the two sets of estimates is related to the variance of the random effect, which is in this case large.

V. Overall Comments:

We considered several models for fitting Poisson data with dropouts.
Which model to choose?

Selection of the appropriate model depends on the scientific question asked.

Is the interest in testing efficacy in the overall population or in a subject drawn at random from the population?

(marginal mean models vs subject specific (random effects) models)

Is the interest in investigating a new therapy on response profile or mechanism or transition between states of possible values of the response?

(marginal vs transition model)

V. Overall Comments-cont.

We considered a generalization of the Poisson INAR(1) to fit the clinical trial setting. The question of interest is whether treatment impacts the 'survival probability' of a lesion until the next time point.

- Technical points:

GEE vs WGEE depends on the dropouts mechanism (MCAR vs MAR)

Selection of reasonable starting values is critical in fitting NLMIXED models.

Selected references

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III. GLM for repeated measurements count data:

As the 2 trt. arms are similar up to week 8, we consider fitting the following model to allow for different changes before and after WK 8

$$\log(E(Y_{ij})) = \beta_0 + \beta_1\, time_{ij} + \beta_2\, (time_{ij} - 4)_+ + \beta_4\, (time_{ij} * trt_i) + \beta_5\, trt * (t_{ij} - 4)_+ \quad (2)$$

Table 2. Estimation results for model (2)

Parameter	Estimate	SE(emp.)	Pr>Z
Intercept	1.770	0.028	<0.0001
$Time_{ij}$	-0.009	0.016	0.561
$(Time_{ij}-4)_+$	-0.0068-	0.018	0.707
Trt_i *$Time_{ij}$	0.0520	0.028	0.065
Trt_i*$(time_{ij}-4)_+$	-0.111	0.039	0.0024