Methods for analyzing repeated measures data subject to dropouts

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* Views expressed in this presentation are those of the author and do not necessarily reflect those of the FDA.

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I. Background: Longitudinal clinical data, missinginess and dropouts

Although studies are designed to collect data on each subject's measurements, different patterns of missinginess and dropouts are quite common. The alternatives for analyzing the data are:

a) Analyze only data for subjects who complete the trial (completers)
b) Analyze only the observed data
c) Use single or multiple imputations to replace the missing data, then analyze the 'completed' data set
d) Build a longitudinal model for the data which includes a model for the dropout.

I. Background: Longitudinal clinical data, missinginess and dropouts

- The underlying assumption for (a) and (b) is that missing data are **ignorable** (Rubin,76); (observed data constitute is a random sample of the observed and unobserved data).
- The underlying assumption for (c) is that a missing value is completely predictable, either from its past (LOCF) or from its 'neighbors' (multiple imputations).
- The last option (d) does not make such strong assumptions and also is the most useful, as it states the assumptions of the model and allows checking the sensitivity of the conclusions to the assumptions about the dependency between dropouts and the response. However, it is the most complex computationally.

  Here we consider option (d), as analysis findings under (a), (b) and (c) are expected to be biased due to their unrealistic and unverifiable assumptions.

I. Background: Longitudinal clinical data, missinginess and dropouts

Focus on:

- Non-ignorable dropouts.
- Count data: Unlike the multivariate normal, there is no unique multivariate distribution (allow for dependency and dropouts)
- Consider joint models for the multivariate outcomes and dropout indicators to correct for the bias. Models for dropouts are generally non identifiable
- The need to place (un-verifiable) assumptions about dropouts

II. Missing data mechanism and impact on modeling and estimation

Notations (standard, e.g. Little & Rubin**)**

$\mathbf{Y_i} = (Y_{i1,} Y_{i2,} ....., Y_{in_i})'$ denotes subject i (i=1,2,…N) measurements made at times $(i_1, i_2, ..., i_{n_i})$

Y_{ij} can be observed or missing.

Define a measurement indicator R_{ij} such that:

$R_{ij} = 1$ if Y_{ij} is observed and

= 0 if Y_{ij} is missing.

Corresponding to $\mathbf{Y}_i$ we have:

$\mathbf{R}_i = (R_{i1}, R_{i2} ....., R_{in_i})'$

The full data set can be represented as: $(\mathbf{Y}_i, \mathbf{R}_i)$

Here we assume missingness is due to dropouts and we could write:

$\mathbf{Y}_i = (\mathbf{Y}_i^o, \mathbf{Y}_i^m)$

II. Missing data mechanism and impact on modeling and estimation

For dropout define a dropout indicator: $D_i = 1 + \sum_{j=1}^{n_i} R_{ij}$

D_i measures the occasion in which the dropout occurs.

The joint model for the outcomes and dropouts indicators (Rubin 1976; Little and Rubin 2002) is:

$$f(\mathbf{y}_i, \mathbf{r}_i / \mathbf{X}_i, \mathbf{W}_i, \boldsymbol{\theta}, \boldsymbol{\Psi})$$

where $\mathbf{X}_i$ and $\mathbf{W}$ denote design matrices for the measurements and missingness, respectively; $\boldsymbol{\theta}$ and $\boldsymbol{\Psi}$ are the corresp. parameters.

The selection model factorization is based on:

$$f(\mathbf{y}_i, \mathbf{r}_i / \mathbf{X}_i, \mathbf{W}_i, \boldsymbol{\theta}, \boldsymbol{\Psi}) = f(\mathbf{y}_i / \mathbf{X}_i, \boldsymbol{\theta}) f(\mathbf{r}_i / \mathbf{y}_i, \mathbf{W}_i, \boldsymbol{\Psi})$$

That is, use a complete data model for the longitudinal outcomes and then model the probability of dropout conditional on the possibly unobserved outcomes, (frequently, computationally intractable).

II. Missing data mechanism and impact on modeling and estimation

The pattern mixture model (Little 93, & 94) is based on factorization:

$$f(\mathbf{y}_i, \mathbf{r}_i / \mathbf{X}_i, \mathbf{W}_i, \boldsymbol{\theta}, \boldsymbol{\Psi}) = f(\mathbf{y}_i / \mathbf{r}_i, \mathbf{X}_i, \boldsymbol{\theta}) f(\mathbf{r}_i / \mathbf{W}_i, \boldsymbol{\Psi})$$

which allows for different response model for each pattern of missing values.

The shared parameter models (Wu and Carroll, 88 and Wu and Bailey, 88 and 89)) is based on the factorization :

$$f(\mathbf{y}_i, \mathbf{r}_i / \mathbf{X}_i, \mathbf{W}_i, \boldsymbol{\theta}, \boldsymbol{\Psi}, \mathbf{b_i}) = f(\mathbf{y}_i, \mathbf{X}_i, \boldsymbol{\theta}, \mathbf{b_i}) f(\mathbf{r}_i / \mathbf{y}_i, \mathbf{W}_i, \boldsymbol{\Psi}, \mathbf{b_i})$$

Includes a vector of unit-specific latent (random) effects $\mathbf{b_i}$ which is shared between both factors in the joint distribution. $\mathbf{b_i}$ is a latent trait driving both the measurement and missingness processes. It is sensible to assume the two processes are conditionally independent given $\mathbf{b_i}$.

II. Missing data mechanism and impact on modeling and estimation

(Rubin 1976; Little and Rubin 2002): Consider the selection model framework:

$$f(\mathbf{y}_i, \mathbf{r}_i / \mathbf{X}_i, \mathbf{W}_i, \boldsymbol{\theta}, \boldsymbol{\Psi}) = f(\mathbf{y}_i / \mathbf{X}_i, \boldsymbol{\theta}) f(\mathbf{r}_i / \mathbf{y}_i, \mathbf{W}_i, \boldsymbol{\Psi})$$

MCAR if the prob. of missing is independent of the response

$$f(\mathbf{r}_i / \mathbf{y}_i, \mathbf{W}_i, \boldsymbol{\Psi}) = f(\mathbf{r}_i / \mathbf{W}_i, \boldsymbol{\Psi})$$

Thus the joint dist. can be simplified to:

$$f(\mathbf{y}_i, \mathbf{r}_i / \mathbf{X}_i, \mathbf{W}_i, \boldsymbol{\theta}, \boldsymbol{\Psi}) = f(\mathbf{y}_{i,} / \mathbf{X}_i, \boldsymbol{\theta}) f(\mathbf{r}_i / \mathbf{W}_i, \boldsymbol{\Psi})$$

MAR if the prob. of missing is independent of unobserved response:

$$f(\mathbf{r}_i / \mathbf{y}_i, \mathbf{W}_i, \boldsymbol{\Psi}) = f(\mathbf{r}_i / \mathbf{y}_i^o, \mathbf{W}_i, \boldsymbol{\Psi})$$

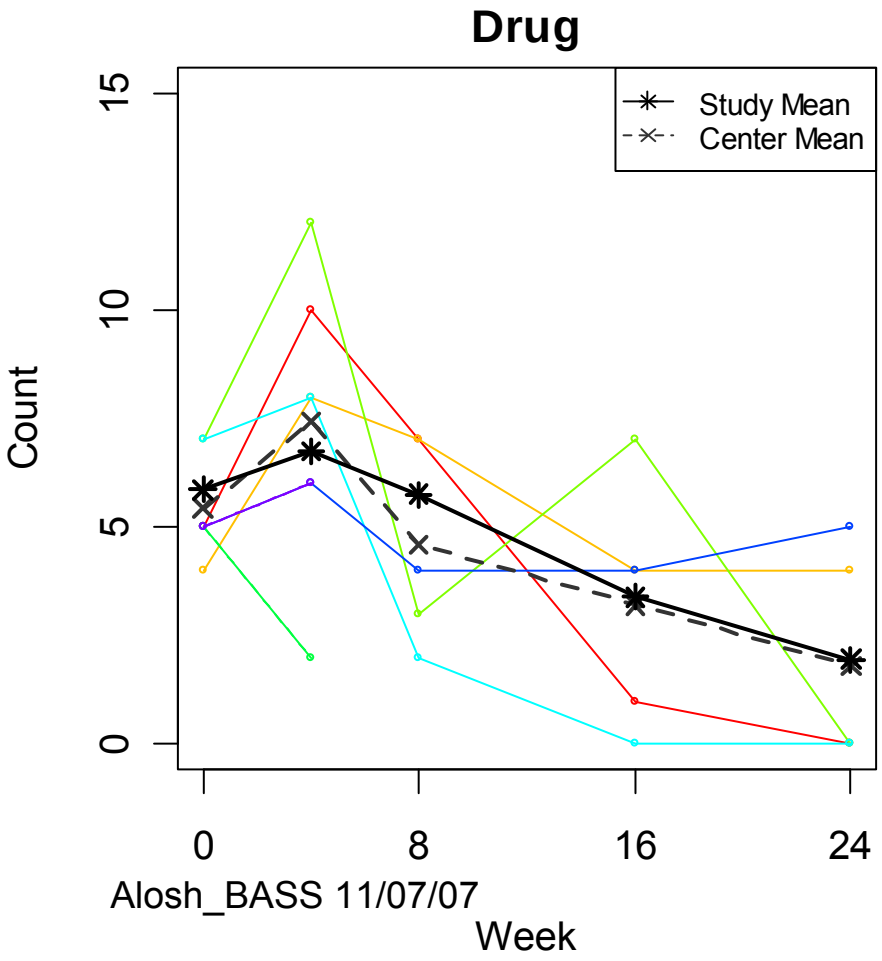
MNAR, neither MCAR nor MAR holds (no simplification for the joint dist. is possible)

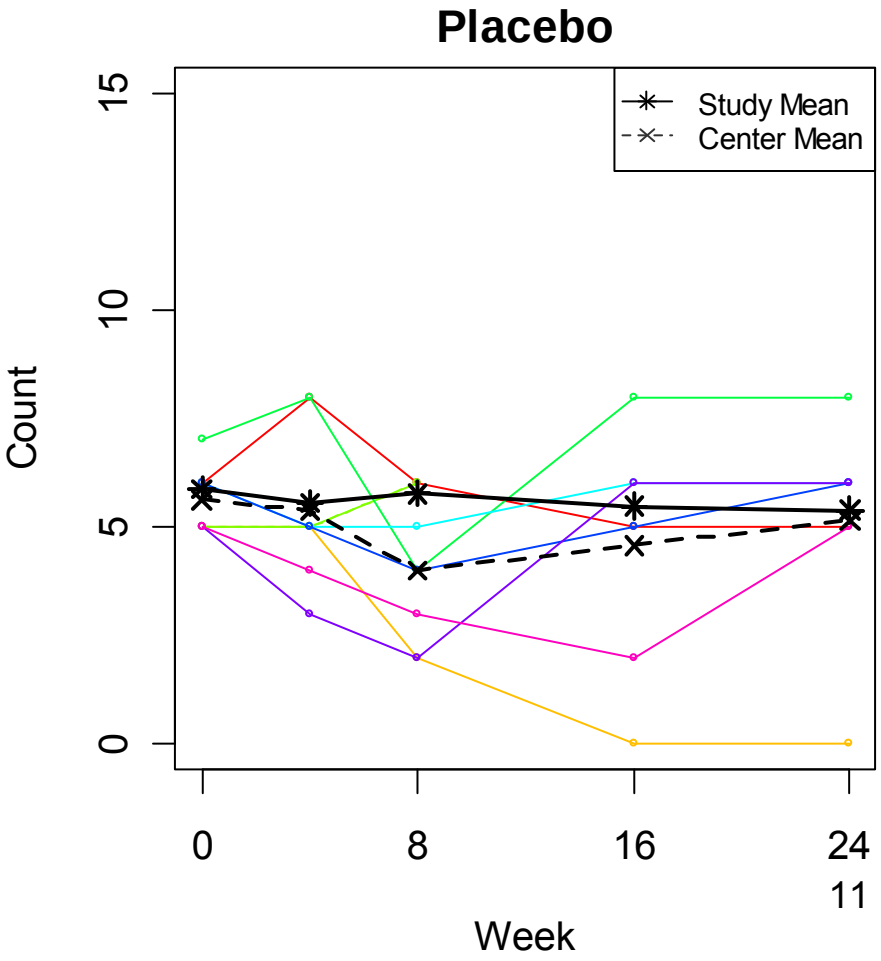
III. A motivating example (actinic keratosis count data)

Data (masked) for a multi-center, placebo controlled, clinical trial for treatment of actinic keratosis (AK) lesions on the face and balding scalp. Treatment is for 16 weeks with efficacy evaluation at week 24. Visits at weeks: 0, 4, 8, 16 and 24. To qualify for enrollment a subject should have 4-8 AK lesions. The objective of the trial is to establish efficacy for the test drug.

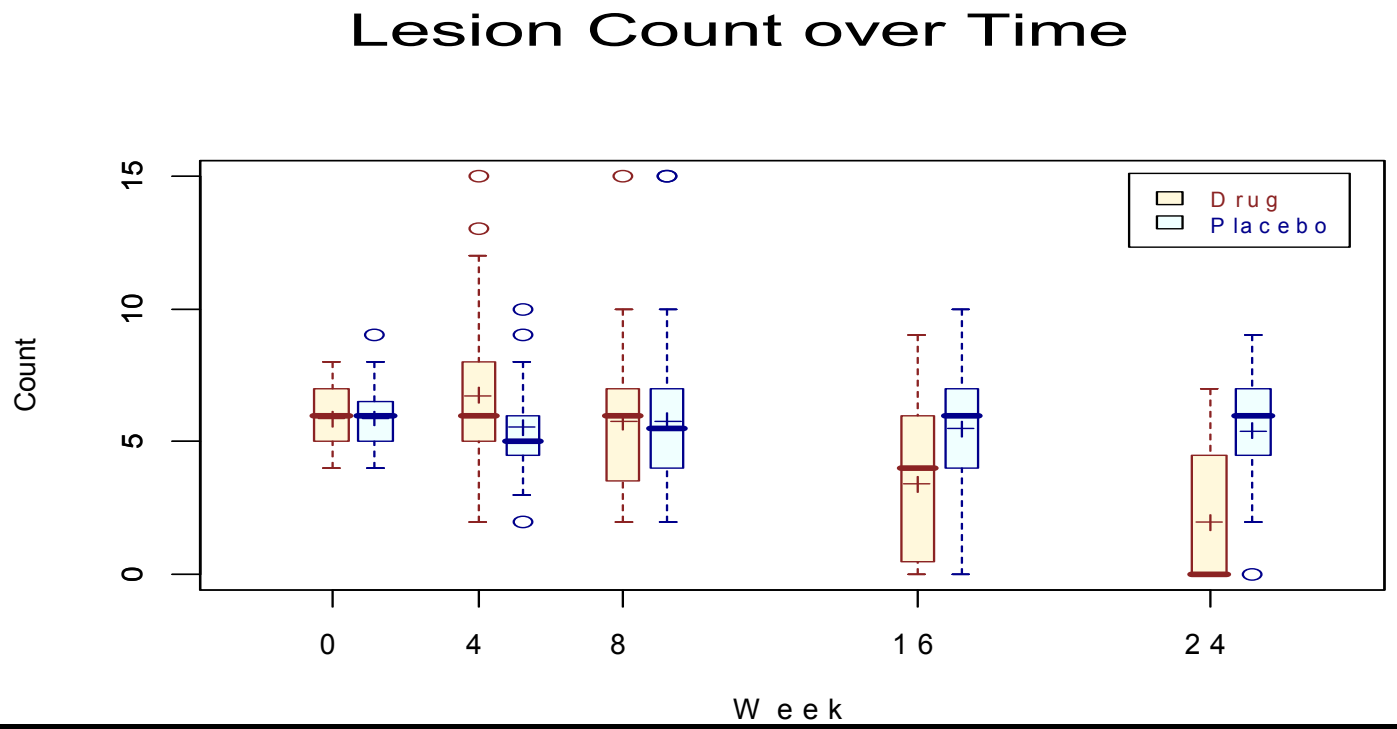
III. A motivating example (actinic keratosis count data)

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





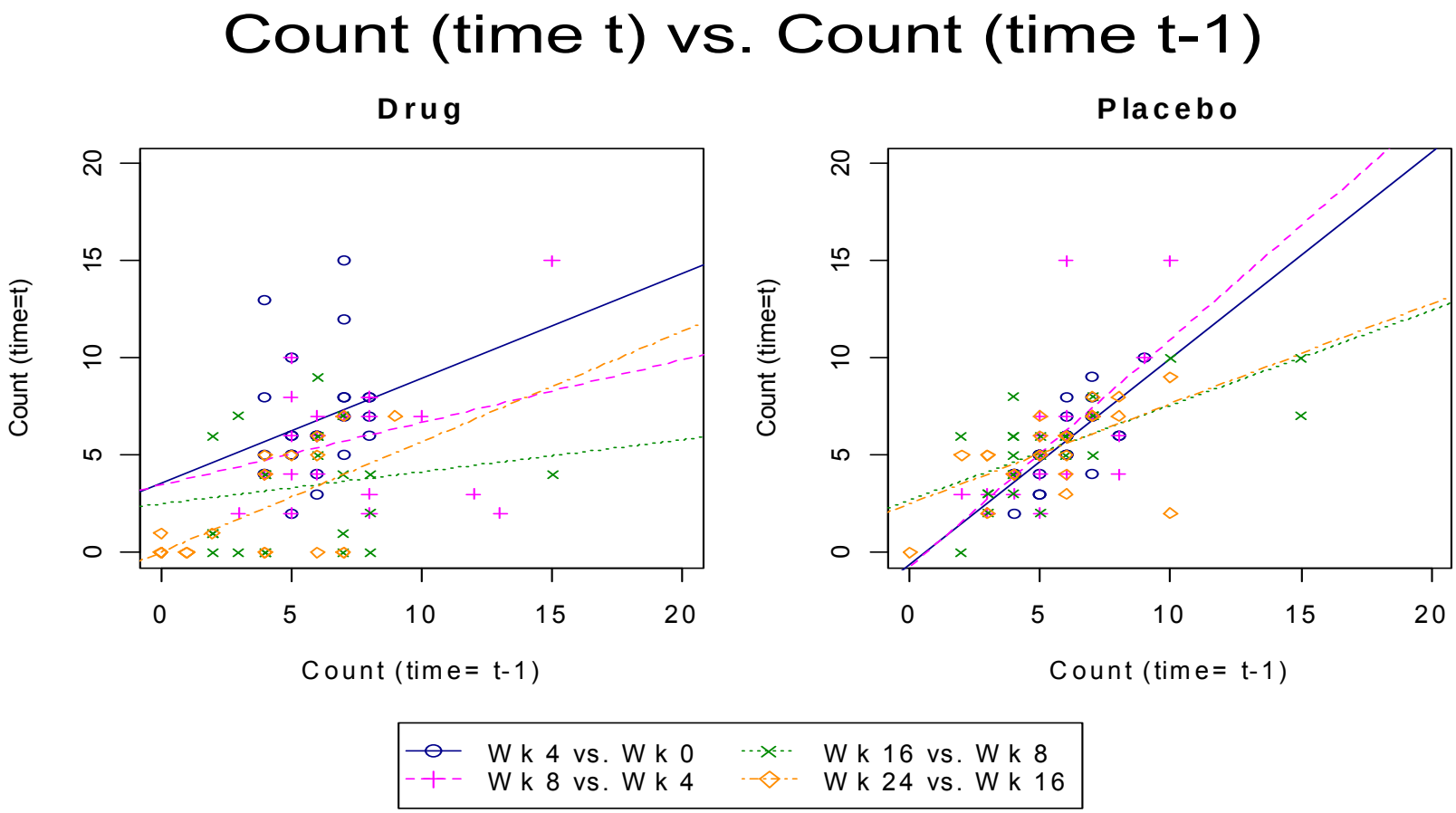
III. A motivating example (actinic keratosis count data)



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)

III. A motivating example (actinic keratosis count data)

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



III. A motivating example (actinic keratosis count data)

Comments:

- 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).
- Impact of subject's AK counts on subsequent time counts (varies by trt 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 models as well as brief discussion of new methodologies.

III. A motivating example (actinic keratosis count data)

Dropouts pattern by trt 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

Is dropout related to time (visit)?
Is dropout related to treatment?
Is dropout related to previous AK counts?
What is the impact of the above questions on the modeling approach?

IV. Marginal Models for Repeated Measurements (MMRM):

a. GEE approach:

Assume AK count data follow Poisson distribution. Then, as Poisson is a member of the exponential family,

$\Rightarrow$ Generalized Linear Model (GLM). The GLM is based on:

$$g(\mu) = \mathbf{X}\boldsymbol{\beta} = \eta; \qquad \mu = h(\eta)$$

$V_i = \phi V(\mu)$ Where ϕ is a dispersion parameter (may be known)

$\Rightarrow$ Use the Generalized Estimating Equation (GEE) of Liang and Zeger (1986) to get estimates for the model parameters: The GEE is based on solving the equation:

$$S(\boldsymbol{\theta}) = \sum_{i=1}^{N} \frac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\theta}'} \; (\phi \, \mathbf{A}_i^{1/2} \, \mathbf{R}_i \, \mathbf{A}_i^{1/2})^{-1} \, (\mathbf{y}_i - \boldsymbol{\mu}_i) = 0$$

where: $Var(\mathbf{y}_i) = \mathbf{V}_i = \phi \, \mathbf{A}_i^{1/2} \, \mathbf{R}_i \, \mathbf{A}_i^{1/2}$

IV. Marginal Models for Repeated Measurements (MMRM):

We consider fitting the following linear model using Proc GENMOD:

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

The results of fitting the final model (exch. correlation structure) are given by:

Table 1. Estimation results for model (1)

Parameter	Estimate	SE(emp.)	Z	Pr > Z
Intercept	1.757	0.056	30.97	< 0.001
Trt	0.186	0.087	2.15	0.032
Time	- 0.003	0.003	- 1.20	0.231
Time*trt	- 0.042	0.011	- 4. 03	< 0.001

IV. Marginal Models for Repeated Measurements (MMRM):

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 week 8.

$$\log(E(Y_{ij})) = \beta_0 + \beta_1\, time_{ij} + \beta_2\, (time_{ij} - 8)_+ + \beta_4\, (time_{ij} * trt_i) + \beta_5\, trt * (t_{ij} - 8)_+ \quad (2)$$

The results of fitting this model are given in Table (2):
Table 2. Estimation results for model (2)

Parameter	Estimate	SE(emp.)	Z	Final model Est. (SE)
Intercept	1.755	0.035	49.96	1.744 (0.058)
Trt	0.063	0.058	1.09	0.062 (0.080)
Time	-0.003	0.009	- 0.31	
$(\text{Time-8})_+$	-0.001	0.014	- 0.06	-0.005 (0.005)
Time*trt	-0.001	0.015	- 0.04	
Trt*(time-8)_+	-0.068	0.029	- 2.32	-0.069 (0.019)

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

- The GEE methodology is valid under the assumption that the missing data is MCAR. Estimation results are expected to be biased if the MCAR assumption is violated.
- 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.

- The WGEE is based on solving the following:

$$S(\boldsymbol{\theta}) = \sum_{i=1}^{N} \frac{1}{\nu_i} \frac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\theta}'} \; (\phi \, \mathbf{A}_i^{1/2} \; \mathbf{R}_i \; \mathbf{A}_i^{1/2})^{-1} \, (\mathbf{y}_i - \boldsymbol{\mu}_i) = 0$$

where: $\mathbf{v}_i = (v_{ij})'$ with: $v_{ij} = p_r(D_i = j)$

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

- The propensities for dropouts can be estimated as a function of observed responses prior to dropout and other covariates that are likely to predict dropout, say, treatment.

  Molenberghs and Verbeke (2005) presented “DROPOUT’ and ‘DROPWGT” macros to construct the variable ‘dropout’ and ‘previous measurements’ and to pass the weights (predicted probabilities) to be used for WGEE.

  For the AK data we consider the following model:

$$\text{logit}\, P(D_i = j / D_i \geq j) = \psi_0 + \psi_1 y_{i.j-1} + \psi_2 trt \qquad (3)$$

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

The results of fitting model (3) for dropouts is given in following table.

Table 3. 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
Trt	1.030	0.705	0.144	1.504	0.474	0.0015
Previous	- 0.058	0.129	0.652			

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

It should be noted that mean AK counts for the completers vs those of dropouts, by treatment and visit, are given in the following

Table 4. 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)

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

- 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 of dropping out.

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

IV. Marginal Models Repeated Measurements (MMRM):
b. WGEE-Modeling Dropouts

- As ‘previous’ counts are not predictive of dropouts
- $\rightarrow$ (strictly speaking) we have MCAR
- $\rightarrow$ Complete Case Analysis ???

- **Here as dropouts are mainly due to irritation**
- Do we need to expand the MCAR def. for drug development to capture other covariates, such as drug, in addition to the ‘previous’ counts?
- If so, what is ‘ an appropriate’ approach for handling dropout in this case ?
- Expanding the MCAR definition, use WGEE to assign weights for completers to compensate for dropouts

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

Following calculation of the weights for the observed data for the WGEE, the results of the final fitted linear model (1) along model (3) for dropouts are given by:

Table 4. Estimation results for the WGEE (model (1) and model (3)) compared with those of the GEE

Parameter	WGEE			GEE
	Estimate	SE (emp.)	Z	Est. (SE)
Intercept	1.686	0.025	67.94	1.757 (0.056)
Treatment	0.204	0.076	2.69	0.186 (0.087)
Time	-0.008	0.008	- 1.01	-0.003 (0.003)
Time*treat.	-0.035	0.014	- 2.51	-0.042 (0.011)

IV. Marginal Models Repeated Measurements (MMRM): b. WGEE-Modeling Dropouts

Table 5. Estimation results for the WGEE (model (2) and model (3)) compared with those of the GEE

Parameter	WGEE			GEE
	Est. (SE)	Est. (SE)	Z	Est. (SE)
Intercept	1.654 (0.03)	1.656 (0.03)	48.74	1.743 (0.058)
Trt	0.059 (0.08)	0.104 (0.07)	1.57	0.062 (0.080)
Time	0.001 (0.01)			
$(Time-8)_+$	- 0.014 (0.01)	- 0.013 (0.01)	-1.11	-0.005 (0.005)
Time*trt	0.012 (0.02)			
$Trt*(time-8)_+$	- 0.075 (0.04)	- 0.059 (0.02)	-2.60	-0.069 (0.019)

IV. Marginal Models Repeated Measurements (MMRM):
b. WGEE-Modeling Dropouts

Comments:

- Although the SE for WGEE estimates are, in general, smaller than their analogues of the GEE, 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 failures, using LOCF or other imputation methods ?**

V. Generalized Linear Mixed Models (GLMM)
Random Effect Model

The ‘marginal model’ might not be adequate to account for the correlation between repeated measurements, as it ignores within group (subject) correlation.

- We consider GLMM which extends the GLM model by allowing the coefficient to vary within group, allowing for within–group correlations
- GLMM is a compromise between the population–average model (GLM) and group-specific model (over parameterized).
- GLMM can be regarded as an extension for LME model to allow flexible class of distribution for response and natural scale for expected values (link function)

V. Generalized Linear Mixed Models (GLMM)
Random Effect Model

GLMM definition:

- $\mathbf{Y}_i, \mathbf{X}_i$ and $\mathbf{Z}_i$ represent response vector, fixed and random effect design matrices corresponding to group i
- $\mathbf{Y}_i / \mathbf{b}_i$ are assumed to be independently distributed according to some exponential family distribution with $\mathbf{b}_i$ representing random effects for group i.
- $\mathbf{b}_i \sim N(\mathbf{0}, \boldsymbol{\psi})$
- $E(\mathbf{Y}_i / \mathbf{b}_i) = \boldsymbol{\mu}_i^{\mathbf{b}} = g(\mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{b}_i)$ for link function g and fixed effect $\boldsymbol{\beta}$
- Var $(\mathbf{y}_i / \mathbf{b}_i) = \phi V(\boldsymbol{\mu}_i^b)$ for variance function V and dispersion parameter ϕ

- $\mathbf{b}_i$ remains fixed for observations made on group i,: within group correlation.

V. Generalized Linear Mixed Models (GLMM)
Random Effect Model

We generalize model (1) by adding random effect (b_{0i}) to allow random intercept for each subject, one might consider subjects to have their own slopes as well. Specifically we consider the model:

$$\log(E(Y_{ij} / b_{0i})) = \beta_0 + b_{0i} + \beta_1\, time_{ij} + \beta_2\, trt_i + \beta_3\, (time_{ij} * trt_i) \quad (4)$$

where $b_{0i} \sim N(0,\sigma^2)$. Table (6) presents the results of fitting model (4).

Table 6. Estimation results for GLMM (model (4)

Parameter	Estimate	SE	t	Pr >|t|
Intercept	1.744	0.066	26.52	<0.001
Treatment	0.187	0.094	1.98	0.049
Time	-0.003	0.004	-0.83	0.409
Time*treat.	-0.042	0.007	-6.15	<0.001
g11=var(b_{0i})	0.047	0.016		

VI. Transition models:

a. Autoregressive-type model:

Consider modeling the mean response as a function of previous counts in addition to other covariates (Zeger (1988) and Zeger and Karim 1988). For the AK counts we consider fitting the following model:

$$\log(E(Y_{ij})) = \beta_0 + \beta_1 Y_{i(j-1)} + \beta_2\ trt_i + \beta_3\ (Y_{i(j-1)} * trt_i) \quad (5)$$

It should be noted that such models do not have an explicit lag structure in the endogenous count variable.

The results of fitting this model using GLIMMIX, with random residual statement are given in Table(7) (interaction was not sig. with p-value= 0.844):

Table 7. Estimation results for model (5)

Parameter	Estimate	SE	t	Pr > |t|
Intercept	1.101	0.090	12.26	< 0.001
Trt	- 0.195	0.071	- 2.73	0.007
$Y_{i(j-1)}$	0.103	0.012	8.29	< 0.001

VI. Transition model
b. Generalized Poisson INAR(1) model

The INAR (1)-Poisson model:

The model is defined by (Al-Osh and Alzaid,1987 and McKenzie,1988):

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

- '$\alpha \, o \, Y_{t-1}$' is the 'survival' or 'carry out' component and
- 'E_t' is an innovation component.

When the two components are independent $\Rightarrow$ stationary Markovian process with Poisson marginal distribution. The INAR(1) is a special case of the Galton-Watson process with immigration.

In modeling the AK context: the AK counts at time t consists of 2 components: (i) # AK lesions 'carried out' or 'survived' from those present at time (t-1), where each lesion has a probability of survival 'α'; and (ii) new lesions developed during the time interval (t-1, t].

VI. Transition model
b. Generalized Poisson INAR(1) model

- The Poisson INAR(1) is parsimonious with interpretational appeals. However, for application it has the Poisson constraints (mean = variance). Several extensions have been proposed (e.g. Jung and Tremayne, 2006, Brannas and Hellstrom 2001, among others) to expand the model's utility.
- A major drawback when modeling the AK counts is the underlying assumption that individual lesions act independently in their 'survival' for next time (t+1].
- We consider an extension of the model to allow (α) 'the probability of survival' to depend on some covariates including treatment. Such an extension would address some of points raised for the AK data, specifically:

  (a) As (α) is the AR parameter $\Rightarrow$ diff. corr for the active and placebo.

  (b) By introducing depend. among the α's $\Rightarrow$ increase in the variance.

- However, such an extension would be at the expense of the simplicity of the model and its marginal distribution structure. Thus, previous extensions of the INAR(1) belong to the class non-Gaussian conditional AR(1) model (Grunwald, et al. 2000).

VI. Transition model
b. Generalized Poisson INAR(1) model

We consider fitting the following conditional INAR(1) model:

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

With: $$\log it(\alpha\,(X_{ij})) = \beta_0 + \beta_1\,time_{ij} + \beta_2\,trt_i + \beta_3\,(time_{ij} * trt_i) \qquad (a)$$

Also, we consider extending model (a) by adding random intercept to allow for variability across subjects. Thus we consider:

$$\log it(\alpha\,(X_{ij})) = \beta_0 + b_{1\,i} + \beta_1\,time_{ij} + \beta_2\,trt_i + \beta_3\,(time_{ij} * trt_i) \qquad (b)$$

The results of fitting this model using Proc NLMIXED are given in the following table:

VI. Transition model

b. Generalized Poisson INAR(1) model

Table 8. 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= varb_{0i}				117.43	97.671	

VI. Transition model
b. Generalized Poisson INAR(1) model

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.

VII. 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)

- We considered a new 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.

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