Pharmacotherapy smoking cessation trials: Exploring the relationship between adverse events, compliance, dropout, and abstinence

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Outline

- Introduction
- Graphical methods
- Some survival modeling
- Discussion

Motivating study

- Randomized dose-ranging smoking cessation study of naltrexone with nicotine patch, for participants motivated to quit smoking.

- Participants needed to be $\geq$ 18 years old, not pregnant, reported to have smoked at least one pack per day over the past year, had tried at least one quit attempt previously, and had a confirmed elevated expired CO reading ($>$ 10 ppm).

- 385 partipicants, on day after quit day, started one of four randomized doses of naltrexone (0, 25, 50, or 100 mg); all received patch on quit day. They stayed on medication for a period of six weeks.

Motivating study (cont.)

- Failure, for this analysis, is based solely on CO readings, during treatment period. If CO $>$ 10 ppm, at any time point over the six week treatment period, participant was assumed to have failed the first week that occurred. *Dropout is also assumed to be a smoking relapse (failure)*. Results in discrete (grouped) survival data.

- Aside from treatment group and CO readings over time, observations were available for a number of other measures: time-independent (e.g., gender, age, ethnicity, marital status) and time-dependent (e.g., adverse events, compliance, weight (bmi)). Note that adverse events considered today will be of moderate and severe categories only.

- Goals today will be to look at exploratory graphs of complex data as well as fit some discrete survival models.

Fig. 1: Event chart of AEs for early dropouts

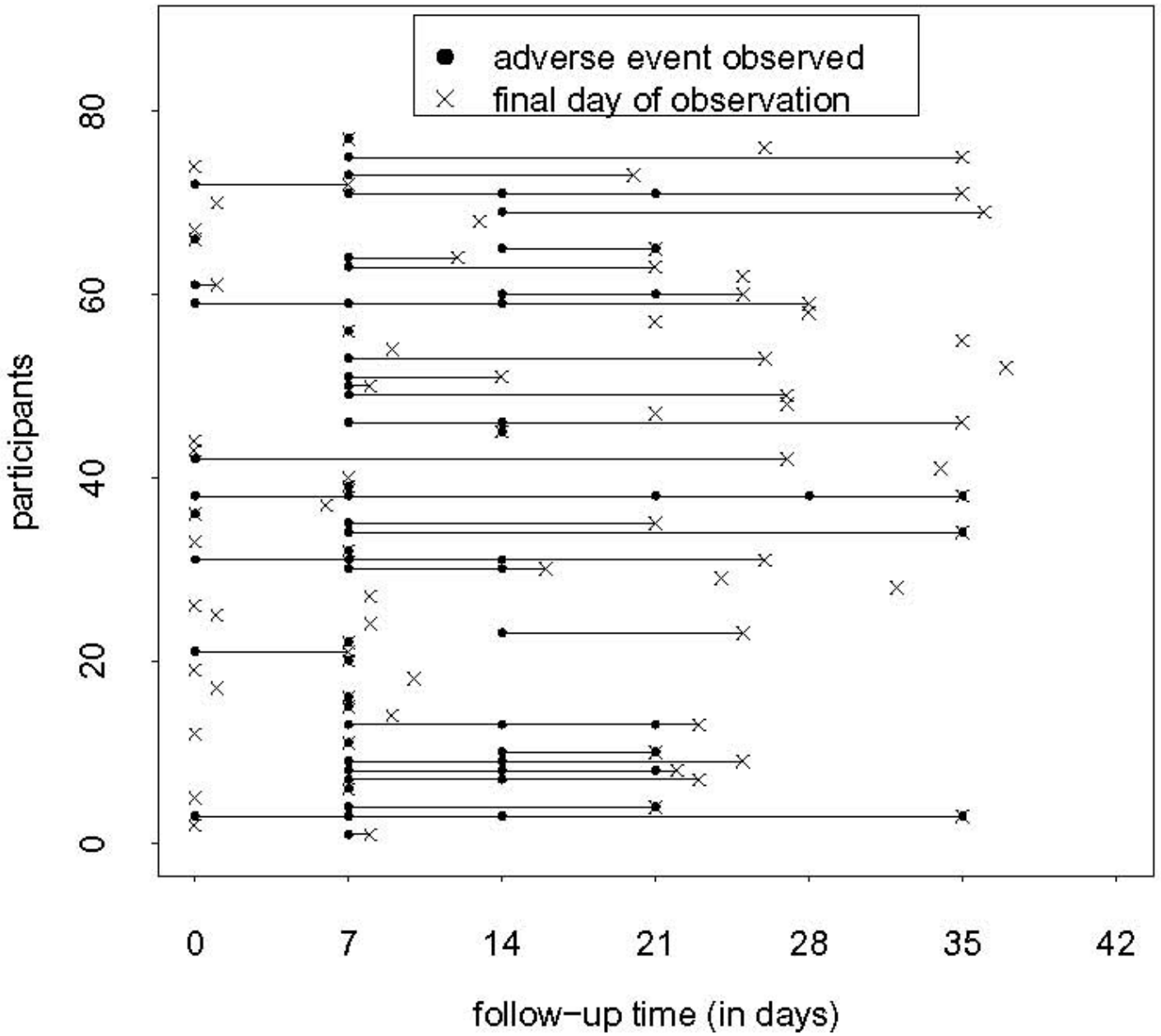


Fig. 2: Event chart of AEs for early dropouts, sorted

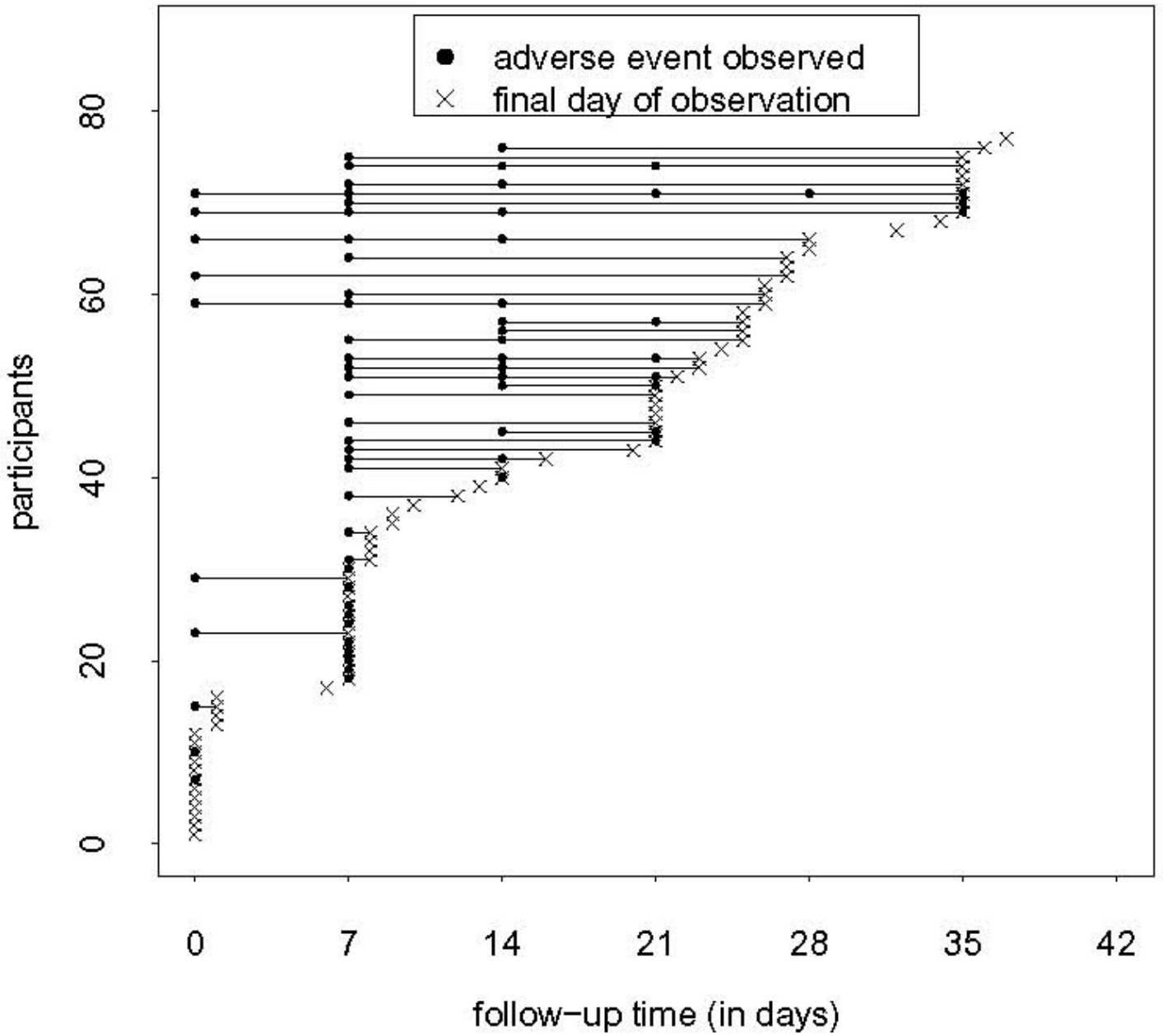


Fig. 3: Event chart of AEs (w/ burden) for EDs, sorted

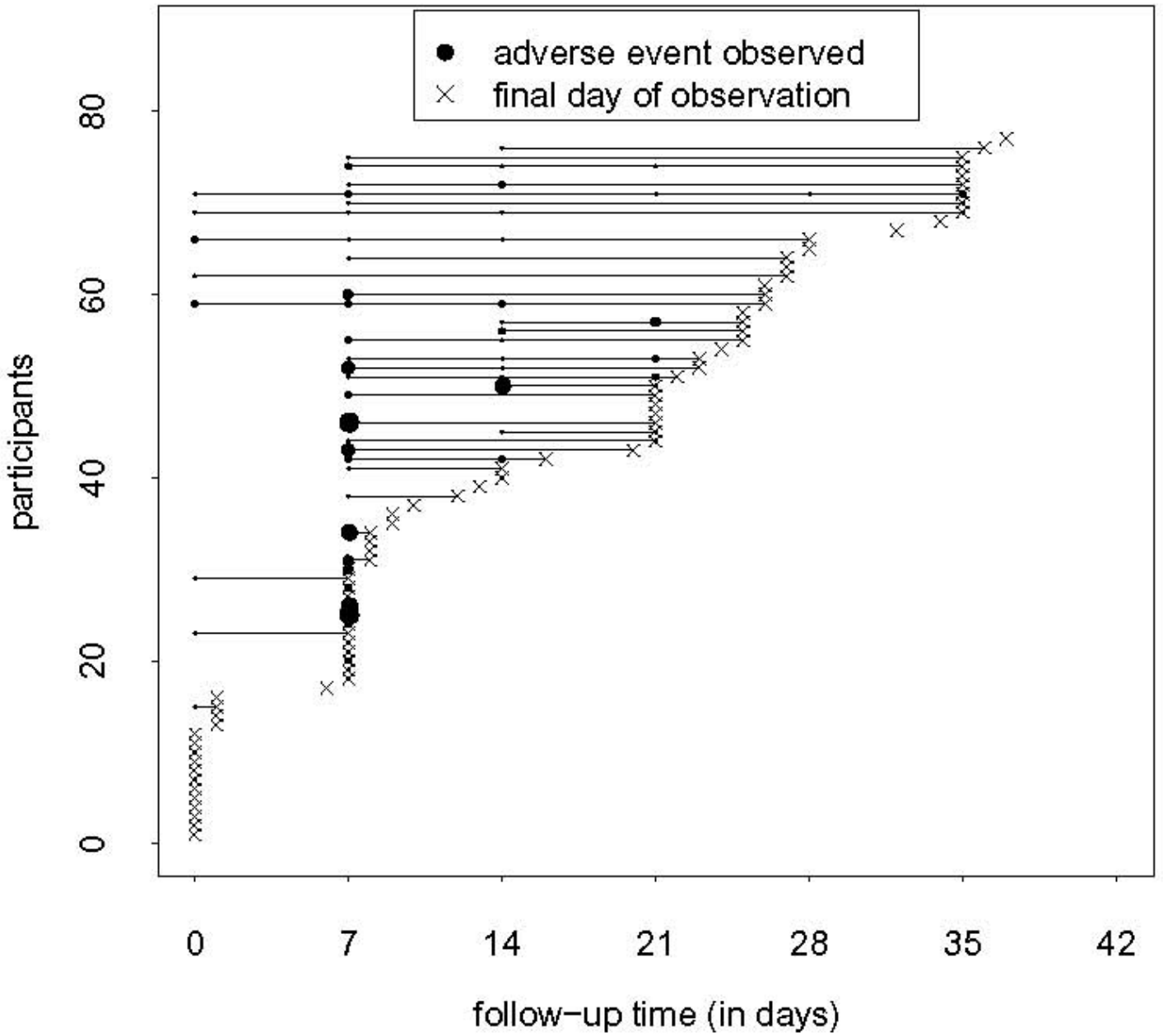


Fig. 4: Event chart of AEs for EDs, sorted by gender, date

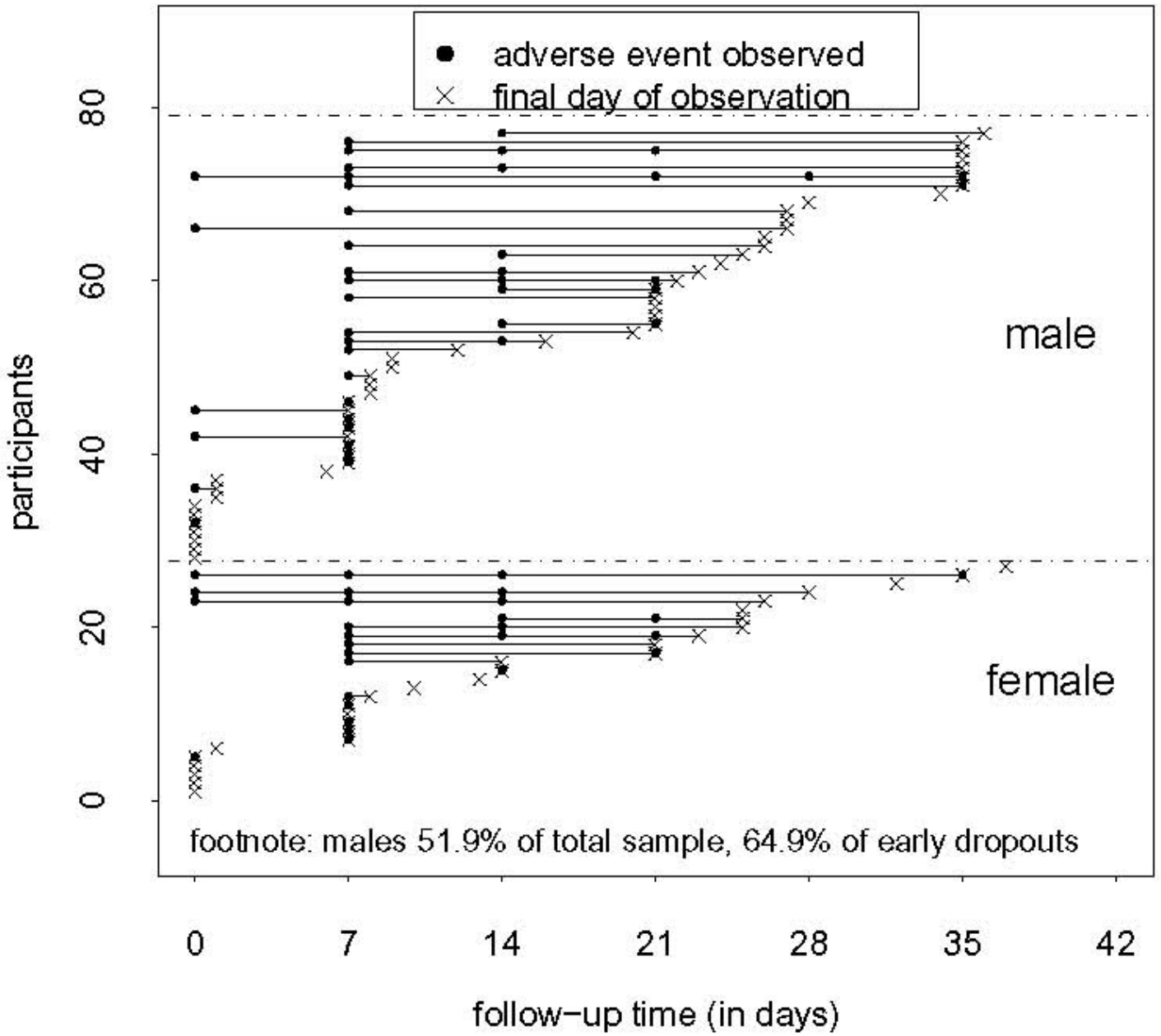
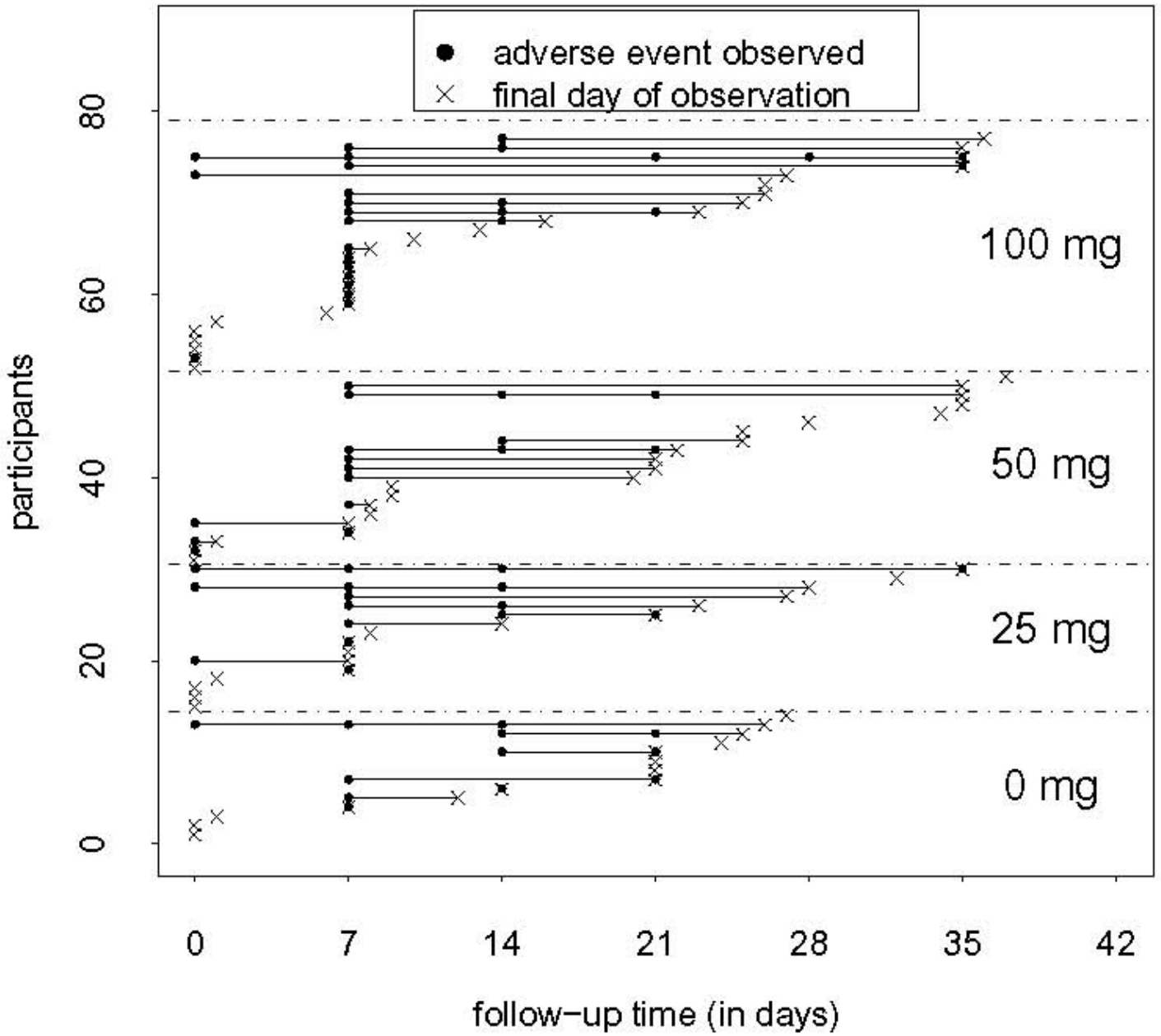


Fig. 5: Event chart of AEs for EDs, sorted by group, date



Initial survival analysis plan

- Consider behavior of hazard (of weekly smoking based on CO $>$ 10 ppm) over time.
- Consider time-independent predictors (gender, ethnicity, etc.).
- Consider lagged time-dependent predictors (compliance, adverse events).
- Fit data using discrete hazard models (using logit link); this approach combines features of logistic regression and traditional survival modeling.

Appearance of hazard over six weeks of follow-up

week	# events	risk set	estimated hazard	estimated odds
1	38	385	.0987	.1095
2	28	347	.0807	.0878
3	19	319	.0596	.0633
4	18	300	.06	.0638
5	14	282	.05	.0522
6	15	268	.056	.0593

- linearly decreasing hazard to start, then fairly constant from week 3 forward
- changepoint might be best approach to take; for simplicity, left linear time term in fitted models

Fitted model on time-independent variables

predictors	adjusted coeff	SE	z-ratio
intercept	-1.190	0.395	-3.014
time	-0.136	0.055	-2.471
gender (M vs. F)	0.427	0.188	2.268
married (Y vs. N)	-0.389	0.189	-2.058
age	-0.026	0.008	-3.107

- treatment group is non-significant (and not listed in table above)
- adjusted odds of smoking decrease by 14% each week
- adjusted odds of smoking increase by 53% for M vs. F
- adjusted odds of smoking decrease by 47.5% for married vs. unmarried
- adjusted odds of smoking decrease by 2.6% for every 1-year age increase.

Fitted model on lagged time-dependent variables

predictors	adjusted coeff	SE	z-ratio
intercept	-1.728	0.588	-2.938
number.AEs.lag	0.245	0.090	2.740
pct.pills.taken.lag	-0.013	0.006	-2.164
gender (M vs. F)	0.481	0.233	2.063
married (Y vs. N)	-0.438	0.230	-1.903

- lower power, as we are losing the entire first week of events
- underlying hazard is now assumed constant over time (could improve this), and age is no longer significant

Fitted model on lagged time-dependent variables (cont.)

- in every week, for every one count increase in number of AE's in previous week, there is a 27.8% increase in current week adjusted odds of smoking
- in every week, for a 1% increase in number of pills taken in previous week, there is a 1.3% decrease in current week adjusted odds of smoking; that is, for a 20% increase in number of pills taken in previous week, there is over a 26% decrease in current week adjusted odds of smoking
- adjusted odds of smoking increase by 61.8% for M vs. F
- adjusted odds of smoking decrease by 54.9% for married vs. unmarried

What have we seen

- event charts can be an effective way to display complex data from smoking cessation trials
- discrete hazard models proved useful for the naltrexone study
- important lagged relationships appear to exist between both compliance and adverse event experience with smoking relapse

Future work

- inclusion of additional time-dependent information in event charts
- misclassification of response?
- accounting for adverse events (including possible weighting)
- inclusion of additional predictors in models (baseline smoking, prior quit attempts, craving, withdrawal, depression, weight, etc.)
- further refinement of models (diagnostics, time variable, unobserved heterogeneity, etc.)
- comparing results for failures due to dropout vs. failures due to observed elevated CO (Borelli, Hogan et al., 2002)
- recurrent events (smoking and AE's)
- multi-state modeling (challenge: state space definition)
- effectiveness of treatment for compliers and completers

A few relevant references

- naltrexone study:
  O'Malley et al. (Archives of Internal Medicine, 2006)

- event charts:
  Lee, Hess, Dubin (American Statistician, 2000)

- is it inappropriate to assign smoking relapse for a dropout the same way as for observed evidence of smoking:
  Borelli, Hogan, et al. (Psychology of Addictive Behaviors, 2002)