Handling of Discontinuation of Treatment in non-ignorable Situations

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Abstract

Background

Clinical studies mostly generate incomplete data. The fraction of non-available data can range from small to substantial, and the reasons can be manifold:

The data was not recorded, the data was lost on its way to the clinical database, or patients discontinued treatment and were lost to follow-up.

In all those cases there is no problem in analyzing the complete data only if the missingness is completely random.

However, if partial or missing data is dependent on other variables, that process must be modeled in order to correct for the bias that would otherwise result.

In such cases, complete case analyses ("per protocol") are inadequate, and so are imputation methods that ignore the underlying mechanism of not observed data. The most prominent of the latter type of methods is LOCF (Last Observation Carried Forward).

This poster outlines a recent study planning using modeling and simulation. In the anticipated scenario,

- 30 percent of patients enrolled are perceived to discontinue treatment before the end of the study
- the probability of discontinuation depends on the well-being (or not) of a patient

In other words, a patient that does not respond well to treatment has a higher likelihood of discontinuing the treatment.

Methods

The model approach is a longitudinal mixed effects model with some model assumptions on the discontinuation process.

Subjects are assumed to have a linear disease progression with different slopes for treatment groups.

The anticipated study setup, conduct, and disease progression were simulated 1,000 times and discontinuation was simulated with probabilities varying due to individual disease progression.

The individual probabilities of discontinuation are based on a function of the random effects, the individual deviations from the population average. Subjects with better than population average disease progression were assigned lower chances of discontinuation, subjects with worse than population average disease progression were assigned higher probabilities of discontinuation.

The evaluations of the incomplete data as observed (simulated) are contrasted against the known true complete data evaluations using a mixed effects model and a standard per-protocol analysis based on complete patient records only (since drug discontinuation is regarded as protocol violation).

Results

In this particular setup we show that using a per protocol analysis results in an underestimation of the treatment effect of 50 percent with a corresponding loss in power.

Conclusion

Discontinuation can have dramatic effects on the analysis of study data and the results thereof. If non-ignorable missingness is present, the process of discontinuation must be modeled and analyzed accordingly.

A per-protocol analysis (complete data only) can yield substantially wrong results.

LOCF (Last Observation Carried Forward) can bias the result substantially in either way.

Patients and Methods

Study Design and Treatment

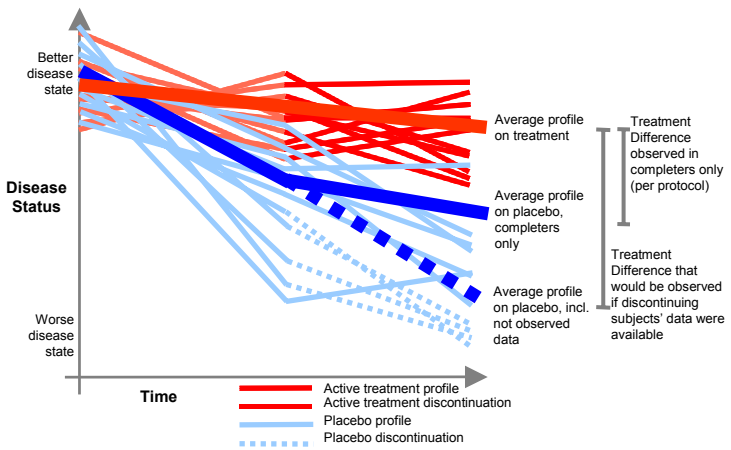
- About 50 patients per dose group
- 3 visits (baseline, on treatment, study end)
- Comparison to placebo
- Patients that discontinue treatment are still followed up such that a placebo model can be built (working hypothesis: patients that discontinue treatment behave like placebo patients from that time onwards)
- Disease is progressive, irreversible
- Patients on treatment experience a stabilization or slow disease progression
- Patients without treatment experience a more rapid disease progression

Discontinuation of Treatment

(See also the illustration on the right)

- Patients possibly discontinue treatment because their well-being is going downhill.
- The chance that a patient discontinues treatment depends on the current status of the patient: the worse the patient feels, the more likely he/she is to discontinue treatment
- The assumption is that placebo patients have less of an effect: they will do worse and are therefore more likely to discontinue than active treatment patients.
- Therefore, the pattern of discontinuation can not be ignored and must be modeled.
- If the patients with worst status discontinue, analyzing per protocol (completers only) underestimates the actual treatment effect

Discontinuation and its effect on treatment effect estimation



Statistical Modeling

Longitudinal mixed effect model

Linear disease progression

Placebo (treatment 0):

$y_i = a_i + b_0 * t + \varepsilon_i, \varepsilon_i \sim N(0, \sigma^2 I)$

Active treatment (treatment 1):

$y_i = a_i + b_1 * t + \varepsilon_i, \varepsilon_i \sim N(0, \sigma^2 I)$

Disease progression is reflected in the slopes, b0 (placebo) and b1 (active)

Treatment differences at time t: (b1-b0)*t

Instant structural break (change point) after discontinuation of treatment (due to limited observations per subject)

Simulation approach using multiple imputations

Estimation of parameters and their corresponding variation

Study Simulation

Simulate a full data set from the model using the anticipated study setup, disease progression, and discontinuation mechanism

Simulate discontinuation for each subject:

- Assign a discontinuation probability based on the disease status
- Toss a coin to simulate if subject discontinues
- If yes, simulate a time of discontinuation and flag the subject as a protocol violator

Subject-specific disease progression is reflected in the deviation of the individual slope from the population average, the random effect:

P (subject i discontinues before end of study | disease progression is average)=0.3

P (subject i discontinues at some time | strong decline)=0.6

P (subject i discontinues at some time | strong response)=0

To obtain the individual probability of discontinuation before study end, interpolate between the two points

($\Phi(+\infty)$=0, 0) and ($\Phi(-\infty)$=1, 0.6),

yielding

P (subject i discontinues) = $2*p(pop)*(1-q(r_i))$

With p(pop) pop avg discontinuation rate,

r_i random effect i on the progression slope

Take out data to mimic discontinuation

Evaluation

Generate a study data set 1,000 times according to the specified assumptions

Per Protocol Analysis

Discard protocol violators (discontinuations)

Estimate the treatment difference in the reduced data set

Power estimation: Count how often the treatment difference is called significant (fraction of hypothesis rejections)

Longitudinal Modeling

Apply a longitudinal model (proc nlmixed)

Estimated treatment difference: (b1-b0)* study length

Power estimation: Count how often the difference in the two slopes is called significant

Results

- In this particular setup, a per protocol analysis results in an estimation of the treatment effect of 49.6 percent of the original value (averaged over 1,000 simulation runs)
- Using the model-based approach, the difference of treatment to placebo is estimated as 117 percent of the simulated value
- Powers (fractions of hypothesis rejections in the simulations) were estimated as 80 and 61 percent, respectively
- If the probability that a subject discontinues depends on how well he is doing, the per protocol analysis always underestimates the treatment effect for further study parameters.
- In the simulated realistic scenarios, the treatment difference is very consistently underestimated by about 50%.
- The longitudinal model reproduces the treatment effect much more accurately (with a small bias, if any)
- If a large fraction of estimations do not converge (here between 0 and 80 percent for different parameters), biases occur in the longitudinal model. The smaller the fraction of converged runs, the larger the bias.
- This might indicate that starting values are difficult to find (starting values in the simulation runs are 10% away from the true values)

Discussion

Statistical Modeling Extensions

- Probability of discontinuation changes with time (possibly increases with time)
- Delayed switch from active profile to placebo profile on discontinuation (needs more data per subject)

Other aspects

Discontinuation depends on a patient's subjective impression of disease progression. The subjective feeling is not necessarily correlated with the objective disease status.

Conclusions

What did we learn from this simulation approach?

LOCF is bad in this case (when there is a trend in the data)

Per protocol analysis is bad if discontinuation depends on patient status (non-ignorable missingness)

Longitudinal modeling is an alternative

Starting values for the algorithm need to be carefully evaluated

Proposal in our case:

PP underestimates treatment effect

Longitudinal model over-estimates (if not all runs converge)

Use starting values somewhere in between

References

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