Facilitating Bayesian Predictive Probability Calculations for Interim Analyses in Early Phase Development at Pfizer

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BACKGROUND

- Bayesian methods and informative priors have become increasingly useful in clinical studies, especially in early phase clinical development
- However, Bayesian methods for interim analyses are currently infrequently used which could in part be due to:
  - Lack of training
  - Complexity of methods
  - Lack of standard approaches
  - Lack of simple software
- The objective of the working group was to:
  - Standardize Pfizer practice
  - Produce a guidance document
  - Provide web-based applications (SHINY) that simplifies the use of Bayesian Interim Analyses

PREDICTIVE PROBABILITIES

- Predictive probabilities are the probability of observing a future, unobserved, event based on existing data. Within a Bayesian framework applied to clinical trials, predictive probabilities can be used at an interim stage of a study to determine the probability that the end of study decision criteria will be met based on the existing interim data. The predictive probability of end of study success evaluated at interim can be calculated by:

$$\text{Predictive Probability} = 1 - \Phi\left(\frac{A}{C}\right)$$

$$A = \Delta + z_\pi \sigma_\delta + \left(\frac{m\bar{x}_{Pr} + n_P^I \bar{x}_P^I}{m + n_P^I}\right) - \bar{x}_A^I$$

$$C = \sigma \sqrt{\left\{\left(\frac{n_A^U}{n_A}\right)^2 \left(\frac{1}{n_A^I} + \frac{1}{n_A^U}\right) + \left(\frac{n_P^U}{m+n_P}\right)^2 \left(\frac{1}{m+n_P^I} + \frac{1}{n_P^U}\right)\right\}}$$

$$\sigma_\delta = \sigma \sqrt{\frac{(m+n_A+n_P)}{n_A(m+n_P)}}$$

$\bar{x}_{Pr}$ is the mean of the placebo prior,
$\bar{x}_A^I$ is the mean of the interim active data and $\bar{x}_P^I$ is the mean of the interim placebo data,
m is the effective number of subjects that the placebo prior is equivalent to (for a normal prior with a variance of σ_{pr}^2, $m = \sigma^2/\sigma_{pr}^2$),
n_A^I and n_P^I are the number of subjects for interim active and placebo data respectively, n_A^U and n_P^U are the number of subjects for future study active and placebo data respectively, and $n_A = n_A^I + n_A^U$ and $n_P = n_P^I + n_P^U$ are the total number of subjects for active and placebo groups,
σ is the group standard deviation,
z_π is the π^{th} quantile of $Normal(0,1)$, and
$\Phi(.)$ is the cumulative $Normal(0,1)$ distribution function.

PRACTICAL APPLICATION

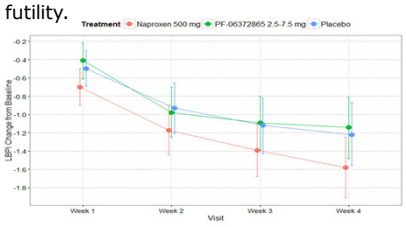
- The effect of PF-06372865, a subtype selective PAM of the $GABA_A$ receptor, on chronic low back pain was investigated in a randomised, placebo and active-controlled Phase 2 clinical trial.
- 300 subjects were to be randomized to receive PF-06372865 7.5mg, naproxen 500 mg BID, or placebo in a 1:1:1 ratio.
- The primary endpoint was change from baseline to week 4 in the daily low back pain intensity measured by 11-point NRS. An informative N (-2.36, 0.54^2) prior was used for the placebo response based on historical results from internal studies.
- Internal decision criteria were:

  C1: At least 50% confident that PF-06372865 effect is 0.8 units better than placebo

  C2: At least 95% confident that PF-06372865 effect is greater than placebo
- An interim analysis was planned after at least 50% subjects had completed
- At the interim, the predictive probabilities of passing each criteria were calculated with the following pre-specified decision rules

  STOP for futility if <20% probability of meeting C2

  Accelerate activities if >80% probability of meeting C1 and C2
- The predictive probability of passing criteria C2 was <1% and the study was stopped early for futility.
- The study was run successfully allowing a clear decision to stop to be made at the interim stage. The positive control, naproxen, performed as expected



GUIDANCE DOCUMENT

- Guidance document produced that includes details of standard formulas that can be used taken from the work from Grieve (1991) and Walley et al. (2015), with some expansions
- Sections cover:
  - Methodology
  - Practical Considerations
  - Implementation (SHINY Apps)
  - Future Development
- Main issue to resolve in writing the document was the large number of potential designs (e.g. with or without a placebo prior, using an analysis of covariance versus a mixed model repeated measures analysis)

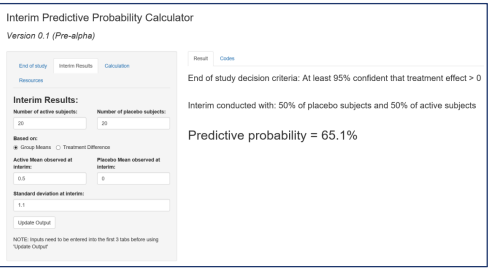
FUTURE WORK

- Training is being planned to help statisticians implement the approaches from the guidance document and utilise the SHINY Apps
- Incorporating additional types of endpoints (e.g. binary & time to event) into the guidance document and SHINY Apps

SHINY APPs

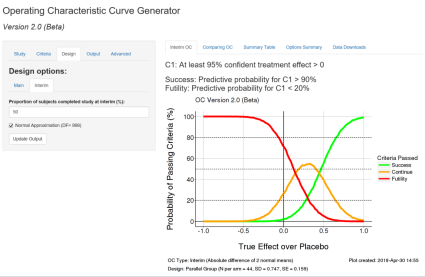
App 1:

- Calculates the predictive probability based on study design and interim results
- Advantages:
  - Determines automatically which formula to use
  - Provides R and SAS code to re-produce the result for ease of documentation



App 2:

- Creates operating characteristics (OCs) based on study design and interim properties
- Advantages:
  - Easy and quick to generate OCs over a wide range of circumstances
  - Allows for high quality and standardised figures to be produced



Grieve AP (1991) Predictive probability in clinical trials: *Biometrics*, 47(1) 323-9.
Walley RJ, Smith CL, Gale JD & Woodward P (2015) Advantages of a wholly Bayesian approach to assessing efficacy in early drug development: a case study: *Pharm Stat*, 14(3) 205-15.
https://shiny.rstudio.com/
https://clinicaltrials.gov/ct2/show/NCT02262754

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