The composite success
Comparing drug development strategies with probabilities of success including benefit-risk assessment to inform decision-making

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Outline

- Introduction

- Predictive probability of success

- Composite definition of success
  - Statistical significance
  - Clinical relevance
  - Positive benefit-risk balance

- Example in Major Depressive Disorders

- Conclusion
Introduction

Decision-making problem

Given what has been observed already, what are the chances of success of the drug development?

- We can calculate the Predictive Probability of Success (PPoS)
- ... but what is a success?
  
  Usually defined as a statistically significant result
  (O'Hagan 2005, Gasparini 2013)
The success of a drug development is driven by the conjunction between a **valuable product** and a **successful development strategy**.

A Marketing Authorization is usually conditioned by the success of the pivotal clinical trials, which must:
- Reach **statistical significance** on their primary endpoint
- While showing a **clinically meaningful effect** of the drug

The **benefit-risk balance** is a strong predictor of the long-term viability of a medicine, and a key element for the regulatory approval process.
Introduction

Composite definition of success

We define the **success of a drug development strategy** as the simultaneous fulfillment of the following criteria in all pivotal trials:

- The **statistical significance** on the primary efficacy criterion
- A **clinically meaningful effect** on the primary efficacy criterion
- A **positive benefit-risk balance** versus the comparator(s)

**PAST**
One or several non-pivotal trials _completed_

**FUTURE**
One or several pivotal trials _planned_

Given what has been observed already, what are the chances of success of the drug development?
**Predictive Probability of Success (PPoS)**

Example: Success = statistical significance on the primary efficacy criterion

\[ \delta = \text{difference between treatments} \]
\[ y_m = \text{observations in trial } m \]
\[ d_m = \text{sample estimate of } \delta \text{ in trial } m \]
\[ f = \text{probability distribution} \]

\[ \text{Success of trial } m: \ d_m > c, \ c > 0 \text{ critical value} \]

\[ \text{PPoS} = P(d_m > c) = \int \int_{d_m > c} f(d_m \mid \delta) f(\delta \mid y_1, ..., y_{m-1}) \, dz \, d\delta \]
Predictive Probability of Success (PPoS)

Example for a Normal distribution

After Trial 1, Predictions for Trial 2

$\text{Prior: } f(\delta)$

$\text{Posterior: } f(\delta | y_1)$

$\text{Predictive: } f(d_2 | y_1)$

$\text{Var (predictive)} = \text{Var (f(d_2 | \delta=x))} + \text{Var (posterior)}$

$\text{d}_1 = 2.5$

$\text{Vague prior}$
Predictive Probability of Success (PPoS)
Example for a Normal distribution

After Trial 1, Predictions for Trial 2

Prior: $f(\delta)$
- Vague prior

Posterior: $f(\delta | y_1)$
- $f(d_2 | \delta=3)$
  - Power = 92%

Predictive: $f(d_2 | y_1)$
- Predictive probability of success*$= 77%$

* Success = statistically significant result
Consider 2 treatments \((i = 1, 2)\) assessed on the primary efficacy criterion, noted criterion 1

- **Criterion performance**
  \(\xi_{i1}\): performance of treatment \(i\) on criterion 1

- **Difference between treatments**
  \(\delta = \xi_{11} - \xi_{21}\)

- **Sample estimate in the considered trial**
  \(d = \text{sample estimate of } \delta\)

- **Statistical significance**
  The null hypothesis \(H_0 : \delta \leq 0\) is rejected at level \(\alpha\) if \(d > c\), for \(c > 0\) some critical value
Composite definition of success

2. Clinical relevance on the primary endpoint

Consider 2 treatments \((i = 1, 2)\) assessed on the primary efficacy criterion, noted criterion 1

- **Criterion performance**
  \(\xi_{i1}\): performance of treatment \(i\) on criterion 1

- **Difference between treatments**
  \(\delta = \xi_{11} - \xi_{21}\)

- **Sample estimate in the considered trial**
  \(d = \) sample estimate of \(\delta\)

- **Statistical significance**
  The null hypothesis \(H_0 : \delta \leq 0\) is rejected at level \(\alpha\) if \(d > c\), for \(c > 0\) some critical value

- **Clinical relevance**
  The treatment effect is clinically meaningful if \(d > d_T\), for \(d_T > 0\) some clinical threshold
Composite definition of success

3. Positive benefit-risk balance

Probabilistic Multi-Criteria Decision Analysis (pMCDA)

\[ u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \ldots + w_n u_n(\xi_{in}) \]

\[ \xi_{ij} \] performance of treatment \( i \) on criterion \( j \)

MCDA is identified by the EMA as the most comprehensive among the quantitative methodologies

\[ u_j() \] used to normalize the performances on the criteria by mapping them on a 0 to 1 scale

\[ w_j \] reflects the importance of the criteria
Consider 2 treatments \((i = 1, 2)\) assessed on \(n\) criteria \((j = 1, ..., n)\) of benefit and risk.

- **Benefit-risk utility score**
  
  \[
  u(\xi_i, w) = w_1 u_1(\xi_{i1}) + ... + w_n u_n(\xi_{in}) = \sum_{j=n}^n w_j u_j(\xi_{ij})
  \]

- **Difference in benefit-risk utility scores**
  
  \[
  \Delta u(\xi_1, \xi_2, w) = u(\xi_1, w) - u(\xi_2, w)
  \]

- **Sample estimate in the considered trial**
  
  \[
  \Delta u(x_1, x_2, w) \text{ where } x_1 \text{ and } x_2 \text{ are sample estimates of } \xi_1 \text{ and } \xi_2
  \]

- **Positive benefit-risk balance**

  Treatment 1 has a positive benefit-risk balance versus treatment 2 if
  \[
  \Delta u(x_1, x_2, w) > 0
  \]
Predictive Probability of the Composite Success and of its components

Predictive probabilities in **one future trial** comparing two treatments:

- **Statistical significance on the primary efficacy criterion**
  \[ PPoS_1 = P(d > c) \quad c > 0 \text{ critical value} \]

- **Clinically meaningful effect on the primary efficacy criterion**
  \[ PPoS_2 = P(d > d_T) \quad d_T > 0 \text{ clinical threshold} \]

- **Positive benefit-risk balance versus the comparator**
  \[ PPoS_3 = P(\Delta u(x_1, x_2, w) > 0) \]

- **Predictive probability of composite success**
  \[ PPoS = P [(d > c) \cap (d > d_T) \cap (\Delta u(x_1, x_2, w) > 0)] \]

\( d, x_1, x_2 \) sample estimates of \( \delta, \xi_1, \xi_2 \) in the future trial
Predictive Probability of the Composite Success
and of its components

Predictive probabilities in **several future trials** comparing two treatments:

- **Statistical significance on the primary efficacy criterion**
  \[ PPoS_1 = \int \left( \prod_{m=1}^{S} P [d^m > c^m \mid \delta] \right) f(\delta \mid y) d\delta \]
  where \( c^m \) is the critical value in trial \( m \).

- **Clinically meaningful effect on the primary efficacy criterion**
  \[ PPoS_2 = \int \left( \prod_{m=1}^{S} P [d^m > d^m_T \mid \delta] \right) f(\delta \mid y) d\delta \]
  where \( d^m_T \) is the clinical threshold in trial \( m \).

- **Positive benefit-risk balance versus the comparator**
  \[ PPoS_3 = \int \int \left( \prod_{m=1}^{S} P [\Delta u(x^m_1, x^m_2, w) > 0 \mid \xi_1, \xi_2] \right) f(\xi_1 \mid x_1)f(\xi_2 \mid x_2) d\xi_1 d\xi_2 \]

- **Predictive probability of composite success**
  \[ PPoS = \int \left( \prod_{m=1}^{S} P [(d^m > \max(c^m, d^m_T)) \cap (\Delta u(x^m_1, x^m_2, w) > 0) \mid \delta, \xi_1, \xi_2] \right) f(\delta, \xi_1, \xi_2 \mid y, x_1, x_2) d(\delta, \xi_1, \xi_2) \]
  \( d^m, x^m_1, x^m_2 \) are sample estimates of \( \delta, \xi_1, \xi_2 \) in trial \( m \).
Example in Major Depressive Disorders
Fictive case-study

**PAST**
Phase II, completed

3 arms: Placebo (N=52)  
Low dose (N=50)  
High dose (N=49)

**FUTURE**
Phase III, planned

2 arms: Placebo (N=114)  
Experimental (N=114) (regimen to be determined)

Results of Phase II
Primary efficacy criterion and 5 more frequent adverse events

Effective treatment
Dose-response relationship for efficacy and safety

Hypokalemia may be a serious adverse effect

Difference in means vs placebo [95% CI]
Difference in proportions vs placebo [95% CI]
First strategy assessment: which dose has the best chances to succeed in Phase III?

### Primary efficacy endpoint

<table>
<thead>
<tr>
<th>Dose</th>
<th>PPoS(_1) (stat. signif.)</th>
<th>PPoS(_2) (clin. relev.)</th>
<th>PPoS(_3) (positive B/R)</th>
<th>PPoS (composite)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>74%</td>
<td>48%</td>
<td>88%</td>
<td>48%</td>
</tr>
<tr>
<td>High dose</td>
<td>93%</td>
<td>78%</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Example in Major Depressive Disorders
Fictive case-study

**Strategy refinement**: is it better to optimize the efficacy of the Low dose or to manage the risks for the High dose?

- Low dose with a possible dose-increase for non-responders
- High dose with potassium supplementation to prevent Hypokalemia

### Predictive distributions

#### Primary efficacy endpoint

- Difference versus Placebo in HAMD17 6w
  - Placebo better
  - Experimental better

#### Benefit-risk balance

- Difference versus Placebo in Benefit-Risk (B/R) utility score
  - Placebo better
  - Experimental better

<table>
<thead>
<tr>
<th>Regimen</th>
<th>$PPoS_1$ (stat. signif.)</th>
<th>$PPoS_2$ (clin. relev.)</th>
<th>$PPoS_3$ (positive B/R)</th>
<th>$PPoS$ (composite)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose suppl</td>
<td>93%</td>
<td>78%</td>
<td>95%</td>
<td>78%</td>
</tr>
<tr>
<td>Dose increase</td>
<td>83%</td>
<td>59%</td>
<td>69%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Concluding remarks

The **predictive probability of composite success** and its components are helpful tools to compare development strategies and to inform decision-making in the pharmaceutical development.

- **Evidence-based approach**
  - Clinical data should be available: may not be appropriate in very early development.
  - Previous and future trials should be done in the same context (endpoint, duration, population).
  - New hypotheses could be combined with the available evidence using priors.

- **What is a good PPoS?**
  - Phase/disease/project/team dependent.
  - Low amount of evidence \( \rightarrow \) PPoS close to 50% \( \rightarrow \) Uncertainty to take a decision.
  - Bayesian framework: PPoS are updated with the accumulation of knowledge from trial to trial.

- **Composite success criteria must be satisfied in each pivotal trial**
  - Consistent with the demand of replicability of the results.
  - But a similar approach could be applied at the development level (e.g. using meta-analyses).
Thank-you!


Hong S and Shi L. Predictive power to assist phase 3 go/no go decision based on phase 2 data on a different endpoint. *Statistics in Medicine, 31*:831–843, 2012.


Back-up slides
Example in Major Depressive Disorders
Fictive case-study

Distributions of the parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample estimate</th>
<th>Prior</th>
<th>Likelihood</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D$_{17}$ mean total score in each arm ($i = 1, \ldots, 3$)</td>
<td></td>
<td>$N(0, \sigma^2_0)$</td>
<td>$N(\xi_i, \sigma^2_i)$</td>
<td>$N\left(\frac{\sigma^2_0}{\sigma^2_0 + \sigma^2_i} m_i, \frac{\sigma^2_0 \sigma^2_i}{\sigma^2_0 + \sigma^2_i}\right)$</td>
</tr>
<tr>
<td>$\xi_{i1}$</td>
<td>$m_i$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D$_{17}$ mean total score, difference versus placebo ($i = 1, 2$)</td>
<td></td>
<td>$N(0, s^2_0)$</td>
<td>$N(\delta_i, s^2_i)$</td>
<td>$N\left(\frac{s^2_0}{s^2_0 + s^2_i} d_i, \frac{s^2_0 s^2_i}{s^2_0 + s^2_i}\right)$</td>
</tr>
<tr>
<td>$\delta_i = \xi_{31} - \xi_{i1}$</td>
<td>$d_i = m_3 - m_i$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurrence of adverse events in each arm ($i = 1, \ldots, 3$; $j = 2, \ldots, 6$)</td>
<td></td>
<td>$Beta(1, 1)$</td>
<td>$Bin(n_{ij}, \xi_{ij})/n_{ij}$</td>
<td>$Beta(r_{ij} + 1, n_{ij} - r_{ij} + 1)$</td>
</tr>
<tr>
<td>$\xi_{ij}$</td>
<td>$r_{ij}/n_{ij}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_0 = 10^4$ ; $s^2_0 = 2 \times \sigma^2_0 = 2 \times 10^4$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Strategy refinement

The two new strategies and their statistical assumptions are as follows:

(i) **High dose with potassium supplements.** The predictions are based on the posterior distribution of $\xi_{32}$ obtained for the placebo for Hypokalemia, and on the posterior distributions obtained for the High dose for all the other criteria.

(ii) **Dose increase.** According to the clinicians, 30% to 40% of the patients would increase to the High dose in the Phase III study, therefore a new parameter with a uniform distribution $\zeta \sim U[0.3, 0.4]$ is introduced in the model as the proportion of patients receiving the High dose. The distributions of the parameters associated to the efficacy and safety criteria are obtained from the distributions of the initial parameters: $(1 - \zeta) \times \xi_{1j} + \zeta \times \xi_{2j}$ for $j = 1, \ldots, 6$. 