Predicting Patient Recruitment in Multicenter Clinical Trials

Xiaotong (Phoebe) Jiang

Department of Biostatistics
The University of North Carolina at Chapel Hill

xiaotong@live.unc.edu

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Overview

- Background & Introduction
- Methodology
- Demo in JMP Clinical
Research studies that test whether a new drug, device, or therapy works and is safe for people

- Have protocols (or action plans)
- Result in three main consequences: Improvement, No Benefit, Harm
- One of the final stages of a long and careful research process
Background: Clinical Trials

Phase

0

Effect on body

I

weeks
	
tens

Safety in humans

II

months
	hundreds

Effectiveness at treating diseases

III

years
	
thousands

Larger scale safety and effectiveness

IV

ongoing

Long term safety

healthy
affected
According to the National Institutes of Health (NIH), more than 80% of clinical trials in the US fail to meet their patient recruitment timelines, which can cause additional costs, shortage in resources, and significant delay in trials.
Background: Patient Recruitment

Predictive Model of Patient Enrollment
Data Set=NICARD, Now=25AUG1989, Current Enrollment=902, #Centers=40

Enrollment Target
=1200

Number of Patients Recruited

Recruitment Date

Target Time
=01MAR1990

Actual Enrollment  ---  Now  ---  Current Enrollment
Poisson-Gamma Distribution, Anisimov and Fedorov (2007)

- The arrival of patients at each center follows an independent Poisson process with parameter $\lambda_i$
- $\lambda_i$ is
  - the recruitment rate at center $i$
  - unknown
  - non-constant across centers but constant within center
  - sampled from a Gamma distribution ($\alpha, \beta$), conjugate prior
The Model: Estimation and Prediction

Given data of current enrollment \((k_i, \tau_i)\):

- **Parameter Estimation**: maximum likelihood \(\hat{\alpha}, \hat{\beta}\)
  
  \[ K \sim \text{NegBin}(p, r) \]

- **Prediction of Remaining Recruitment Time**
  - If \(\# \text{ center} > 20\), Bayesian Simulation
    
    \[ \tilde{T}_1 = \frac{\text{Gamma}(K_2, 1)}{\sum_i \text{Gamma}(\alpha + k_i, \beta + \tau_i)} \]
  
  - If \(\# \text{ center} \leq 20\), MLE
    
    \[ \tilde{T}_2 = \frac{\text{Gamma}(K_2, 1)}{\sum_i \frac{k_i}{\tau_i}} \]

- **Adaptive Adjustment**, if necessary
  
  \[ \tilde{T}(M) = d + \frac{\text{Gamma}(K_3, 1)}{\tilde{\Lambda}_1 + \text{Gamma}(\alpha M, 1) m/\alpha} \]
The dialog

Patient Recruitment

**Options**

**General**
- **Target Enrollment**
  - 1000
- **Target Date**
  - 01Feb1993
- **Use the Last Randomization Date as Current Date**
- **Truncate Early Recruitment Data**
- **Use site active date from the Risk Data Set, if available**

**Options**
- **Number of Simulations**
  - 10000
- **Seed Number**
  - 123
- **Amount of Increment in the Remaining Enrollment (How Often to Simulate)**
  - 10
- **Number of Days Delayed at New Centers**
  - 30
- **Maximum Probability of Meeting the Target Date to Initiate Adaptive Adjustment**
  - 0.85
- **Minimum Probability of Meeting the Target Date to Stop Adding New Centers**
  - 0.85
- **Initial Number of Additional Centers**
  - 1

* Required Parameter
When we meet the deadline

**Predictive Model of Patient Recruitment**

- **Target Recruitment**: 2500
- **Current Recruitment**: 902
- **Start Date**: 12 Oct 1987
- **Current Date**: 26 Sep 1989
- **Target Date**: 1 Feb 1993

- **Actual Enrollment**
- **Predicted 2.5%**
- **Predicted 97.5%**
- **Predicted Mean**
When we miss the deadline
Adaptive adjustment

Probability of Meeting the Deadline

Minimum Probability of Meeting the Deadline: 0.85

Number of new centers vs. Probability of meeting the target date with the additional centers added.
<table>
<thead>
<tr>
<th>Number of new centers</th>
<th>Probability of meeting target date with the additional centers added</th>
<th>Average predicted date of enrollment completion</th>
<th>2.5th percentile date of predicted completion</th>
<th>97.5th percentile date of predicted completion</th>
<th>Target date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.77%</td>
<td>06May1992</td>
<td>19Feb1992</td>
<td>25Jul1992</td>
<td>01Feb1992</td>
</tr>
</tbody>
</table>
Predictive Model of Patient Recruitment

Target Recruitment: 2500

Actual Enrollment
Predicted 2.5%
Predicted 97.5%
Predicted Mean

Number of Patients Recruited


Start Date: 02 May 1989
Current Date: 26 Sep 1989
Target Date: 01 Feb 1993

Current Recruitment: 902
Thank you for your attention

Special thanks to co-author Richard Zink, Kelci Miclaus, and the rest of JMP Clinical team!
Thoma A, Farrokhyar F, McKnight L, Bhandari M.
How to optimize patient recruitment.

Anisimov, V. V. and Fedorov, V. V.
Modelling, prediction and adaptive adjustment of recruitment in multicentre trials.