Guiding clinical trial design for a rare disease using natural history data and Bayesian disease progression modeling

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Pathogenetic insights from quantification of the cerebriform connective tissue nevus in Proteus syndrome

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\textit{Bethesda, Maryland}
Rare disease
Proteus syndrome

• Disease characterization and manifestation
  – Genetic mutation
  – Overgrowth of skin, bone, and other tissues
  – Plantar cerebriform connective tissue nevus (CCTN)

• Challenges in clinical trial design
  – Small, heterogenous patient populations
  – Insufficient understanding of disease etiology
  – Poorly developed study endpoints
Natural history study

CCTN disease progression

Nathan et. al.
Natural history study
CCTN disease progression

Subject CCTN proportion of whole foot by age
Natural history study data

Age (years) vs. Proportion CCTN of whole foot

Nathan et. al
Natural history study
CCTN disease progression

Can we leverage data from this natural history study (NHS) to:
-understand natural rate of progression
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Natural history study
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- design a single arm trial that
  - compares disease progression of treated patients to NHS
  - defines a final analysis using the DPM
- understand the operating characteristics of this design
Natural history study
CCTN disease progression

Fit a mixed model to estimate random slope and intercept for age
For subject s at visit i: \( \logit(CCTN_{si}) = \beta_{0,s} + \beta_{1,s} \times \text{Age}_{si} + \epsilon_{si} \)
Fit a mixed model to estimate random slope and intercept for age
For subject $s$ at visit $i$: $\logit(CCTN_{si}) = \beta_{0,s} + \beta_{1,s} \times Age_{si} + \epsilon_{si}$

**Estimates:**
- $\mu_{\beta_0}$: mean random intercept
- $\sigma^2_{\beta_0}$: variance random intercept
- $\mu_{\beta_1}$: mean random slope
- $\sigma^2_{\beta_1}$: variance random slope
- $\sigma^2_{\epsilon}$: residual error
CCTN simulation model
Virtual patient simulator

Use mixed model estimates to simulate virtual patients

For subject $s$ at visit $i$: $\logit(CCTN_{si}) = \beta_{0,s} + \beta_{1,s} \times Age_{si} + \varepsilon_{si}$

Natural history of disease progression
CCTN simulation model
Virtual patient simulator

Use mixed model estimates to simulate virtual patients

For subject $s$ at visit $i$:

$$\text{logit} (\text{CCTN}_{si}) = \beta_{0,s} + \beta_{1,s} \times \text{Age}_{si} + \varepsilon_{si}$$

Natural history of disease progression

$$\beta_{0,s} \sim \text{Normal} (\mu_{\beta_0}, \sigma_{\beta_0}^2)$$

$$\beta_{1,s} \sim \text{Gamma} \left( \frac{\mu_{\beta_1}^2}{\sigma_{\beta_1}^2}, \frac{\mu_{\beta_1}}{\sigma_{\beta_1}^2} \right)$$

$$\varepsilon_{si} \sim \text{Normal} (0, \sigma_{\varepsilon}^2)$$
CCTN simulation model
Virtual patient simulator

Use mixed model estimates to simulate virtual patients

For subject s at visit i: \( \text{logit}(\text{CCTN}_{si}) = \beta_{0,s} + \beta_{1,s} \times \text{Age}_{si} + \varepsilon_{si} \)

Natural history of disease progression

\( \beta_{0,s} \sim \text{Normal}(\mu_{\beta_0}, \sigma_{\beta_0}^2) \)

\( \beta_{1,s} \sim \text{Gamma}(\frac{\mu_{\beta_1}}{\sigma_{\beta_1}^2}, \frac{\mu_{\beta_1}}{\sigma_{\beta_1}^2}) \)

\( \varepsilon_{si} \sim \text{Normal}(0, \sigma_{\varepsilon}^2) \)

Use mixed model parameter estimates to create a virtual patient simulator that can generate patients with the same characteristics as the NHS patients.

Assume that baseline age is distributed as a truncated normal.
Simulating a treatment effect
Proportional slowing of CCTN progression

• Treatment effect may *slow, stop, or reduce* disease progression of CCTN (measured as a proportion of the whole foot)

• *Here, we are simulating CCTN and examining treatment effects applied to CCTN measurements*
Simulating a treatment effect
Proportional slowing of CCTN progression

- Treatment effect, $\theta$, is applied to the slope parameter of the simulation model
  - Only for the years during which the patient was treated

$logit(CCTN_{si}) = \beta_{0,s} + (\beta_{1,s} \times Age_{s0}) + (\theta \times \beta_{1,s} \times (Age_{si} - Age_{s0})) + \varepsilon_{si}$

Years treated

Natural history of disease progression

Treated disease progression
Simulating a treatment effect

Proportional slowing of CCTN progression

- Treatment effect, $\theta$, is applied to the slope parameter of the simulation model
  - Only for the years during which the patient was treated
- The addition of $\theta$ effectively models proportional slowing of CCTN progression

$$\text{logit}(\text{CCTN}_{si}) = \beta_{0,s} + (\beta_{1,s} \times \text{Age}_{s0}) + (\theta \times \beta_{1,s} \times (\text{Age}_{si} - \text{Age}_{s0})) + \epsilon_{si}$$

- Natural history of disease progression
- Treated disease progression

Years treated
Simulating a treatment effect
Proportional slowing of CCTN progression

Subject CCTN proportion of whole foot by age
Simulated data, treated: theta=0.1

Age (years)
Proportion CCTN of whole foot

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Simulating a treatment effect
Proportional slowing of CCTN progression

Subject CCTN proportion of whole foot by age
Simulated data, treated: theta=0.1

<table>
<thead>
<tr>
<th>Theta</th>
<th>Mean change in proportion CCTN of whole foot per year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.032</td>
</tr>
<tr>
<td>0.9</td>
<td>0.029</td>
</tr>
<tr>
<td>0.8</td>
<td>0.026</td>
</tr>
<tr>
<td>0.7</td>
<td>0.024</td>
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<tr>
<td>0.6</td>
<td>0.020</td>
</tr>
<tr>
<td>0.5</td>
<td>0.017</td>
</tr>
<tr>
<td>0.4</td>
<td>0.014</td>
</tr>
<tr>
<td>0.3</td>
<td>0.010</td>
</tr>
<tr>
<td>0.2</td>
<td>0.007</td>
</tr>
<tr>
<td>0.1</td>
<td>0.004</td>
</tr>
<tr>
<td>0</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*based on 10,000 simulated trials
Bayesian disease progression model (DPM)  

Primary analysis

For each subject, s, at visit, i, assume:

\[
\text{logit}(\text{CCTN}) \sim \text{Normal}(\mu_s, \sigma^2)
\]

\[
\mu_s = \alpha_s + \beta_s \text{Age}_{s,0} + \gamma \beta_s (\text{Age}_{s,i} - \text{Age}_{s,0})
\]

Quantifies rate of disease progression
Bayesian disease progression model (DPM)

Primary analysis

For each subject, $s$, at visit, $i$, assume:

$$\text{logit}(\text{CCTN}) \sim \text{Normal}(\mu_s, \sigma^2)$$

$$\mu_s = \alpha_s + \beta_s \text{Age}_{s,0} + \gamma \beta_s (\text{Age}_{s,i} - \text{Age}_{s,0})$$

Quantifies rate of disease progression

Test $\text{Pr}(\gamma < 1) \geq 0.994^*$

* This threshold, found via simulation ensures 2.5% Type I error control
Bayesian disease progression model (DPM)

Primary analysis

For each subject, s, at visit, i, assume:

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\]

\[
\mu_s = \alpha_s + \beta_s \text{Age}_{s,0} + \gamma \beta_s (\text{Age}_{s,i} - \text{Age}_{s,0})
\]

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This model integrates NHS patients into the analysis and allows for differential length of follow up
Bayesian disease progression model (DPM)

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\[
\mu_s = \alpha_s + \beta_s \text{Age}_{s,0} + \gamma \beta_s (\text{Age}_{s,i} - \text{Age}_{s,0})
\]

Quantifies rate of disease progression

\[
\alpha_s \sim \text{Normal}(\mu_\alpha, \sigma^2_\alpha) \quad \mu_\alpha \sim \text{Normal}(-3, 1^2) \quad \sigma_\alpha \sim \text{Uniform}(0, 10)
\]

\[
\beta_s \sim \text{Gamma}\left(\frac{\mu_\beta}{\sigma^2_\beta}, \frac{\mu_\beta}{\sigma^2_\beta}\right) \quad \mu_\beta \sim \text{Gamma}(0.3^2, 0.3) \quad \sigma_\beta \sim \text{Uniform}(0, 1)
\]

\[
\sigma \sim \text{Uniform}(0, 10)
\]

\[
\gamma \sim \text{Uniform}(0, 2)
\]

Test \(\Pr(\gamma < 1) \geq 0.994^*\)

* This threshold, found via simulation, ensures 2.5% Type I error control

This model integrates NHS patients into the analysis and allows for differential length of follow up
**Trial operating characteristics**

\[ \Pr(\gamma < 1) \geq 0.994^* \]

<table>
<thead>
<tr>
<th>Rate of disease progression, (\gamma)</th>
<th>4 years of follow up on treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 treated feet</td>
</tr>
<tr>
<td>1</td>
<td>0.016</td>
</tr>
<tr>
<td>0.9</td>
<td>0.088</td>
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<tr>
<td>0.8</td>
<td>0.362</td>
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<tr>
<td>0.7</td>
<td>0.696</td>
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<tr>
<td>0.6</td>
<td>0.928</td>
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<tr>
<td>0.5</td>
<td>0.996</td>
</tr>
<tr>
<td>0.4</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>0.3</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>0.2</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>0.1</td>
<td>&gt;0.999</td>
</tr>
<tr>
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</tbody>
</table>

**Trial - using Bayesian model**
- All natural history data included
- 4 years of follow up for each treated subject
- 53 OR 63 (unique) feet:
  - 23 from natural history
  - 30 OR 40 treated
- Analysis of a single parameter, \(\gamma\), which quantifies disease progression defined by proportion of whole foot CCTN

*Threshold selected to ensure one-sided 2.5% Type I error control

500 simulations per scenario

Bayes 2019
Design comparison

OPC vs. DPM

**OPC analysis**
- 40 treated feet
- 4 years of follow up
- Analysis of lower confidence bound
- Powered to detect a treatment effect equivalent to at least 50% slowing in CCTN progression
Design comparison
OPC vs. DPM

OPC analysis
40 treated feet
4 years of follow up
Analysis of lower confidence bound
Powered to detect a treatment effect equivalent
to at least 50% slowing in CCTN progression

DPM analysis
40 treated feet
4 years of follow up
Analysis of Bayesian disease progression model
Powered to detect a treatment effect equivalent
to at least 30% slowing in CCTN progression