Accelerating Clinical Trials: Use of Historical Subject Level Data for Controls

The TransCelerate Placebo/Standard of Care Database

Josephine Wolfram, Astellas Pharma
EFSPI statistics leaders meeting

12 July 2018
AGENDA

- High-level overview of TransCelerate
- PSoC History, Milestones and Activities
- Current data available within the database
- Using historical data to substitute control arm
What is TransCelerate?

2012
TransCelerate Founded

10
MEMBER COMPANIES

10
INITIAL INITIATIVES

2016
BioCelerate Founded

Today

19
MEMBER COMPANIES

19
Novartis most recent member

25+
INITIATIVES

25+
including 4 pharmacovigilance initiatives

BREADTH & DEPTH
Over 30 solutions being delivered across 25+ initiatives, across 3 strategic priorities

CULTURE OF COLLABORATION
With an effective and proven governance structure have increased the ease and desire to collaborate

ENABLING PLATFORM TRIALS
12+ initiatives deliver solutions that enable future platform trials

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TransCelerate has seen Significant Growth

**Growth of Global Impact:**
- Country Network of 22-Countries
- Engagement with 11+ Global Regulatory Authorities

**TransCelerate Founded**
- 2012
  - 10 Founding Members
  - 5 Active Initiatives
  - 17 Member Companies
  - 12 Active Initiatives
  - 1 Exploratory Initiative

2014
- Initial launch

2015
- Launch of BioCelerate
- 18 Member Companies
- 11 Active Initiatives
- 6 Realized Initiatives

2016
- PSoC – FDA Meeting

2017
- 19 Member Companies

Today
- 19 Member Companies

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Placebo/Standard of Care Data Sharing

**Unmet Need:** Lack of ability to reuse data, leverage historical data, and utilize readily available context information

**Objective:** To establish a database to share de-identified Placebo and Standard of Care data

**Benefits:** Improved clinical trial design, faster clinical trial execution, ethical clinical equipoise, and a better understanding of disease
**PSoC History, Milestones and Activities**

<table>
<thead>
<tr>
<th>Year</th>
<th>1&amp;2Q15</th>
<th>3&amp;4Q15</th>
<th>1&amp;2Q16</th>
<th>3&amp;4Q16</th>
<th>1&amp;2Q17</th>
<th>3&amp;4Q17</th>
<th>1&amp;2Q18</th>
<th>3&amp;4Q18</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Establish workstream &amp; defined use cases</td>
<td>Designed &amp; Built the Data Sharing Database</td>
<td>10-MCs agree to share data; Database live</td>
<td>10-studies shared; 1st control arm data set leveraged</td>
<td>44 studies converted &amp; 50,000 patients in database</td>
<td>85 studies &amp; 75,000 patients in database</td>
<td>Manuscript Submission</td>
<td>16th MC joins PSoC</td>
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**Key Milestones**

- **Whitepaper:** guidance on the potential applications PSoC database and use case details
- **Manuscript:** Minimizing Patient Burden through the Use of Historical Subject-Level Data in Innovative Confirmatory Clinical Trials
- **PSoC Multi-Stakeholder Workshop**

**Timeline**

- **HA Meeting:** FDA CPATH
- **HA Meeting:** EMA engaged PSoC. FDA
- **Harvard:** Pending Collaboration

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The PSoC Data Sharing initiative seeks to operationalize key use cases that drive efficiencies.

<table>
<thead>
<tr>
<th>Use Case</th>
<th>Value Drivers</th>
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<tbody>
<tr>
<td></td>
<td>Reduced Cycle Times</td>
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<tr>
<td>1. Enhanced Safety Signal Interpretation</td>
<td>✓</td>
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<tr>
<td>2a. Control Arm Substitution (Early Phase Trials)</td>
<td>✓</td>
</tr>
<tr>
<td>2b. Control Arm Substitution (Late Phase Trials)</td>
<td>✓</td>
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<tr>
<td>3. Precision Powering</td>
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<tr>
<td>4. Inclusion/exclusion Criteria Optimization</td>
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</tr>
<tr>
<td>5. Disease Modeling Capabilities</td>
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</tr>
<tr>
<td>6. Improved Understanding of Geographic Differences</td>
<td>✓</td>
</tr>
<tr>
<td>7. Biomarker Development</td>
<td>✓</td>
</tr>
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</table>
## A key use case is control arm substitution or supplementation

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<tr>
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Part or all of the control arm for the study can be comprised of historical data that could be pulled from the database (and/or elsewhere).
PSoC Data Sharing Initiative Overview

*As of 27, June 2018

118* Clinical Trials Shared

19 Disease Areas

82,419 Patients

Current Database Metrics

Disease Area

Diabetes
Rheumatoid Arthritis
Schizophrenia
Cardiovascular Disease
Alzheimer's Disease
Asthma
Ulcereative Colitis
Stroke
Hypercholesterolemia
Systemic Lupus Encephalitis
Fibromyalgia
Ankylosing Spondylitis
Pemphigus Vulgaris
Duchenne’s
Vaccine

# of studies

Patient Population (Thousands)
PSoC Multi-Stakeholder Workshop
Using historical data to accelerate confirmatory clinical trials

Key challenges identified:

- **Controlling bias** in the trial population and in **appropriate selection** of data to use as a historical control
- Understanding **traceability challenges** around maintaining integrity and quality of the original source data

**Health Authorities Engagement**

**Public Multi-Stakeholder Workshop**

- **May 15, 2018**
- **Bethesda, MD**

**Attendees:**

- Health Authorities
- Academia
- Patient Advocates
- Industry

**Workshop Outcomes**

- Create series of **best practices/publications**
- Explore new solutions in feasibility pilots
- Sponsors encouraged to **submit to PDUFA VI Complex Innovative Design Pilot Program**
- **Continue engagement** with health authorities and key stakeholders (e.g. academia)
There is a sense of urgency in developing medicines for patients in need.

Regulators have a record of accepting historical control data for interventions for medical devices and/or indications with very small populations.

The methods covered in this paper give us the tools to use fewer subjects in late-phase confirmatory clinical trials. Bayesian and frequentist approaches are outlined including how the operating characteristics for such a trial can be obtained. Examples of approved new treatments that incorporated historical controls in their confirmatory trials are presented.

Industry & regulatory science has matured to the point where high quality data exists to support these approaches; the statistical methods have evolved to provide a robust understanding of risk; & our evolution to a patient-centric model demands that we leverage these methods more broadly.
# One Proposed Approach for Using Historical Control Data in Confirmatory Trials

## Prospective selection

Historical trials should be carefully selected prospectively to **reduce any systematic differences** (trial conduct/design, changes in **SOC** over time, etc) between the current and historical trials in order to reduce the risk of bias.

## Choose relevant controls

If necessary (e.g. to adjust for differences between historical and current trials in **inc/exc** criteria, or in order to reduce the size of the historical data to prevent it overwhelming the concurrent data), use a **method such as propensity score matching to quantitatively identify the most relevant subset of historical control subjects.** This will build confidence that the historical prior is appropriate.

## Robust prior *

Incorporate the subjects from step 2 into a robust prior that down weights the influence of the historical control data when it is discordant with the concurrent control data.

*Note that this is just one proposed Bayesian approach, but frequentist methods could also be used.*

## Adaptive design

Finally, where feasible, use an adaptive trial design with an interim analysis to assess the comparability of the historical control data to the concurrent control. If they are not comparable then additional control subjects would be included in the study. If they are comparable then the number of control subjects would not increase.
Incorporation of Historical Control Data Using Bayesian Priors: Benefits and Risks

Total # concurrent controls needed to achieve effective control N=200 when combined with historical controls

Historical response=0.65

Maxine Bennett, MRC Biostatistics Unit, UK (Unpublished results)
Example: Supplement safety data in control arm with data from another trial by same sponsor

<table>
<thead>
<tr>
<th>Trial A</th>
<th>To demonstrate safety of Drug X in Trial B when given less frequently</th>
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</table>
| • Very large Ph III trial of extended duration that is designed to demonstrate the safety of the once a day regimen of Drug X.  
  • 1:1 randomization Drug X:SOC | • Use information in Trial B on SOC from Trial A through the use of a Bayesian framework (dynamic borrowing using two approaches: commensurate prior and robust mixture prior) |

<table>
<thead>
<tr>
<th>Trial B</th>
<th></th>
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</table>
| • Single confirmatory trial that is designed to demonstrate the efficacy and safety of a less frequent regimen of Drug X.  
  • 2:1 randomization Drug X:SOC | |
Conclusion

“All the forces in the world are not so powerful as an idea whose time has come.”

- Victor Hugo