Innovations in Early Clinical Trial Designs: Application to New Drug Development in Pharma

Robert Schmouder, MD, MPH
Translational Medicine Head
Novartis Institutes for BioMedical Research (NIBR)
Cambridge, MA

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Disclaimer

The views and opinions expressed in this presentation are my own and do not necessarily represent the official policy or position of Novartis.
Plenty of drug targets remain

Compound attrition during pharmaceutical R&D

- Preclinical
- Clinical

Hopefully to market sooner

Experiment in Man – Proof of Concept (PoC)
Mission

- **Bring medicines rapidly into the clinic:**
  Focus on tractable biological targets with excellent rationale for addressing unmet medical need

- **Establish a new grammar for drug discovery:**
  Increase access to genomic and chemical universe
What diseases to pursue?

Understanding of mechanism

Unmet Medical Need
Translation of the genome to therapeutics

Defining the key druggable nodes within the network
Selection of drugs to enter exploratory development

- High unmet medical need
  - Current treatment

- Well understood mechanism

- A path forward
  - Proposed proof of concept (PoC) study is feasible

and none of these guys...
The old paradigm

“Compounds tossed over the wall”

Research → Toxicology → Phase I → Phase II → Phase III → Phase IV

PK\(^1\) → Efficacy → Approval → Market

Initial safety
The new paradigm: “tear down this wall”

Translational Medicine

Target discovery and validation → PoC¹ clinical trials → Further clinical development

Exploratory Phase

Target → PoC¹

Confirmatory Phase

Efficacy → Approval → Market

¹Proof-of-Concept
What does the exploratory phase look like?

- **First in human**
- **De-risking studies**
  - For example proving that a candidate drug has no clinically significant drug-drug interaction with the regimen with which it will be paired
- **Proof of Concept (PoC)**
  - It’s not just a good idea, it’s the LAW
  - The permissive step into full development
PoC: Subjects

- Subjects are typically the patient group of interest
  - Example: Muckle-Wells patients to measure efficacy of anti-IL-1β

- Many studies conducted in patients with rare disease
  - Currently >40 projects
  - Examples: medulloblastoma, Noonan’s, pulmonary artery hypertension, lymphangioleiomyomatosis, Netherton’s, hematopoietic stem cell transplantation, Gorlin’s, Cushing’s, etc.

- Attempt to genetically define patient population *a priori*
  - Commonly done with oncology/hematology studies
  - Examples: epigenetic features in Fragile X syndrome, K-RAS and B-RAF mutations in solid tumors
PoC: Design

- “20 subjects, 2 weeks, $2M”
- Typically short duration: 1-3 months
- Typically small N: 20-40
- 20-30% use a cross over design
- 30-40% have an active comparator group
- Biomarkers can be a key intermediate endpoint to de-risk the remainder of the trial. Drive a NO GO decision.
- Most studies have adaptive features, some are heavily adaptive
PoC: Study conduct

- Many are multicenter, multinational
  - Current record: 22 sites in 5 countries

- Continuous safety and activity data streaming to the study physician over the course of the study. Real time analysis using software such as Spotfire.

- Increasing interest in changing from “triple blind” to “double blind” exploratory approaches
  - Triple blind: subject, investigator, sponsor
  - Double blind: subject, investigator
PoC: Analysis

- PoC Go and No Go criteria are defined and formally agreed upon *a priori*

- Primary end point is typically as close as possible to clinical activity
  - Examples: FEV1, cognitive battery, ventricular energetics, macular thickness, stand and walk time

- Go criteria typically tested using Bayesian statistics
  - Confidence level set at 60-70%
  - Cardinal Sin: false negative!

- Careful attention also to possible responder subsets

- Several “N of 1” studies conducted each year
“N of 1” Patient with Gastrointestinal stromal tumor

Pre-treatment

Post 3 months treatment

imatinib
“N of 1” Patient with Muckle-Wells Syndrome

Pre-treatment

Anti-IL-1β

Single dose at 24 hours
Biomarkers: Every PoC’s got’em
Do you want PIE with that PoC?

Q: What else does a PoC permit besides entry into full development

A: Parallel indications expansion (PIE)

- We follow the pathway
- If the pathway maps to other diseases of high unmet medical need, we will pursue those indications

Two examples...mTOR inhibitor, anti-IL-17 mAb
Targeting Key Nodes to Develop New Drugs

Everolimus

[Diagram showing the mTOR pathway with Everolimus as a targeting molecule]
mTOR Pathway in Multiple Indications

- Tuberous sclerosis
- Retinitis pigmentosa
- Cancer (colon/breast/kidney)
- Immune diseases, Tx rejection
- Vascular proliferation (stent implant)

mTOR pathway
Rising complexity and burden of clinical research

<table>
<thead>
<tr>
<th>Metric</th>
<th>1999</th>
<th>2005</th>
<th>Percentage change</th>
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<tbody>
<tr>
<td>Unique Procedures per Trial Protocol (Median)</td>
<td>24</td>
<td>35</td>
<td>46%</td>
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<tr>
<td>Total Procedures per Trial Protocol (Median)</td>
<td>96</td>
<td>158</td>
<td>65%</td>
</tr>
<tr>
<td>Clinical-Trial Staff Work Burden (Measured in Work-effort Units)</td>
<td>21</td>
<td>35</td>
<td>67%</td>
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<tr>
<td>Length of Clinical Trial (Days)</td>
<td>460</td>
<td>780</td>
<td>70%</td>
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<tr>
<td>Clinical-Trial-Participant Enrollment Rate</td>
<td>75%</td>
<td>59%</td>
<td>-21%</td>
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<tr>
<td>Clinical-Trial-Participant Retention Rate</td>
<td>69%</td>
<td>48%</td>
<td>-30%</td>
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Change is starting to happen: (2)
The most relevant species in drug development: *Homo sapiens*
Conclusions

- The PoC study can be a focus and driver of innovation
- These studies are the culmination of years of integrated chemical, biological, and medical efforts
- PoC studies have many moving parts and the organization, deployment, conduct and analysis of these studies can be challenging
- Trials of the Future: Bring the PoC study to the patient
- Exclusion of commercial and/or marketing input from early development could, in itself, be considered an innovation
- PoC studies both energize early development and de-risk late development
Questions
Multiple Choice Question 1

- What are some attributes of PoC studies (choose all that apply):
  - A) Typical size is 100-200 subjects
  - B) False positive result is “the worst sin”
  - C) Typically done only if the Net Present Value is positive
  - D) Provides confirmation of the patho-biologic pathway
  - E) Is powered to understand the safety of a new drug
  - F) Typically <6 months duration
Multiple Choice Question 2

What is the value of Marketing / Commercial input in pathway based early development:

• A) Allows building the “business case” to continue development
• B) Provides free lunches at meetings
• C) Helps to prioritize the business portfolio
• D) There is minimal / no value of Marketing / Commercial input
Multiple Choice Question 3

Which combination of attributes below defines the “sweet spot” of pathways based early drug development:

• A) High Net Present Value (NPV) and high unmet medical need
• B) Low NPV and high unmet medical need
• C) High unmet medical need and clear understanding of the drug-disease mechanism
• D) High NPV and clear understanding of the drug-disease mechanism
• E) Clear understanding of the drug-disease mechanism and high NPV