Efficient Early Clinical Research to Achieve Clinical Proof-of-Concept Requires Patients

J. Fred Pritchard PhD
Vice President, Global Drug Development
Questions

- What are the latest measures of efficiency in drug development?
- How is early clinical research changing?
- What are some ways of making first-in-human studies more informative and efficient?
- What are some challenges and strategies for engaging patients in early clinical studies?
- What innovations are making early clinical research more efficient and effective?
- What are some challenges in conducting complex early clinical studies in patients?
- Is there globe warming to early clinical research?
New Drug And Biologics Approvals/R&D Spending

Reprinted with Permission: Tufts CSDD: PhRMA 2014 industry Profile
Phase Transition Rates

Tufts CDSS 2014

Clinical Phase Transition Probabilities and Overall Clinical Approval Success Rate*:

- Phase I-II: 59.52%
- Phase II-III: 35.52%
- Phase III-NDA/BLA Sub: 61.95%
- NDA/BLA Sub-NDA/BLA App: 90.35%
- Phase I-NDA/BLA App: 11.83%

*Therapeutic new molecular entities and new therapeutically significant biologic entities first tested in humans, 1995-2007

Hays 2014

Bar charts showing transition rates and overall clinical approval success rates:

- Phase 1 to phase 2: 67% (lead indications), 64% (all indications)
- Phase 2 to phase 3: 39%, 32%
- Phase 3 to NDA/BLA: 68%, 60%
- NDA/BLA to approval: 86%, 83%
- LOA from phase 1: 15.3%, 10.4%
Changing Paradigm

Traditional Paradigm: Phased Approach

- Pre-Clinical
- Phase I
- Phase II
- Phase IIb
- Phase III

Test each scarce molecule thoroughly

Emerging Paradigm: POC / Confirmation Approach

- Pre-Clinical
- Proof of Concept
- Confirm

Regional and Ethnic Differences

Searching for More Efficient Ways of Managing Risk in Drug Development

**Engineered Process**
- Stepwise
- Early studies structured same as later studies – primary objectives and endpoints
- Influenced by “rules-based” regulations

**Preclinical**
- Phase I: safety, tolerance, PK (healthy participants)
- Phase II: dose response (small groups of patients)
- Phase III: safety and efficacy (statistically robust)
- Phase IV: post-approval surveillance
- Filings for new indications

**Adaptive Development**
- Feedback loops to discovery (Translational Medicine)
- Early studies fused with multiple objectives and endpoints
- Influenced by emerging “risk-based” guidances

**Learn**
- Preclinical
  - Human Microdose - PK
  - Early Clinical: safety, tolerance, PK (healthy subjects and patients)
  - Proof-of-Presence
  - Proof-of-Mechanism
  - Proof-of-Concept
  - Dose Response

**Confirm:**
- Safety and efficacy (statistically robust)

**Uptake:**
- Simultaneous global filings
- Post-approval surveillance
- Filings of new indications
What’s Driving Evolution of New Paradigm?

**Clinical Proof-of-Concept is where a new drug acquires real value**

- Increase in novel drugs from discovery research
- More difficult disease states to study and treat
- Greater regulatory expectations on clinical trials
- Need for more informed decisions at clinical Proof-of-Concept
- Increased cost of clinical research
- Regulatory acceptance of adaptive-like study designs
- Expanding universe of new technology applications

**Clinical Proof-of-Concept** is where a new drug acquires real value.
Attrition Rate of NME Due to PK/ADME

NME: New Molecular Entity
PK: Pharmacokinetic
ADME: Absorption, Distribution, Metabolism & Excretion

Nat. Rev. Drug Disc. 2004
Characteristics of an Efficient First-in-Human Study

- Establishes drug does not elicit acute, treatment-limiting adverse events
- Characterizes the ADME properties:
  - Peak exposure
  - Overall exposure
  - Half-life
- Identifies influences for future patient exposure
  - Effect of food for oral dosing
  - Site of administration for Subcutaneous (SC)
  - Timing of dose
- Minimizes time and cost to Proof-of-Concept (POC) step
Efficient First-in-Human Designs

- SAD HS – 1st dose level
- SAD HS – 2nd dose level
- SAD HS – 3rd dose level
- SAD HS – 4th dose level
- MAD HS – 2nd dose level
- MAD HS – 3rd dose level
- MAD HS – 4th dose level
- MAD HS – 5th dose level

Simulate exposure using non-compartmental or compartmental approach

SAD HS = Single Ascending Dose – Healthy Subjects
MAD HS = Multiple Ascending Dose – Healthy Subjects
What Do We Know/Understand Regarding the Target Population?

- Will it be likely the POC population will be on conmeds known to perpetrate DDIs?
- Indicated in obese patients?
  Is meal time important?
- CYP1A Substrate, will smokers receive drug in POC?

**CYP**: Cytochrome P450 Enzyme  
**POC**: Proof-of-Concept  
**DDI**: Drug-Drug Interaction
Integrate Intrinsic/Extrinsic Factors into SAD/MAD

- SAD HS – 1st dose level
- SAD HS – 2nd dose level
- SAD HS – 3rd dose level
- SAD HS – 4th dose level
- MAD HS – 1st dose level
- MAD HS – 2nd dose level
- MAD HS – 3rd dose level
- MAD HS – 4th dose level
- MAD HS – 5th dose level

Simulate exposure using non-compartmental or compartmental approach

Patient population?

Intrinsic factors (e.g. obese, elderly?)

Extrinsic factor (e.g. smoking, DDI)

X-Over Food Effect

Time
Integrate Intensive Electrocardiographic (ECG) Monitoring for Early Cardiovascular Signal

Each Cohort
- ECG Extractions
- Single 24hr Holter monitoring session
- Three triplicate baseline timepoints
- 6-9 triplicate post-dose timepoints
- Proactively plan for extended supine periods
SAD Allows for Evaluation of Potentially Supra-Therapeutic Exposure

ΔΔQTcF: Fridericia corrected QT interval

msec: millisecond

Δ: Greek letter ‘Delta’ represents change from baseline, change from placebo
Important “Proofs” in Early Clinical Research

- **Proof-of-Presence**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept**
  - Is there a sufficient signal that the drug favorably impacts the disease with acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$

**Pharmacokinetics**
- Tissue concentrations
- Healthy subjects (HS) or patients

**Biomarkers reflecting**
- Target engagement
- Toxicity (liver, kidney effects)
- Healthy subjects or patients

**Biomarkers reflecting**
- Impact on disease
- Toxicity (liver, kidney effects)
- Patients
Early Signals of Clinical Safety and Efficacy are the Key to Applied Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

Patients
- Small number
- Stable disease
- Minimal confounding treatments
- Appropriately motivated

Investigators / Clinical Trial Units
- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global GCP standards
- Ethical
Access to Patient/Special Populations and Specialists

Special Populations
- Renal Impairment
- Hepatic Impairment
- Elderly
- Women
- Pediatric/Adolescent

Patient Populations
- Diabetes Mellitus
- Asthma
- Chronic Obstructive Pulmonary Disease (COPD)
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus (SLE)
- Psoriasis
- Alzheimer’s Disease
- Schizophrenia
- Depression
- Cancer
- Hypertension
- Hyperlipidaemia
- Infectious Diseases
The Challenge of Recruiting Patients to Early Clinical Studies

- Disease Prevalence
- Alternative Treatments
- Benefit to the Patient

**Otherwise Healthy Patient**

**Disease Prevalence**

**Benefit to the Patient**

- Usually no drug benefit
  - Not dosed long enough
  - Optimal dosing not established
- Risks to patient unknown
- Can negatively impact health insurance coverage for their disease
- Financial compensation
  - Sometimes allowed like HS studies
- Appeal to altruism
- Single disease
- Withdrawal from current treatment
- Number and type of co-medications
- Gender, age, race and ethnicity
Early Clinical Research Requires Resources Dedicated to Research
Complex sample collection schedules and processing procedures

Example: First-in-Patient study – 14 tests, 7 labs

Lab D
Pharmacogenomic assay

Lab B
Clinical chemistry

Lab G
Future proteomics

Lab C – LC/MS/MS assay pathophysiological substrate and product

Lab E
Target enzyme assays

Lab F
Stimulated cell assay

Lab A
LC-MS/MS assay parent drug and metabolites

Lab B
Urinalysis

Heparinized blood

Plasma

Freeze

Urine

Non-coagulated blood

Serum

WBCs

Add stabilizer

Add stabilizer

Tissue Biopsy
A Perfect Scenario for Fast-to-Patient Strategy

- Single Ascending Dose (SAD) Study
- Novel Dipeptidyl Peptidase-4 (DPP4) Inhibitor in Mild Diabetic Patients
- No other drugs

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Patients</th>
<th>Treatment Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P1</td>
</tr>
<tr>
<td>1</td>
<td>N = 5</td>
<td>PLA 25 mg</td>
</tr>
<tr>
<td>2</td>
<td>N = 5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>N = 5</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Patients</th>
<th>Treatment Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P’1</td>
</tr>
<tr>
<td>4</td>
<td>N = 5</td>
<td>PLA 50 mg</td>
</tr>
<tr>
<td>5</td>
<td>N = 5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>N = 5</td>
<td>50 mg</td>
</tr>
</tbody>
</table>
Results of SAD Study in Mild Diabetic Patients: Early Evidence of Efficacy

**Drug Plasma Concentration**

- AMG 222 Concentrations (ng/mL)
- Time (h): 0, 1, 2, 4, 6, 12, 24
- Lower limit of quantitation

**Percent DPP4 Inhibition**

- Percent (%) Inhibition in DPP-IV Activity
- Time (h): 0, 1, 2, 4, 6, 12, 24
- Placebo

**Glucagon-Like Peptide-1 Concentration**

- GLP-1 Concentrations (pM)
- Time (h): 0, 1, 2, 4, 5, 6, 11, 12, 24, 25, 26
- Lower limit of quantitation

**Glucose Concentration**

- Glucose Concentrations (mg/dL)
- Time (h): 0, 1, 2, 4, 5, 6, 11, 12, 24, 25, 26
- Placebo

F=4-8%

Good Activity

**X**

- Drug Plasma Concentration

- Percent DPP4 Inhibition

- Glucagon-Like Peptide-1 Concentration

- Glucose Concentration
Innovations in Early Clinical Research

- New Biomarkers of drug action and effect
  - Imaging (SPECT, functional MRI/PET), microRNAs, tracking genetic changes in tumors or microbiome, digital high resolution EEGs and ECGs

- Patient Recruitment
  - Social media tools to recruit patients
  - Electronic patient records to quickly assess impact of I/E criteria on recruitment and suitability of patients for a study

- Data Acquisition
  - Digital capture of data – real-time review and monitoring for quality
  - Video for remote viewing of study conduct in real time
  - Tablets and smart phones to capture patient data
  - Electronic tracking to confirm study compliance

- Data Analysis
  - Data repositories that allow comparison across studies and advanced modelling to predict drug response in specific patient settings
Global Clinical Pharmacology Unit Networks

- Most patient needs in early clinical research cannot be met by a single center
- Increasing the number of sites has its own challenges
- Need to evolve similar partnering and alliance models among groups of clinical pharmacology units
  - Work to same quality standards (undergo common systems Quality Assurance audits)
  - Coordinated through a group which also brings in other study services as protocol preparation, bioanalysis, pharmacokinetics, data management and statistics, clinical study report preparation
Celerion Locations and Partner Sites
A Global Network of Specialty Clinics and Labs
# Examples of networks and therapeutic clusters

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Celerion Site</th>
<th>External Site Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes / Obesity (asthma, COPD, cystic fibrosis)</td>
<td>Phoenix, Lincoln</td>
<td>Supporting networks in North America (NA), Europe, South Korea and Singapore</td>
</tr>
<tr>
<td>Respiratory and Inflammatory (asthma, COPD, cystic fibrosis)</td>
<td>Belfast</td>
<td>Strong network in UK and Germany (therapeutic cluster) Current US study at Temple Lung Center</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Belfast, Phoenix</td>
<td>Strong network in UK and Germany (therapeutic cluster)</td>
</tr>
<tr>
<td>Cardiovascular (hypertension, hypercholesterolemia, hyperlipidemia, thrombosis)</td>
<td>Belfast, Phoenix</td>
<td>Strong networks in Europe and Korea (therapeutic cluster)</td>
</tr>
<tr>
<td>Oncology (blood, breast, colon, lung, pancreatic, ovarian, skin)</td>
<td>Belfast, Phoenix</td>
<td>Strong networks in Korea (therapeutic cluster) Good access in Europe Major academic cancer centers dominate NA</td>
</tr>
<tr>
<td>Renal or Hepatic Insufficiency</td>
<td>Belfast</td>
<td>Strong network in US and Europe</td>
</tr>
<tr>
<td>Rheumatoid Diseases (RA, OA, SLE)</td>
<td>Belfast</td>
<td>Strong networks in Korea and in Europe (therapeutic cluster)</td>
</tr>
<tr>
<td>CNS /Neurology (Alzheimer’s, schizophrenia, anxiety, depression, pain, Parkinson’s, convulsion)</td>
<td>Belfast</td>
<td>Collaborative neuroscience network in US Good access in Europe and Korea</td>
</tr>
<tr>
<td>Infectious Disease (HIV, HCV, HSV, influenza, bacterial)</td>
<td></td>
<td>HCV – Europe and Korean sites (Asian phenotypes), Influenza/bacterial: access in Europe and Korea</td>
</tr>
</tbody>
</table>
Reasons for Performing Clinical Pharmacology Studies in Asia-Pacific Region

Market Drivers

1. Access to patients for early clinical assessment of safety, PK and signals of efficacy and dose response
2. Bridging PK and PK/PD studies to support registrations of drug products in Asian markets
3. Support First-in-Human assessments of drugs discovered and developed in Korea, Singapore, China, Japan and other Asian nations

Operational Factors

1. Modern, well equipped clinical trial centers at major medical centers with ready access to many patient populations
2. Some regulatory environments similar to North America and Europe
3. Well-trained scientific and medical staff that can communicate in English

Needs

1. Pharma companies need studies to support products for Asian markets
2. Asian clinical trial centers need access to global pharma study opportunities and best operating practices for running efficient operations
South Korea Has Developed the Resources Required to Support Early Clinical Research
## Regulatory Environment in Five Asia/Pacific Countries

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>China</th>
<th>South Korea</th>
<th>Singapore</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory Review Time</strong></td>
<td>No queries – 30 days after CTN submission</td>
<td>11 Months</td>
<td>30-60 Days</td>
<td>15-30 Days</td>
<td>No approval for healthy subject studies</td>
</tr>
<tr>
<td><strong>Ethics / IRB Review Time</strong></td>
<td>Variable</td>
<td>60 Days</td>
<td>2-4 Weeks</td>
<td>1-4 Weeks</td>
<td>12-16 Weeks (patients)</td>
</tr>
<tr>
<td><strong>Parallel or Sequential</strong></td>
<td>Parallel</td>
<td>Sequential</td>
<td>Parallel</td>
<td>Parallel</td>
<td>Clinical Trial Notification acknowledged in days</td>
</tr>
<tr>
<td><strong>Clinical Trial Centers</strong></td>
<td>Hospital and CRO-owned</td>
<td>SFDC-accredited CTCs</td>
<td>15 Hospital-based CTCs</td>
<td>1 Pharma-owned and 3 Hospital CTCs</td>
<td>5 Academic hospital clinics</td>
</tr>
<tr>
<td><strong>Other Comments</strong></td>
<td>Government funding new CTCs</td>
<td>Difficult to ship samples out of China</td>
<td>MFDS built on US FDA model</td>
<td>Translational medicine focus</td>
<td>Less CMC and preclinical safety</td>
</tr>
</tbody>
</table>
## Audit Results of 7 Asian CTCs 2013-2014

<table>
<thead>
<tr>
<th>Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 CTC (facilities)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Processing/Sample Management</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Set Up, Execution, Logistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI Oversight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy (including Security)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data Management</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality Control (inc. Documents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment (Calibration, Maintenance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computer System Validation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information Technology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archives / Document Storage (Security)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC Facility and Security</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCP/DCP and Testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality Systems (SOPs &amp; Policies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Document Process</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality Assurance (QA/QI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPA Process</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC Organizational Chart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff Qualification Records (CVs, JDs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff Training and Records</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vendor Management</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory Inspection History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accreditations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Inadequate or missing**
- **Work needed to pass global audit**
- **Some changes needed to pass global audit**
- **Acceptable for global audit**
Quality

- Most sites never had a full systems audit against global standards/ expectations
- Variability across sites in areas of strength and weakness
- Strengths: Across all sites were Phase I CTC facility and Security, Principal Investigator (PI) Oversight and Institutional Review Board (IRB) or Ethics Committee.
- Weaknesses: Staff Qualification records (6 of 7 sites), IT and Computer System Validation (4 of 7 sites), QA (4 of 7 sites), Vendor Management (4 of 7 sites), Staff Training Records (4 of 7 sites), Pharmacy (3 of 7 sites) and CAPA process (3 of 7 sites)
Five Key Elements of Clinical Success in Applying Translational Medicine

- **Expertise:** Scientific and medical staff with the portfolio of skills to design, conduct and interpret complex clinical studies.

- **Experience:** Leveraging knowledge gained from conducting early clinical pharmacology studies with high density sampling.

- **Facilities and Equipment:** Modern confinement clinics and laboratories equipped with innovative technologies to meet the varying and evolving demands of early clinical research.

- **Access to Patients:** Recruiting the right participant or patient to meet the needs of specific study designs in a timely and ethical way.

- **Access to Biomarkers:** Leveraging capabilities resident within the participating clinics or laboratories or with qualified vendor labs to create the appropriate palate of tests to ascertain the drug’s effect in humans.
Bridging Strategy

Start design of CPoC study first
- What is “Proof”? Endpoints?
- What patients? How many?

How to get to CPoC?
- What can I do in healthy participants?
- Are biomarkers available?
- Develop novel biomarkers:
  - Biochemical assays
  - Imaging and imaging agents
  - MicroRNA panels
- Would microtracer studies be valuable?
- Can PK/PD modeling be applied?

What preclinical work is needed to support the early clinical program?
Brief Answers to Questions

- Latest metrics of efficiency in clinical research
  - 10-15% of drugs entering clinical trials make it to market

- How is early clinical research changing?
  - **Focus on Clinical Proof-of-Concept – fail early**

- How are traditional FIH studies changing?
  - **Fusion studies answering multiple questions on safety, PK, DDIs**

- What are some challenges and strategies for engaging patients early clinical studies?
  - **Patient benefits vs risk**
  - **Regional differences, patient networks**

- What are some challenges in conducting early clinical research studies in patients?
  - **Access to biomarkers, specialty equipment and specialist researchers**
  - **Sample logistics**

- What innovations are making early clinical research more efficient and effective?
  - **Digital communications, real-time acquisition and access to data, apply complex analysis and modeling, new biomarkers**

- Why is there increasing attention to Asia-Pacific region in early clinical research?
  - **Access to patients, modern clinical trial centers, educated staff, rapidly emerging biotechnology industry, large market**