Critical Path for Parkinson’s
A consortium aimed at accelerating treatments for PD

September 14, 2015
Agenda

- Welcome – Arthur Roach/Diane Stephenson
- Current needs in PD drug development...why now?
- Genesis of Critical Path for Parkinson’s (CPP)
  - Parkinson’s UK
  - Critical Path Institute & CAMD
- Rationale and focus of CPP
- CPP Stakeholders, Engaging the Broader Community
- Consortium Overview and Governance
- Membership categories
- Upcoming Meetings and Logistics
- Questions? – All
The Science of Parkinson’s Disease Drug Discovery is Advancing yet, the Tools for Clinical Development are Lagging

- To date, multimillion dollar investments have aimed to advance disease modifying therapies for PD without success

- The science is continuing to develop and new, promising therapeutic opportunities are emerging

- Early intervention is key and accurate diagnosis at early stages is challenging; often patients note that non-motor features of PD are most burdensome early in disease

- Yet, challenges in clinical trial testing persist:
  - The current trial paradigm is slow, large and expensive
  - High failure rate with little reason to expect a different outcome

Biomarkers and quantitative models of disease progression are essential to achieve near-term hopes for needed therapies
Patients Voice on the Need for Early Treatment

• Parkinson’s UK is the world’s largest member-based organisation for people with the condition (30,000 members across the UK)

• 80% of budget is dedicated to direct work with persons living with Parkinson’s

• 2013-4 survey of patient’s needs from research highlighted strong needs for BOTH new symptomatic treatment AND stopping/slowing progression

STopping PROGRESSION AT AN EARLY STAGE was the strongest desire of persons with Parkinson’s.

This will only be possible through successful trials in early stage patients.
Recent publications emphasize the need for patient stratification tools targeting early PD.

**Original Investigation**

Cerebrospinal Fluid Patterns and the Risk of Future Dementia in Early, Incident Parkinson Disease

David C. Bäckström, MD; Magdalena Eriksson Domellöf, PhD; Jan Linder, MD, PhD; Bob Olsson, PhD; Annika Öhrfelt, PhD; Miles Trupp, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD, PhD; Lars Forsgren, MD, PhD

**ALZFORUM**

Biomarkers Differentiate Parkinsonian Diseases and Forecast Decline

21 Aug 2015  It can be hard to tell one parkinsonian disorder from another based on clinical tests alone. Though their underlying pathologies differ, these degenerative brain disorders all affect movement, and at early stages they resemble one another. Parkinson’s disease (PD) looks like multiple

**JAMA Neurol.** doi:10.1001/jamaneurol.2015.1449  Published online August 10, 2015.

- PPMI
- PDBP (Parkinson’s disease and controls)
- PARS (Parkinson’s disease, controls, and at-risk)
- 23andMe (Parkinson’s disease and controls)
- LABS-PD (SWEDD and Parkinson’s disease)
- Penn-Udall (Parkinson’s disease)

**Diagnosis of Parkinson’s disease on the basis of clinical and genetic classification: a population-based modelling study**

Mike Nalls, Cory Y. Mellon, Jacqueline Rix, Shelley Eberly, Samantha J. Hutton, Katrina Gwinn, Margaret Sutherland, Maria Martinez, Peter Heutink, Nigel M Williams, John Hardy, Thomas Gasser, Alexis Bonje, T'Ryan Price, Aude Nicolas, Margaux P. Keller, Osama Melehy, J Raphael Gibbs, Alice Chen-Pitkin, Erican Suh, Christopher Lehrer, Massimo S. Frideres, Mark Mapstone, Howard J. Fédoroff, Alexis J. Noyce, How Morini, Viviana M. Van DerKruik, Doinel Weintraub, Cyrus Zabetian, Dena G. Hernandez, Suzanne Lesage, Meghan Mullins, Emily D. Brant Conley, Carrie A. M. Northover, Mark Frasier, Ken Marek, Aaron F. Day-Williams, David J. Stone, John P. Ioannidis, Andrew B. Singleton, for the Parkinson’s Disease Biomarkers Program and Parkinson’s Progression Markers Initiative investigators

**Prediction probability of PD from 5 independent data sources**

Nalls et al., Lancet Neurol 2015
Parkinson’s UK – Who Are We?

- Membership-based charity – 35,000 members in England, Scotland, Wales and Northern Ireland
- 2015 budget: $40M
  - $8M Research – planned increase to $16M by 2020
  - $32M Direct patient support
  - 120 staff in London HQ, 250 in the regions
- Our 2015-2019 strategy has three themes:
  - Taking Control
  - Better Services
  - Better Treatments and a Cure
- Strong involvement of people with Parkinson’s in our research.
Research Strategy – New Paradigm

- MORE novel and better treatments FASTER
- Working across all stages of research and development to impart urgency and focus
- Working in collaboration to bring everyone’s strengths to Parkinson’s research and development
  - Some non-profit models: Michael J Fox Foundation, Alzheimer’s Research UK, ALS Therapy Development Foundation, National Multiple Sclerosis Society, Cystic Fibrosis Society...
  - Unique implementation: each charity according to its situation, budget, values, etc.
Parkinson’s UK and CAMD

- Member of CAMD
- Big Data meeting, London May 2014
- More can be done in PD, especially for early trials
- How to construct an initiative that brings more resources and focus to Parkinson’s issues?
  - Expertise
  - Industry participation
  - Deep knowledge of Parkinson’s from patients and neurologists
  - Patient data from academic and industry studies in early disease
  - Guarantee of adequate, stable funding
Parkinson’s UK and Today’s Proposal

- **Spin-out from CAMD**
  - Preserves best of CAMD (true collaboration!)
  - Stronger and dedicated focus on PD issues
  - New valuable deliverables for drug development in PD
  - Increase in resources: **guarantee of $2M from Parkinson’s UK, options for more**

- **Critical Success Factors**
  - Industry partners
  - Data sets (including academic studies)
  - Retaining know-how of CAMD and C-Path
  - Recreate success from Alzheimer’s disease
  - Focus on regulatory science and innovation
### Critical Path Institute Consortia

<table>
<thead>
<tr>
<th>Consortium Name</th>
<th>Description</th>
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<tr>
<td>Coalition Against Major Diseases</td>
<td>Focusing on diseases of the brain</td>
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<tr>
<td>Critical Path to TB Drug Regimens</td>
<td>Testing tuberculosis drug combinations</td>
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<td>Multiple Sclerosis Outcome Assessments Consortium</td>
<td>Measuring drug effectiveness in MS treatment</td>
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<td>Polycystic Kidney Disease Consortium</td>
<td>New imaging biomarkers</td>
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<tr>
<td>Patient-Reported Outcome Consortium</td>
<td>Measuring drug effectiveness</td>
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<td>Electronic Patient-Reported Outcome Consortium</td>
<td>Electronic capture of drug effectiveness</td>
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<td>Predictive Safety Testing Consortium</td>
<td>Drug safety</td>
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<tr>
<td>Coalition For Accelerating Standards and Therapies</td>
<td>Data standards development</td>
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<tr>
<td>International Neonatal Consortium</td>
<td>Developing safe and effective therapies for neonates</td>
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<tr>
<td>Duchenne Regulatory Science Consortium</td>
<td>Developing drug development tools for Duchenne Muscular Dystrophy</td>
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- Biomarkers
- Clinical Outcome Assessment Instruments
- Clinical Trial Simulation Tools
- Data Standards
- In Vitro Tools

Ten global consortia collaborating with 1,300+ scientists and 61 companies.
CAMD Successes in Alzheimer’s Disease

- Therapeutic area specific clinical data standards (CDISC)
- Unified clinical trial database of Alzheimer’s disease clinical trials available to qualified researchers
- First imaging biomarker qualified by EMA for early AD clinical trials
- First regulatory endorsed model based clinical trial simulation tool for Alzheimer’s disease clinical trials
- Letters of support for the use of imaging and CSF biomarkers in early AD trials
CAMD successes in AD pave the way for PD

Development of a unified clinical trial database for Alzheimer’s disease

Jon Neville, Steve Kopko, Steve Broadbent, Enrique Avilés, Robert Stafford, Christine M. Solinsky, Lisa J. Bain, Martin Cisneroz, Klaus Romero, Diane Stephenson, for the Coalition Against Major Diseases

Coalition Against Major Diseases (CAMD), Critical Path Institute, Tucson, AZ, USA

The Future Is Now: Model-Based Clinical Trial Design for Alzheimer’s Disease

K Romero, K Ito, JA Rogers, D Polhamus, R Qin, D Stephenson, R Mohs, R Lalonde, V Sinha, Y Wang, D Brown, M Isaac, S Vamvakas, R Hemmings, L Pani, LJ Bain, B Corrigan, for the Alzheimer’s Disease Neuroimaging Initiative for the Coalition Against Major Diseases

Alz. & Dem. doi: 10.1016/j.jalz.2014.11.005. [Epub ahead of print]

Clin. Pharm. & Ther. 97(3): 210-4
Parkinson’s Disease Drug Development is Positioned to Advance and Follow the Path of AD

- Large, global, clinical and observational datasets are available
- Increased understanding of disease progression and sub-clinical syndromes
- Emerging biomarkers and available technologies and biospecimens
Successful Development of a Disease Modifying Therapy in PD Will Require Doing Things Differently

Traditional Drug Development Approach

Reliance on limited information and experience based on:

- A small set of KOLs
- Small, possibly outdated, datasets
- Last paper bias

Data and Quantitative Model Based Drug Development Approach

A modern approach based on:

- Integrated global datasets including relevant populations and endpoints
- Quantitative models of disease progression, patient population and endpoint behavior
Precompetitive Data Sharing as a Catalyst to Address Unmet Needs in Parkinson’s Disease

Diane Stephenson\textsuperscript{a,*}, Michele T. Hu\textsuperscript{b}, Klaus Romero\textsuperscript{a}, Kieran Breen\textsuperscript{d}, David Burn\textsuperscript{e}, Yoav Ben-Shlomo\textsuperscript{f}, Atul Bhattaram\textsuperscript{g}, Maria Isaac\textsuperscript{h}, Charles Venuto\textsuperscript{i}, Ken Kubota\textsuperscript{j}, Max A. Little\textsuperscript{k}, Stephen Friend\textsuperscript{l}, Simon Lovestone\textsuperscript{c}, Huw R. Morris\textsuperscript{m}, Donald Grosset\textsuperscript{n}, Margaret Sutherland\textsuperscript{o}, John Gallacher\textsuperscript{p}, Caroline Williams-Gray\textsuperscript{q}, Lisa J. Bain\textsuperscript{r}, Enrique Avilés\textsuperscript{a}, Ken Marek\textsuperscript{s}, Arthur W. Toga\textsuperscript{t}, Yafit Stark\textsuperscript{u}, Mark Forrest Gordon\textsuperscript{v} and Steve Ford\textsuperscript{w}

Acknowledgements: Lisa Bain, Karl Kieburtz, Sue Dubman, Kieran Breen, Katie Le Blonde, FDA colleagues Vikram Sinha, Richard Moscicki
Maximizing Use of Existing Data to Create New Clinical Development Tools

- **Existing Studies**
  - Data acquisition and harmonization
  - Modeling

- Integrated standardised database
  - **NATURAL HISTORY (COHORT) STUDIES** (early PD)
  - **RCT STUDIES** (early PD)

- Clinical Trial Simulation Tool
  - Drug effects
  - Drop-out rates
  - Placebo effect

**Comprehensive in silico model of early PD progression**
The Parkinson’s UK/C-Path PD Initiative has access to the global datasets and developed a roadmap to meet the outlined deliverables.
The Parkinson’s UK/C-Path PD Initiative is a Coordinated Approach, that Combines Data Standards, Modeling and Regulatory Strategy

• The 3 year project (stage 1) will deliver:
  1. Unified clinical trial database of >6000 subjects
  2. EMA qualified prognostic imaging biomarker
     • EMA letter of support for imaging biomarker
  3. CDISC v2.0 PD standards
  4. Model-based clinical trial enrichment tool

• Biomarker: DAT Imaging as an Enrichment biomarker for early onset PD Clinical Trials
  - EMA path

• Disease Model: PD Disease Progression Model
The Parkinson’s UK/CAMD PD Initiative is a Coordinated Approach, that Combines Data Standards, Modeling and Regulatory Strategy

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<tr>
<th>Data Track</th>
<th>Science Track</th>
<th>Regulatory Track</th>
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<tr>
<td><strong>STAGE 1</strong></td>
<td></td>
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<tr>
<td>PD data standards update</td>
<td>Disease progression model</td>
<td>FDA/EMA endorsement of model-based clinical trial enrichment strategy</td>
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<tr>
<td>Integrated database</td>
<td>Packaged as a model-based clinical trial enrichment platform</td>
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<tr>
<td><strong>STAGE 2</strong></td>
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<tr>
<td>Standards revisions based on experience with clinical trial data</td>
<td>Drug-disease-trial model</td>
<td>FDA/EMA endorsement of clinical trial simulation tool</td>
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<td>Expanded database with clinical trial data</td>
<td>Packaged as a clinical trial simulation platform</td>
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<tr>
<td><strong>STAGE 3</strong></td>
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<td>Standards revisions based on experience with wearable devices data</td>
<td>Expanded drug-disease-trial model that includes wearable devices</td>
<td>FDA/EMA endorsement of updated quantitative drug development platforms</td>
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<td>Expanded database with wearable devices</td>
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The 3 year stage 1 project will deliver:
- Unified clinical trial database of >6000 pts
- EMA qualified prognostic imaging biomarker
- PD CDISC standards
- Model-based clinical trial enrichment tool

Future stages:
- PD Clinical Trial Simulation Tool
- Wearable devices/remote technologies
- Others can be added
Work-plan is ready to proceed: Data Sources for Integration

• An integrated and standardized database of patient-level PD data from the following sources:
  - PPMI *
  - PRECEPT *
  - Oxford DC
  - Tracking PD
  - CamPaIGN

*Critical Path Institute has acquired patient level data
The Parkinson’s UK/CAMD PD Initiative Will Enable PD Drug Development in the First Year and Includes Significant Milestones Throughout Stage 1 (3 years)

**STAGE 1**

- Year 1: Updated PD CDISC data standards (2017 FDA mandate)
- Year 2: EMA-qualified enrichment biomarker for PD clinical trials
- Year 3: Integrated “natural history” + RCT database

**STAGES 2 and beyond ($ nyd)**

- Year 4: Expand Integrated “natural history” + RCT database
- Year 5: FDA and EMA-endorsed quantitative clinical trial simulation platform for PD studies
  - Integrated “natural history” + RCT + wearable devices database
CPP Proposed Governance Structure

Critical Path Institute

Parkinson’s UK

COORDINATING COMMITTEE

Executive Director

Co-Director

Co-Director

All Regular members

All Non-voting Members

Company 1

Company 2

Company 3

Working Group 1
  e.g. DAT Biomarker

Working Group 2
  TBC

Working Group 3
  TBC

University 1

University 2

University 3
Roles & Responsibilities of CPP Coordinating Committee

- Strategic planning
  - Alignment with CPP mission
  - Members volunteering to drive the project
- Establishing workgroups, including recommending participants
- Reviewing progress of workgroups
- Providing input on manuscripts for publication and regulatory submissions (e.g. white papers, briefing packages, etc.)
- Communication and Coordination with other PD initiatives
- Electing CPP Co-Chairs and setting terms of service
- Voting on accepting new members
- Recommend new work streams, particularly beyond year 3 and other funding streams
CPP Membership Categories

• Managing Members
  - Parkinson’s UK
  - Critical Path Institute

• Regular Members
  - Industry - paying member; vote in Coordinating committee
  - Academic institutions contributing important data (no fee)
  - Access to all data
  - Tiered payment structure based on revenue of member revenue ($50k/yr or $10k/yr)

• Nonvoting Members
  - Academic key experts, patient stakeholder groups
  - Nonpaying member, nonvoting
  - Access to data on case by case basis

All categories asked to sign confidentiality agreement
CPP Membership Categories

• Managing Member (Critical Path Institute & Parkinson’s UK)

  - Obligations:
    - Managing the execution of the Research Plan as outlined in the work plan
    - Providing foundation funding for Research Plan
    - Negotiating and signing on behalf of the Consortium certain Data Contribution Agreements and other agreements as required for the Research Plan
    - Preparing and presenting for vote to the coordinating Committee proposals for specific new activities or other changes to the Research Plan
    - Managing Consortium membership issues including the addition of Members joining, collection of applicable membership fees, etc.

  - Benefits:
    - One vote on the Coordinating Committee
    - Access to and right to use the results of the Research Plan
    - Access to data collected for use in the Research Plan
    - The right to propose to the Coordinating Committee modifications to the Research Plan and to participate in all prioritization and strategy discussions of the Coordinating Committee
CPP Membership Categories (cont.)

• **Regular Member**
  
  - Obligations:
  
    • Payment of Annual Fees
      
        - Industry / For-Profit organization
          
            • Annual Fee: $50,000 (if annual revenue is **above** $500M)
            
            • Annual Fee: $10,000 (if annual revenue is **below** $500M)
        
        - Non-profit organization / Academic institution
          
            • Annual Fee: waived, if contribution of unique data or expertise is provided; needs approval via Coordinating Committee vote
  
  - Benefits:
    
    - One vote on the Coordinating Committee
    
    - One vote in election of Member’s Co-director
    
    - Access to and right to use the results of the Research Plan
    
    - Access to data collected for use in the Research Plan
    
    - The right to propose to the Coordinating Committee modifications to the Research Plan and to participate in all prioritization and strategy discussions of the Coordinating Committee
• **Non-voting Member**

  - **Obligations:**
    - To assist in execution of the Research Plan by contributing data, expertise, in-kind knowledge

  - **Benefits:**
    - No vote in the Coordinating Committee
    - No access to data collected for use in the Research Plan
    - Access to and right to use the results of the Research Plan
    - The right to propose to the Coordinating Committee modifications to the Research Plan and to participate in all prioritization and strategy discussions of the Coordinating Committee

  - **Annual Fee:**
    - waived
Value added propositions and outcomes:

CAMD members:
• Disease models for Parkinson’s Disease based on integrated data that would not be otherwise available
• New publications; leadership in field of regulatory science in Parkinson’s
• Data & model needed to influence clinical study design
• Builds on leadership role in AD disease modeling w/ CAMD
• Infrastructure in place for successful regulatory submissions
• Spares internal resources required to build models
• Global regulatory endorsement of drug development tools
• Alliances with Key opinion leaders globally

Parkinson’s UK:
• Enable drug development for PD patients with implications across multiple targets and industry stakeholders
• Publications; making a tangible difference for patients

Regulatory Agencies:
• Builds on leadership role in AD disease modeling w/ FDA and EMA
• Infrastructure in place for successful regulatory paths
• Regulatory endorsed tools facilitate regulatory review of NDAs
Upcoming Meetings and Logistics

- **Additional CPP prelaunch teleconferences**
  - September 14, September 28

- **CPP business meeting in conjunction with CAMD annual meeting**
  - October 14th, noon – 5PM plus dinner, Marriott Pooks Hill, Maryland

- **CPP launch**
  - October 15th, FDA

- **NEXT STEPS**
  - CPP membership agreement to be signed by interested members
    
    **TARGET DATE, by October 15?**
CPP Potential Stakeholders & Members

• Co-directors
  - Parkinson’s UK
  - C-Path
• Regulators (FDA and EMA)
• Academic key opinion leaders
• Data scientists (CDISC)
• Other Governmental Organizations
  - NINDS
• Industry
  - Large pharmaceutical companies
  - Small companies
• C-Path Staff/regulatory consultant(s)
• People with PD
• PD Advocacy Organizations

* Voting members will weigh in on strategy and other fiscal decisions
CAMD’s PD regulatory path paves the way for near term successes

FDA Gives a Nod for Alzheimer's and Parkinson's Biomarkers

03 Apr 2015  In the age of the Internet, don’t you love it when you get a real letter? Especially a letter

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 16, 2015

ATTN: Diane Stephenson, Ph.D.
Executive Director, Coalition Against Major Diseases (CAMD)
Critical Path Institute
1730 E River Rd.
Tucson, Arizona 85718

Subject: Biomarker Letter of Support

Dear Dr. Stephenson:

We are issuing this Letter of Support to the Critical Path Institute’s Coalition Against Major Diseases (CAMD) to encourage the further study and use of molecular neuroimaging of the dopamine transporter (DAT) as an exploratory prognostic biomarker for enrichment in trials for Parkinson’s disease (PD).

Sincerely,

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration