Linking clinical neuropsychiatry and quantitative neurobiology

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Background

- Neuropsychiatric drug discovery has almost completely stalled in the past years
- Both psychotic and affective disorders still present significant issues
  - speed and level of treatment response, relapse, resistance, compliance, side-effect profile etc. remain major unmet needs
- Treatments for other aspects of neuropsychiatry, e.g. cognitive dysfunction, have only minimal effect
- There are no licensed / approved treatments for neuropsychiatric disorders associated with dementia
- Many of the patient groups are growing in size with the aged population increasing.
- Effective neurodegenerative retardation could exacerbate these scenarios

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Need for public-private collaboration

- Breakthroughs in psychiatric drug discovery have occurred almost entirely serendipitously
- Understanding is usually post hoc rather than from hypothesis
- There are a number of explanations and contributory factors but:

Diagnosis of neuropsychiatry conditions is still based on *qualitative* assessment of symptoms, defined by convention, rather than *quantitative* analysis of aberrant biology

Truism: Drugs work on biological substrates not symptoms

- Consequently, there is a pressing need to establish a more quantitative framework to support treatment, research and drug discovery

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Pre-competitive nature

The scale of the problem is too large to be address by individual researchers or companies. To address these challenges a pre-competitive research effort is needed including:

- Pharmaceutical industry scientist experts in drug discovery
- Academic investigators with neuropsychiatric research experience
- Hospitals, clinical research centers, and practicing physicians with access to patients
- Patient, and Patient organizations, engagement in collection of clinical data, genetic information and biosamples
- Biotechnology and diagnostics company expertise in assay development, delivery and analysis
- Regulatory authorities
- Health care payers and economists

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Objectives of the full project

- Establish a quantitative biological battery to asses subjects in an unbiased manner both clinically and by homology pre-clinically
- Target one or more traditional symptom domains (e.g. psychosis) identifiable in two, or more, patient groups for comparison (e.g. dementia and schizophrenia)
- By post-hoc analysis identify amongst other objectives:
  - A minimal diagnostic set and rational criteria for stratification
  - Causal relationships with underlying biological substrates
  - Parameters for reverse translation to pre-clinical studies
- Facilitate the initiation pre-clinical studies utilising these new learnings

Project structured as 3 + 2 years. Option to grow in Phase 2 if strong, focused «Pilot» data can be achieved in Phase 1

Expected impact on the R&D process

- **A successful project is expected to advance neuropsychiatric research, clinical practice and drug development by:**

- Establish that quantitaive biological parameters can be used to effectively stratify psychological patient groups in at least one symptom domain
- Provide a starting point the standaristion of proceedures
- As a consequence validate parameters, identify systems, suggest manipulations that can be back translated to pre-clinical studies
- In turn this will provide a template for forward translation of novel therapeutics with pre-validated biomarkers and stratifcation tools for a specific target patient population

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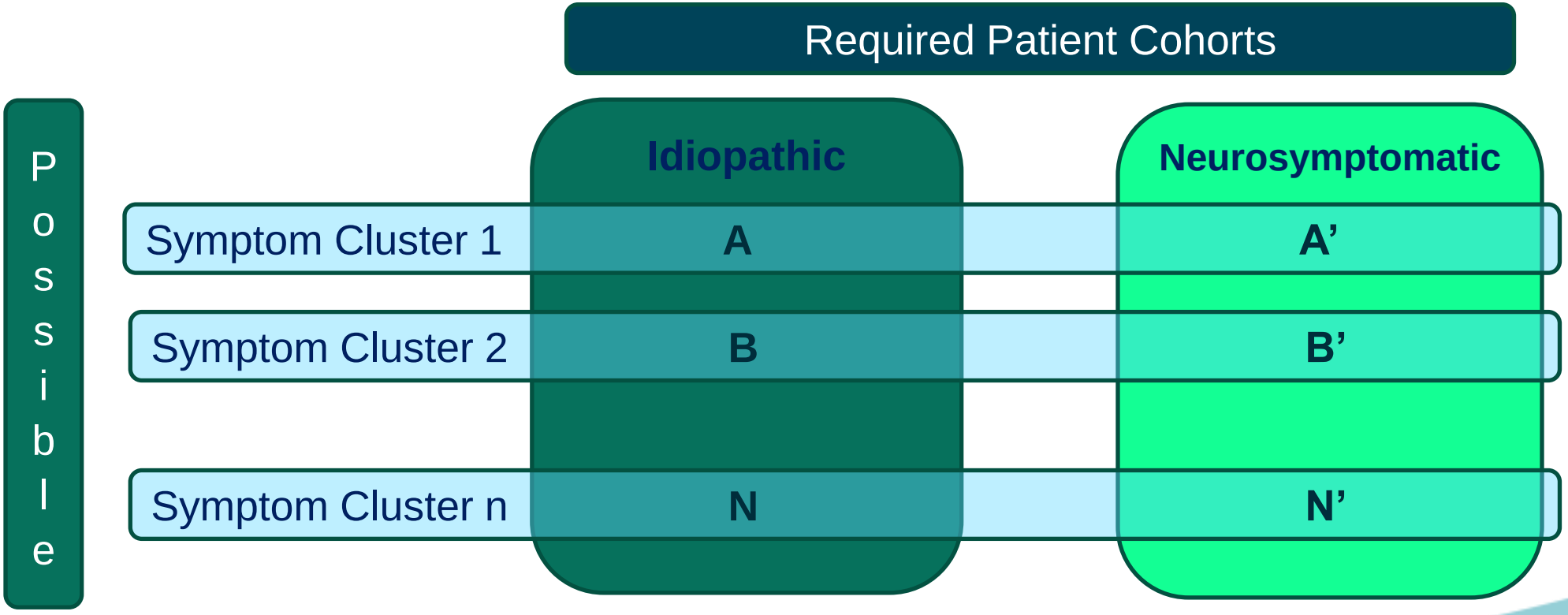
Suggested architecture of the project - 1

- The successful consortia would select symptom constellations that are widely present in neuropsychiatric and degenerative disorders
  - Examples of that could be addressed and offer reverse translation:
  - Cognition (Working memory, Episodic, Reasoning and Problem solving, Attention), Reward, Stress, Affect, Agitation, Perception and sensory processing.
- Appropriate study cohorts of patients could stem from disease populations, for which selected symptom domains are described, such as:
  - Neurological diseases, Alzheimer's disease, Parkinson's disease or FTLD
  - Affective disorders such as Major Depressive Disorder/Treatment Resistant Depression or Schizophrenia

Suggested architecture of the project - 2

Examples	Idiopathic	Degenerative
Psychosis	A=Schizophrenia	A'=Alzheimer's
Executive Function	B=Schizophrenia	B'=Parkinson's
Affect	B=TRD	B'=Alzheimer's



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Suggested architecture of the project - 3

- WP1 Consortium management and governance
- WP2 Scientific consensus (Clinical/Pre-clinical) on study designs, instruments and methodology
- WP3 Data management and statistics - to allow integrated analysis of data set
- WP4 Clinical study implementation and operations
- WP5 Clinical harmonization of experimental approaches
  - Imaging, Electrophysiology, Biosample analysis, Neuropsychology
- WP6 Pre-clinical harmonization of experimental approaches
  - Imaging, Electrophysiology, Biosample analysis, Neuropsychology
- WP7 Engagement with regulatory groups, agencies and other stakeholders
- WP8 Dissemination and communication

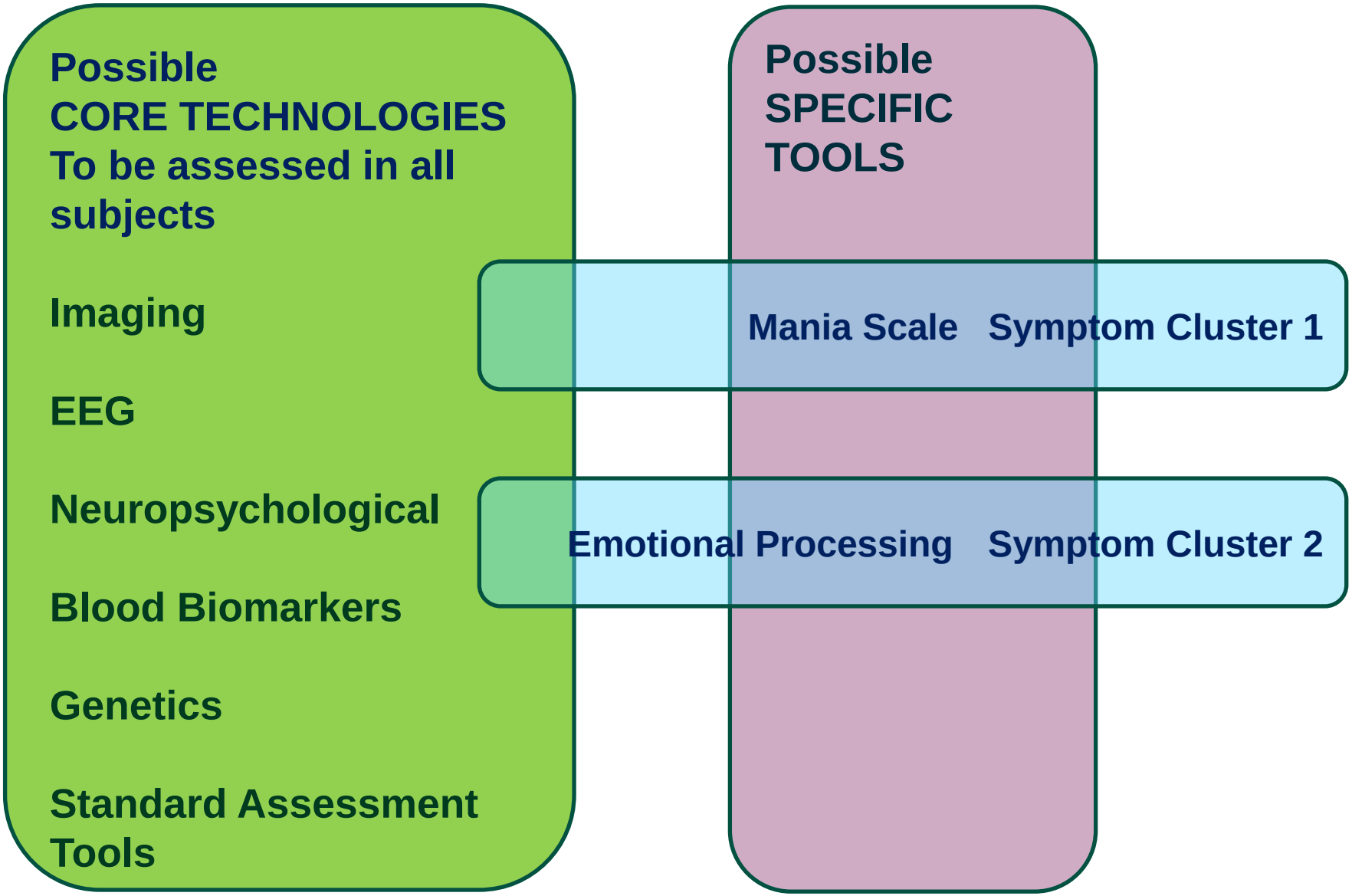
Expected contributions of the applicants

Expected Expertise & Capabilities

- A range of clinical Imaging and Biomarker platforms
- Statistics and study design
- Clinical study support
- IT – Data communication and data basing
- Pre-clinical imaging and biomarkers
- Pre-clinical technologies
- Regulatory expertise
- Project management

Valuable Assets

- Relevant existing datasets and existing clinical studies
- Relevant Clinical cohorts and registries
- Relevant bio-banks and bio-samples
- Involvement of patient organizations and its ethical considerations



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Expected (in kind) contributions of EFPIA members

Participating pharmaceutical companies in the project:

Eli Lilly & Boehringer-Ingelheim (Hugh Marston & Bernd Sommer co-leads), Lundbeck, Roche, Pfizer, Novartis and Takeda

EFPIA companies will contribute expertise in

- Data analysis
- Prospective clinical trial design
- Homologous pre-clinical technologies for reverse translation
- Biomarker discovery and validation
- Assay development and scaling

- Other IMI projects may well be able to provide tools and support, e.g. eTricks – data knowledge management for translational research

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What's in it for you?

Participation in this project will enable:

- Academic researchers to access resources to advance quantitative neuropsychiatry research and drug development
- SMEs to contribute technical expertise to support quantitative neuropsychiatry research, project management, and diagnostics development
- Regulators to influence development of new approaches for disease quantification and treatment
- Economic experts and payers to influence development of approaches to improve effective treatment of neuropsychiatry conditions

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Key deliverables of the full project

- A battery of techniques, standardised protocols and a clinical network capable of exploring the quantitative biology of a defined population of neuropsychiatric patients with different disease aetiologies
- A statistically validated subset of biological parameters that can identify and stratify the patient population
- An equivalent pre-clinical capability designed to back translate the clinical findings into a rational drug discovery context
- Novel insights into the neuro- and psycho-pathology of the chosen patient cohorts
- Clear routes for future translation and regulatory approval
- Through the above provide new means to address the growing public health challenges of neuropsychiatry

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Questions?

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