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ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®

JULY 16–20 > LONDON, ENGLAND

THE FUTURE OF ELECTRONIC HEALTH RECORDS AND BIG DATA IN DEMENTIA RESEARCH

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Disclosures

- Consultancy
  - Optum labs
  - Eisai
  - SomaLogic
  - Janssen/J&J
- Research funding/collaboration
  - AstraZeneca
  - Lilly
  - EFPIA companies through IMI
- Intellectual property
  - Patents related to biomarkers for AD held by KCL and Proteome Sciences

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What is Big data?

Overwhelming

Transformative

Worrying

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What is Big data?

Volume

Variety

Velocity

Complexity

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Agenda

- Enabling cohort and real world data for dementia research
  - European Medical Information Framework (IMI-EMIF)
  - Case Records Interactive Search (UK-CRIS)
- Using molecular and real world clinical data in drug development
  - From phase 0 to phase IV
- Looking ahead
  - Future platforms for better dementia research and care

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European Medical Information Framework (IMI-EMIF)

ACADEMIC PARTNERS 38

SME PARTNERS 9

EFPIA PARTNERS 10

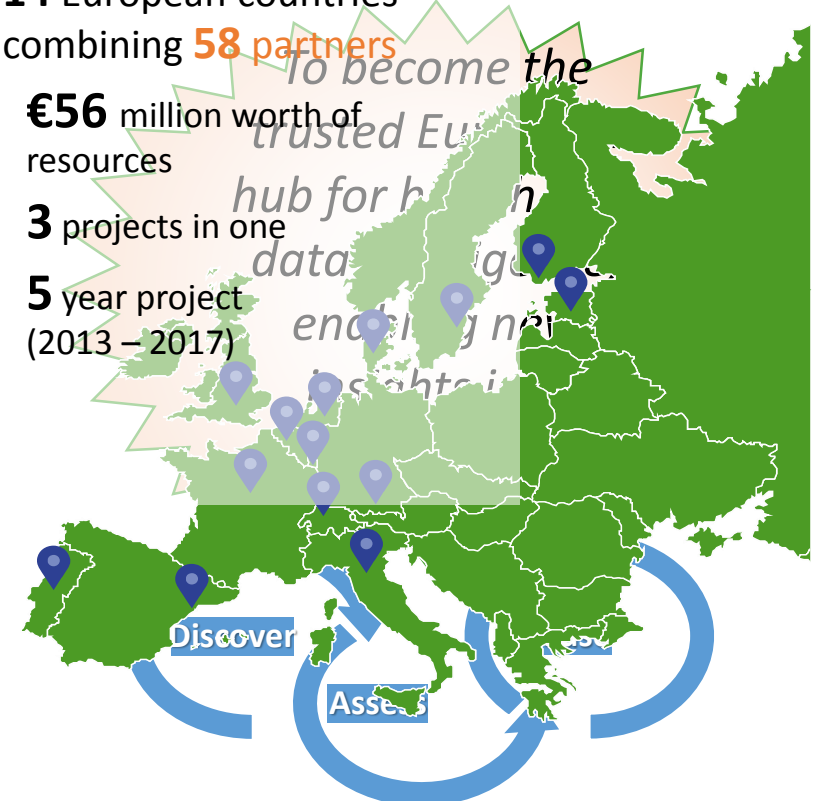
PATIENT ORGANISATION 1

14 European countries combining **58** partners

€56 million worth of resources

3 projects in one

5 year project (2013 – 2017)



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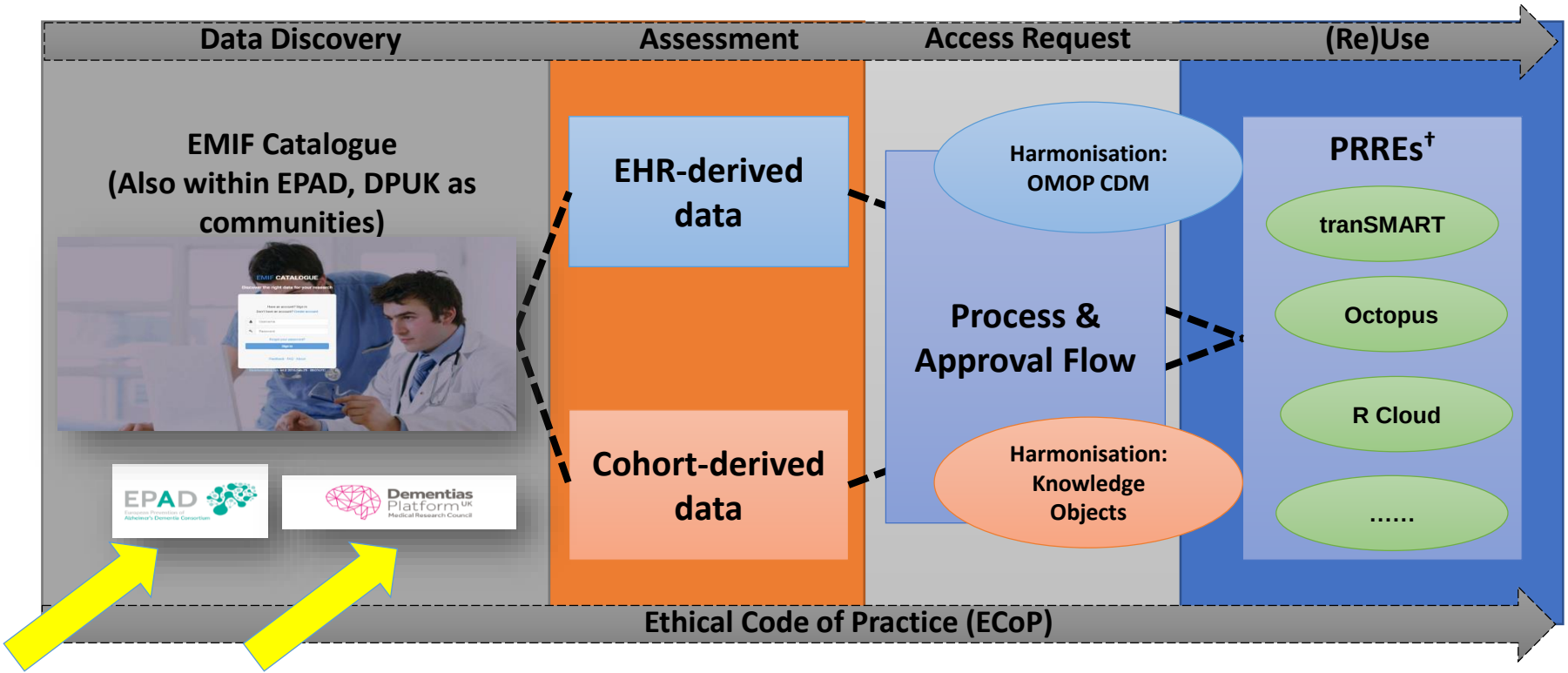
EMIF pipeline – discover, assess, use



† Private Remote Research Environment

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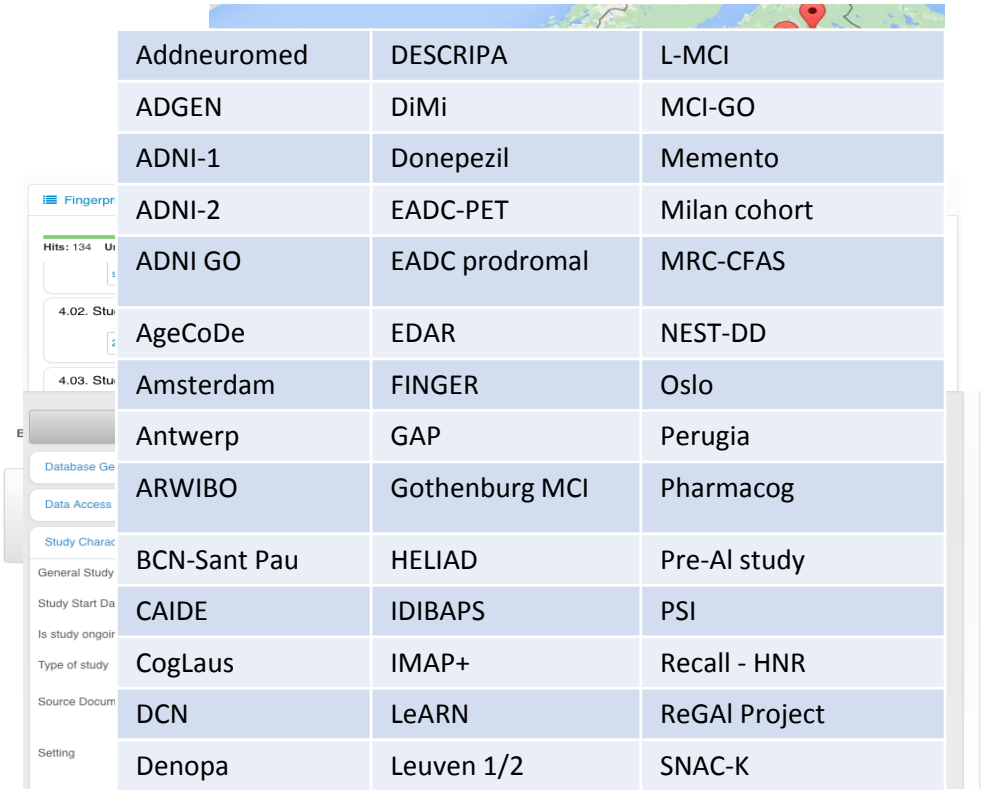
EMIF-AD data discovery: catalogue (emif-catalogue.eu/index)

- Overview of Alzheimer's disease studies in Europe
- Detailed information from every study
- Advanced search techniques
- Compare cohorts



Addneuromed	DESCRIPA	L-MCI
ADGEN	DiMi	MCI-GO
ADNI-1	Donepezil	Memento
ADNI-2	EADC-PET	Milan cohort
ADNI GO	EADC prodromal	MRC-CFAS
AgeCoDe	EDAR	NEST-DD
Amsterdam	FINGER	Oslo
Antwerp	GAP	Perugia
ARWIBO	Gothenburg MCI	Pharmacog
BCN-Sant Pau	HELIAD	Pre-AI study
CAIDE	IDIBAPS	PSI
CogLaus	IMAP+	Recall - HNR
DCN	LeARN	ReGAI Project
Denopa	Leuven 1/2	SNAC-K

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EMIF-AD data discovery: research cohorts and real-world

Research cohorts for dementia	Number of subjects
Normal cognition	31,376
Subjective cognitive complaints	4,369
Mild cognitive impairment	11,287
Probable/possible Alzheimer's disease	9,754
Other dementia	2,453
Total	**~ 60,000**

Real world datasets	Number of subjects
Aarhus (DK)	2.3 million
Regional DB Tuscany (IT)	4.8 milion
GePaRD (DE)	17 million
THIN (UK)	> 11 million
IPCI (NL)	2.9 million
Health Service (IT)	>2 million
Pharmo (NL)	> 7 million
UK cohorts (CVS, diabetes)	~ 500,000
EGCUT (EE)	52,000
Total	**~ 48 million**

EMIF

Pre-competitive reutilisation of research and real-world data

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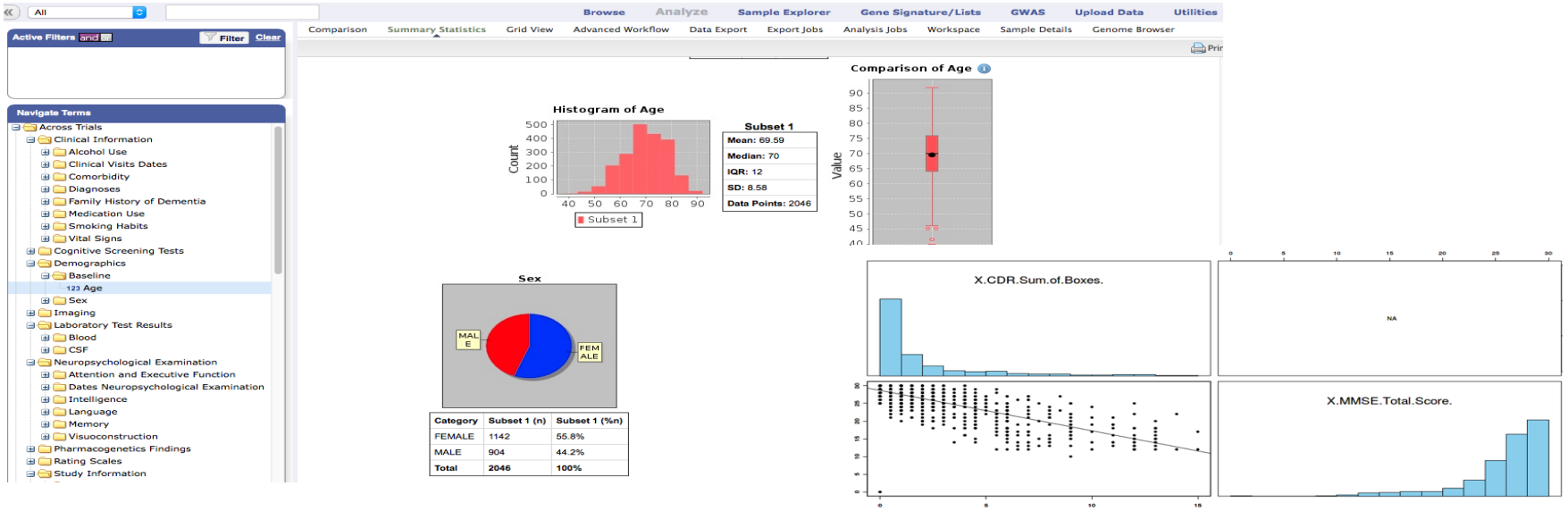
EMIF-AD infrastructure: TranSMART platform



10 cohorts; > 4000 subjects; multiple phenotypes – demographics, imaging biomarkers, cognitive scores; molecular phenotypes and genotypes in process

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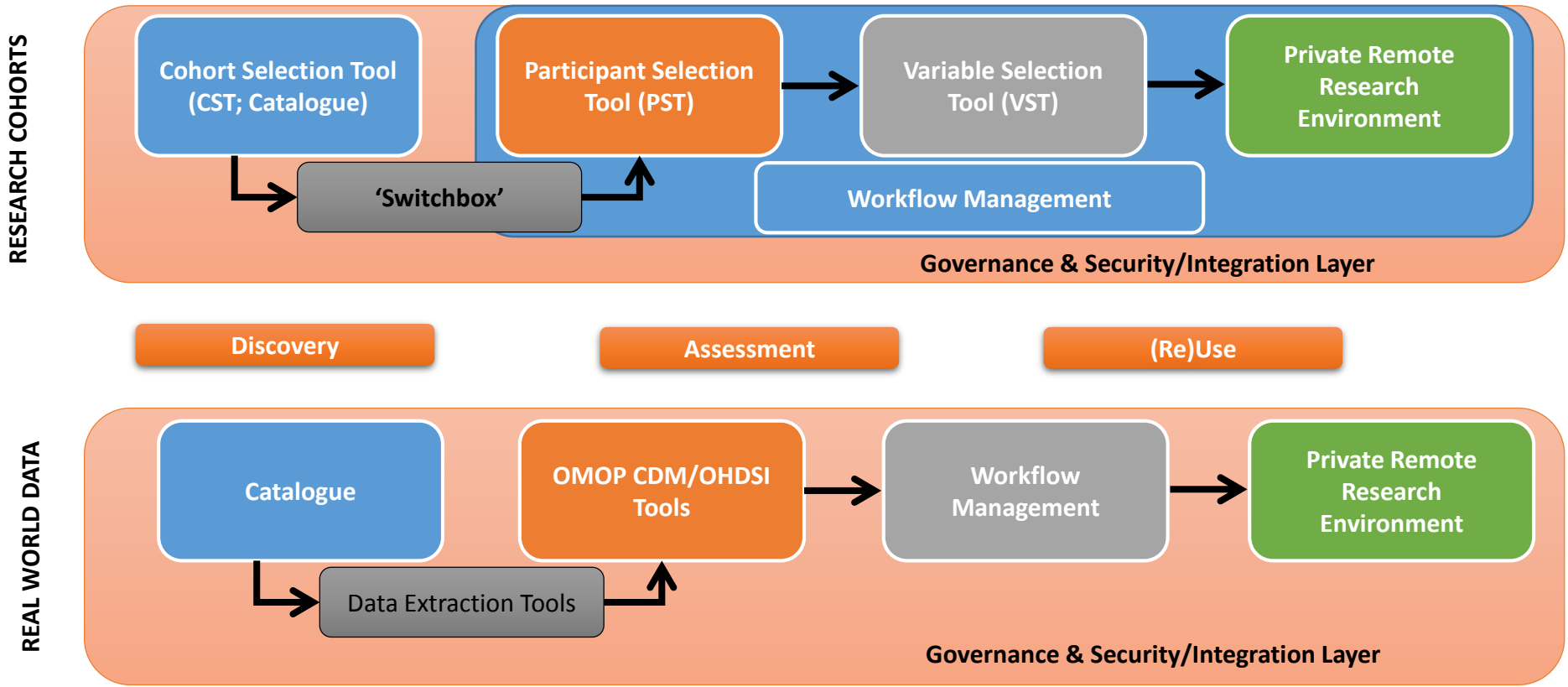

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Case Records Interactive Search (UK-CRIS)

14

NHS Mental Health Trusts across the UK

2.5m+

De-identified electronic patient records

1. Avon and Wiltshire Mental Health Partnership NHS Trust
2. Cambridgeshire and Peterborough NHS Foundation Trust
3. Camden and Islington NHS Foundation Trust
4. Devon Partnership NHS Trust
5. Kent and Medway NHS and Social Care Partnership Trust
6. Mersey Care NHS Foundation Trust
7. North East London Foundation Trust
8. Nottinghamshire Healthcare NHS Foundation Trust
9. Northumberland, Tyne and Wear NHS Foundation Trust
10. Oxford Health NHS Foundation Trust
11. Southern Health NHS Foundation Trust
12. South London and Maudsley NHS Foundation Trust
13. South West London and St George's NHS Foundation Trust
14. West London Mental Health NHS Trust

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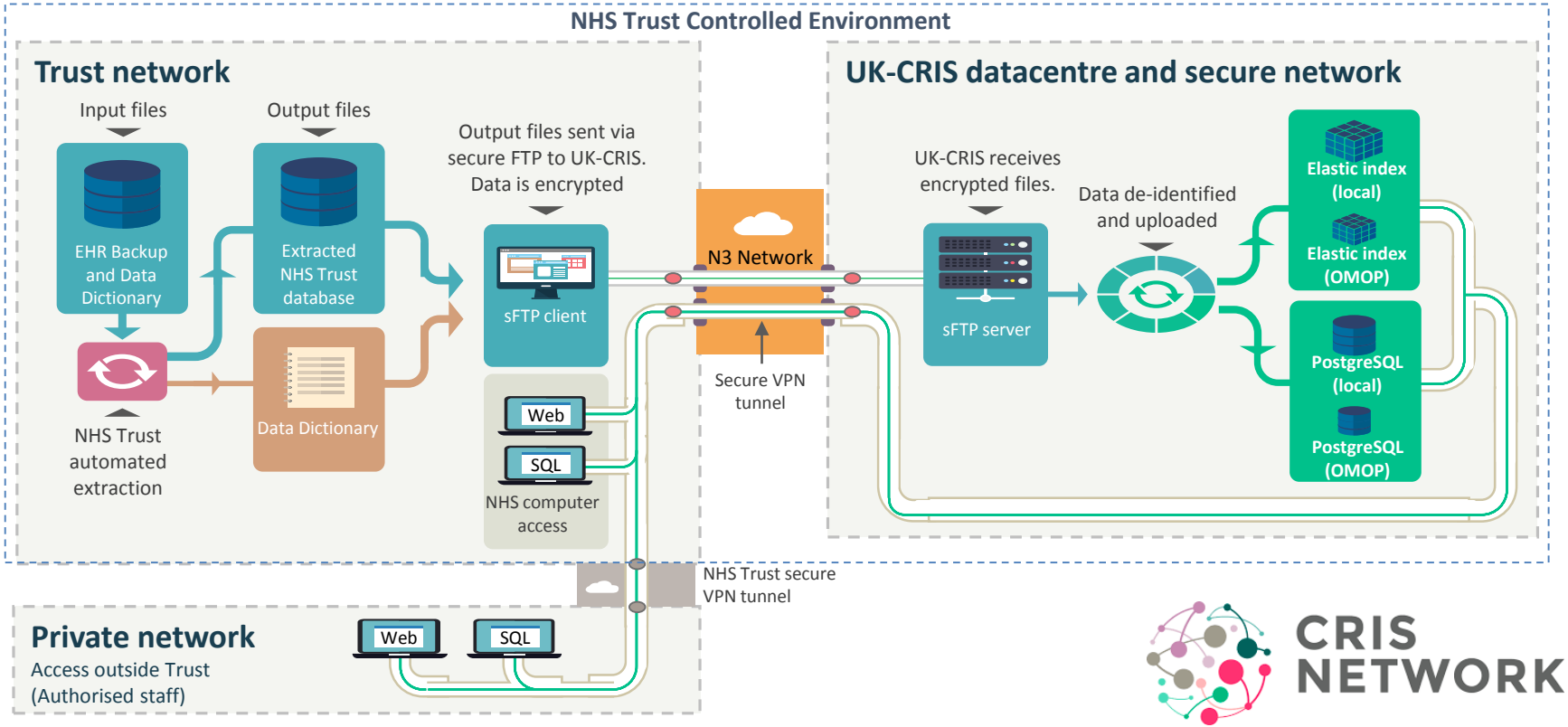
UK-CRIS: safe, secure and ***complete***



CRIS NETWORK

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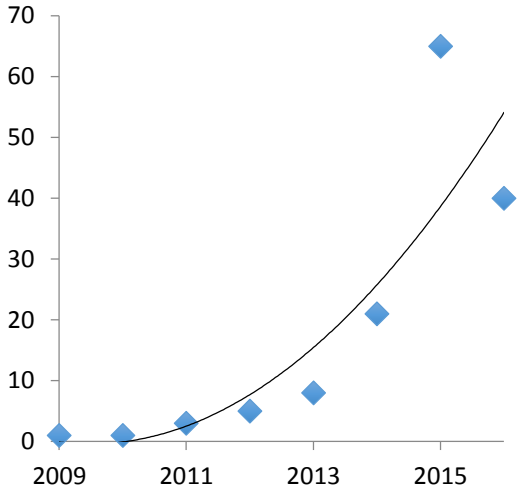
Data reutilisation for research

- EMIF publications
  - http://www.emif.eu/results
    - or search EMIF EU references
  - > 85 papers 2012-2017

- CRIS publications
  - http://www.maudsleybrc.nihr.ac.uk/facilities/clinical-record-interactive-search-cris/cris-publications/
    - or search CRIS BRC references
  - > 65 papers 2009-2017



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Data reutilisation to accelerate drug development in AD

- Target nomination and proof of concept
- Biomarkers for clinical trials
- Participant identification and recruitment
- Phase IV
- Regulatory / payer approval

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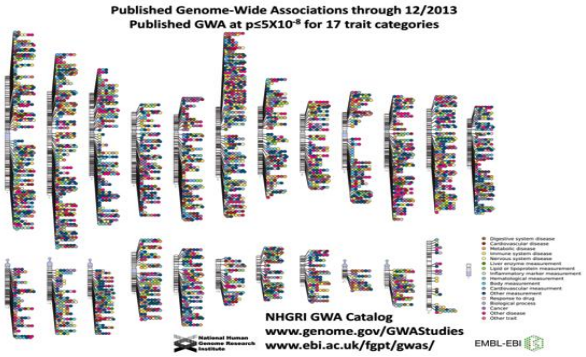
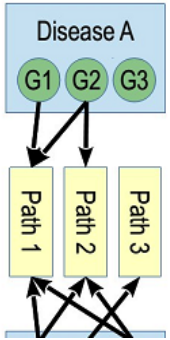
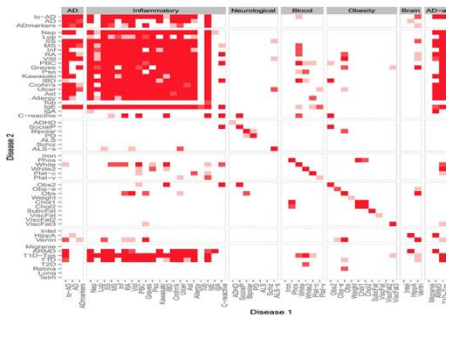
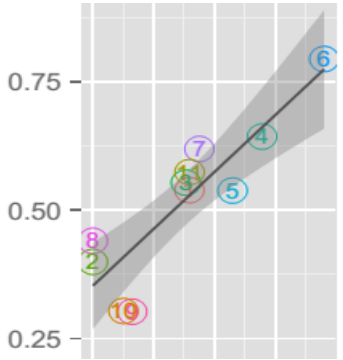
Target nomination









- Generate pathways from complete GWAS datasets and perform clustering analysis for shared pathways

- Correlate pathway load per disease with risk relationship between disease and Alzheimer's ***from real world data***

- Perform proof of concept in human samples ***using EMIF catalogue***

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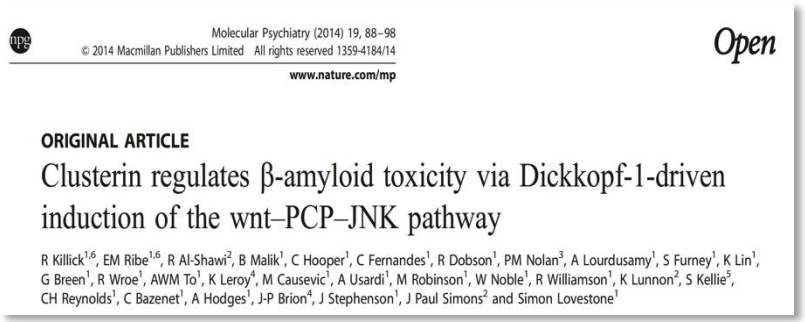
Proof of concept

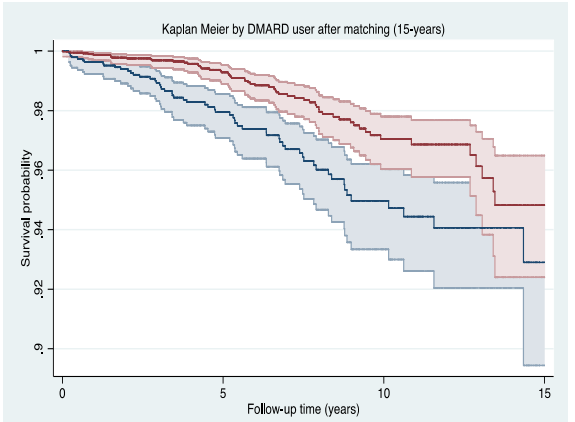

Molecular Psychiatry (2014) 19, 88–98
© 2014 Macmillan Publishers Limited All rights reserved 1359-4184/14
www.nature.com/mp

Open

ORIGINAL ARTICLE

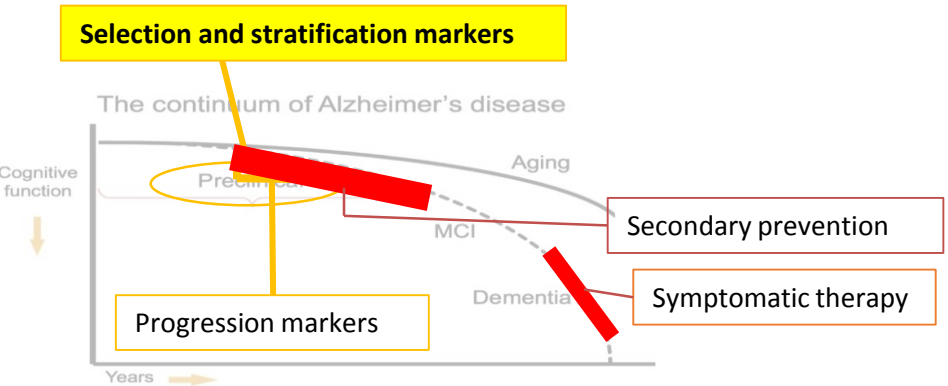
Clusterin regulates β-amyloid toxicity via Dickkopf-1-driven induction of the wnt–PCP–JNK pathway

R Killick[1,6], EM Ribe[1,6], R Al-Shawi[2], B Malik[1], C Hooper[1], C Fernandes[1], R Dobson[1], PM Nolan[3], A Lourdusamy[1], S Furney[1], K Lin[1], G Breen[1], R Wroe[1], AWM To[1], K Leroy[4], M Causevic[1], A Usardi[1], M Robinson[1], W Noble[1], R Williamson[1], K Lunnon[2], S Kellie[5], CH Reynolds[1], C Bazenet[1], A Hodges[1], J-P Brion[4], J Stephenson[1], J Paul Simons[2] and Simon Lovestone[1]



- Generate disease signature using differential transcriptomics with validation in vitro and in vivo using ***open access and repurposed datasets***
- Identify compounds from 90k screen and in silico using Broad cMAP; confirm hits
- Proof of concept for compound hit class using ***real world data***

Biomarkers for clinical trials



- Finding 'impossible' cohorts
  - ***EMIF 500 and EMIF 1000***
  - discovery of blood based correlates of CSF and PET measures of amyloid load
  - Replicating markers with PPV 0.86

Clinical study	'n'	Cost of Aβ PET screen failure	Cost of Aβ /tau PET screen failure	Screen failure saving with a blood biomarker
Deep and Frequent trial	250	£450k	£1.2m	£318k / £848k

Assumptions: screen failure rate ~40%; cost per amyloid PET £3k; cost per dual PET £8k; PPV of blood marker 0.86

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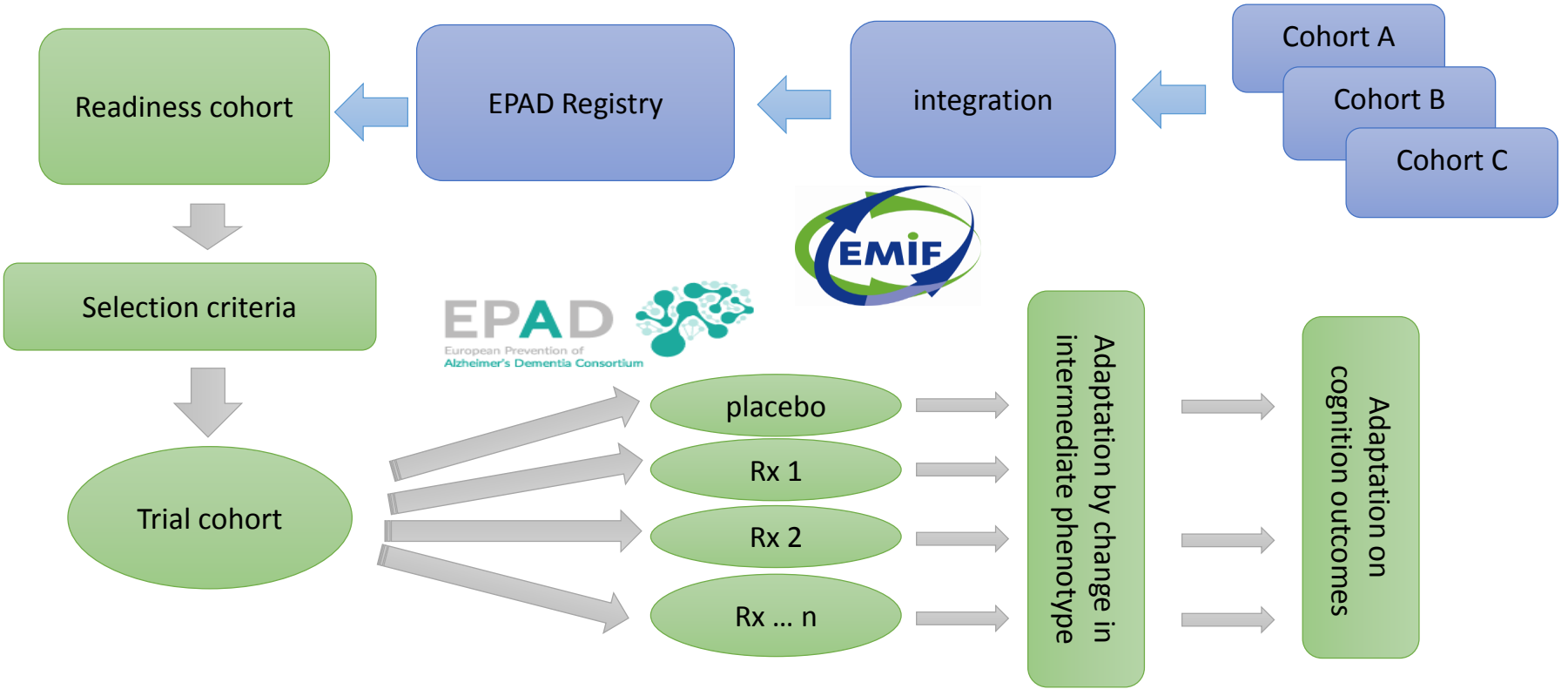
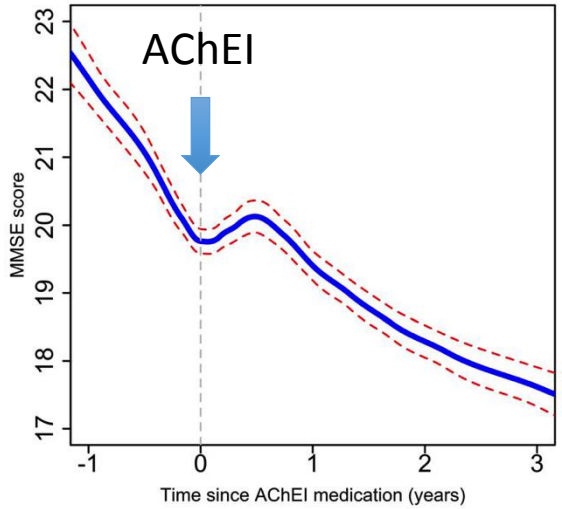
Participant identification and recruitment



Potential to deliver post-marketing data at scale and in real-world contexts



- South London & Maudsley NHS FT ***CRIS*** data
- n=2460; dementia treatment with AChEIs
- MMSE derived from **coded and uncoded** data
- Improvement by 4.2 units per year in first 6 months
- Predictors of response:
  - Better early response in non-white patients
  - Worse early response in vascular dementia

G. Perera, *et al.*, Factors associated with response to acetylcholinesterase inhibition in dementia: a cohort study from a secondary mental health care case register in London. *PLoS One* **9**, e109484 (2014).

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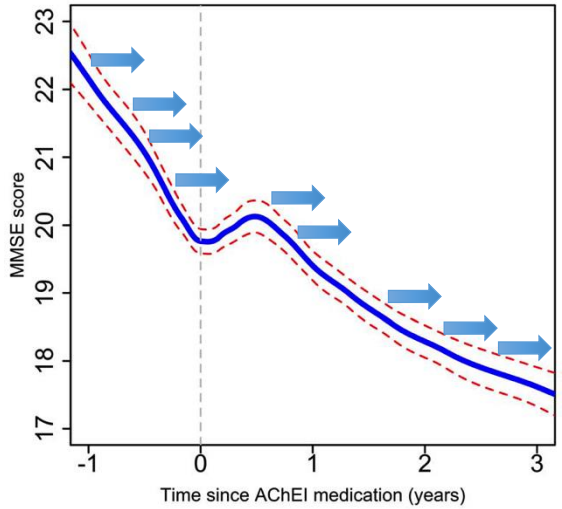
Payer approval

Beyond research data modeling - using CRIS for real-world, individual level costs



- Destination from uncoded data and linkage
- N=3075 (5624 6m windows)
  - 25% alone; 52% ADL problems
  - 37% physical illness; 45% moderate severity
- Mean costs of severe dementia >2x that for mild
- Increased care costs associated:

  with severity, functional problems, agitation, living alone

  but not physical illness, depression or gender

M. Knapp *et al.*, Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: findings from a large London case register. *BMJ open* **6**, e013591 (2016).

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Big data – velocity missing

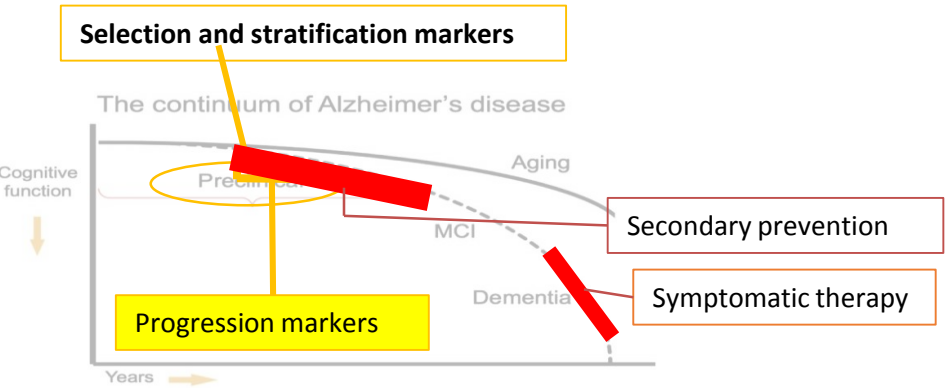
Volume

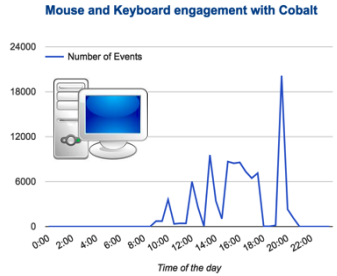
Variety

Velocity

Complexity

Deep & Frequent Phenotyping





- **Deep phenotyping**
  - Amyloid and tau PET
  - Blood, CSF, MRI, MEG, EEG, retinal, cognition, gait, connected devices for activity and function
- **Frequent phenotyping**
  - ~2-3 month repeat measures
  - Near continuous measures possible
- **Open science**
  - data sharing planned from outset

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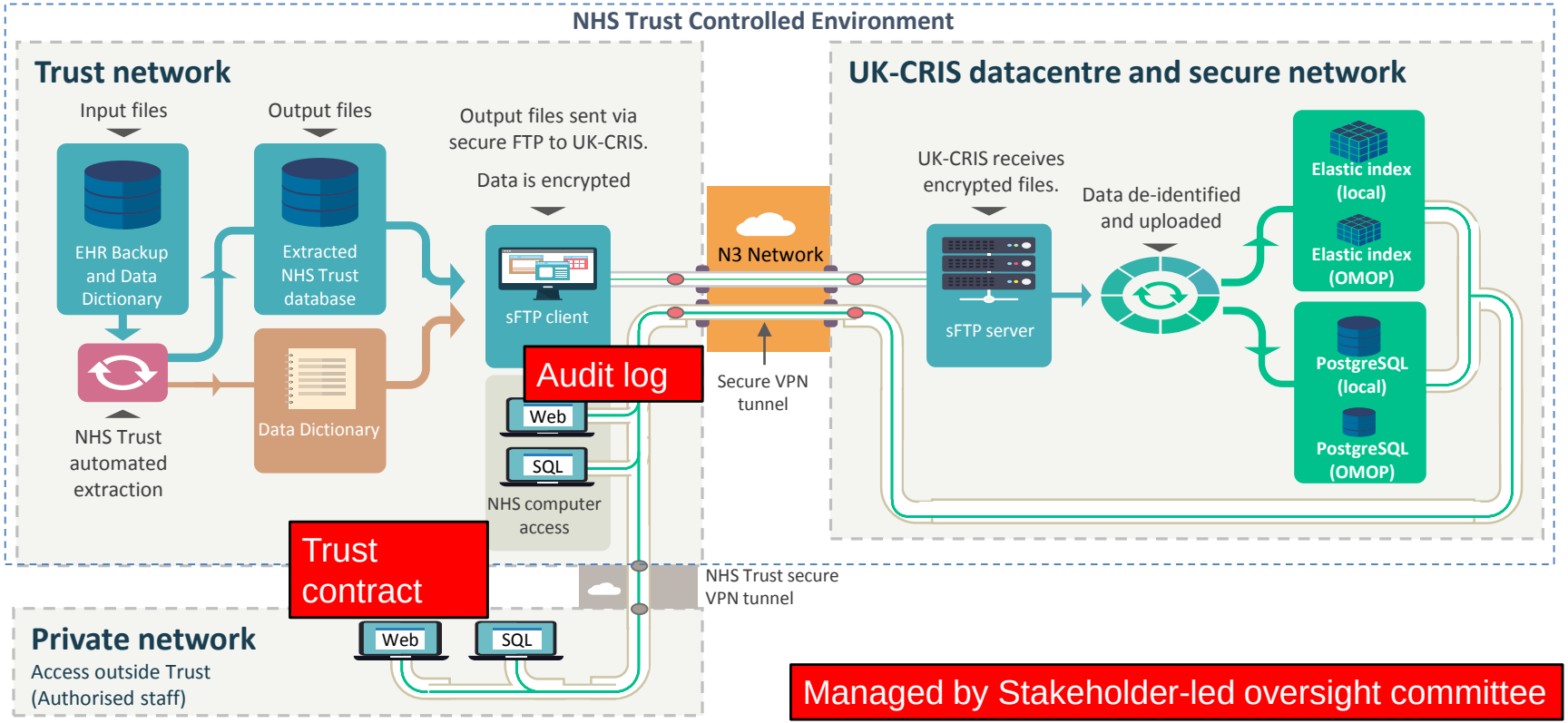
Information governance



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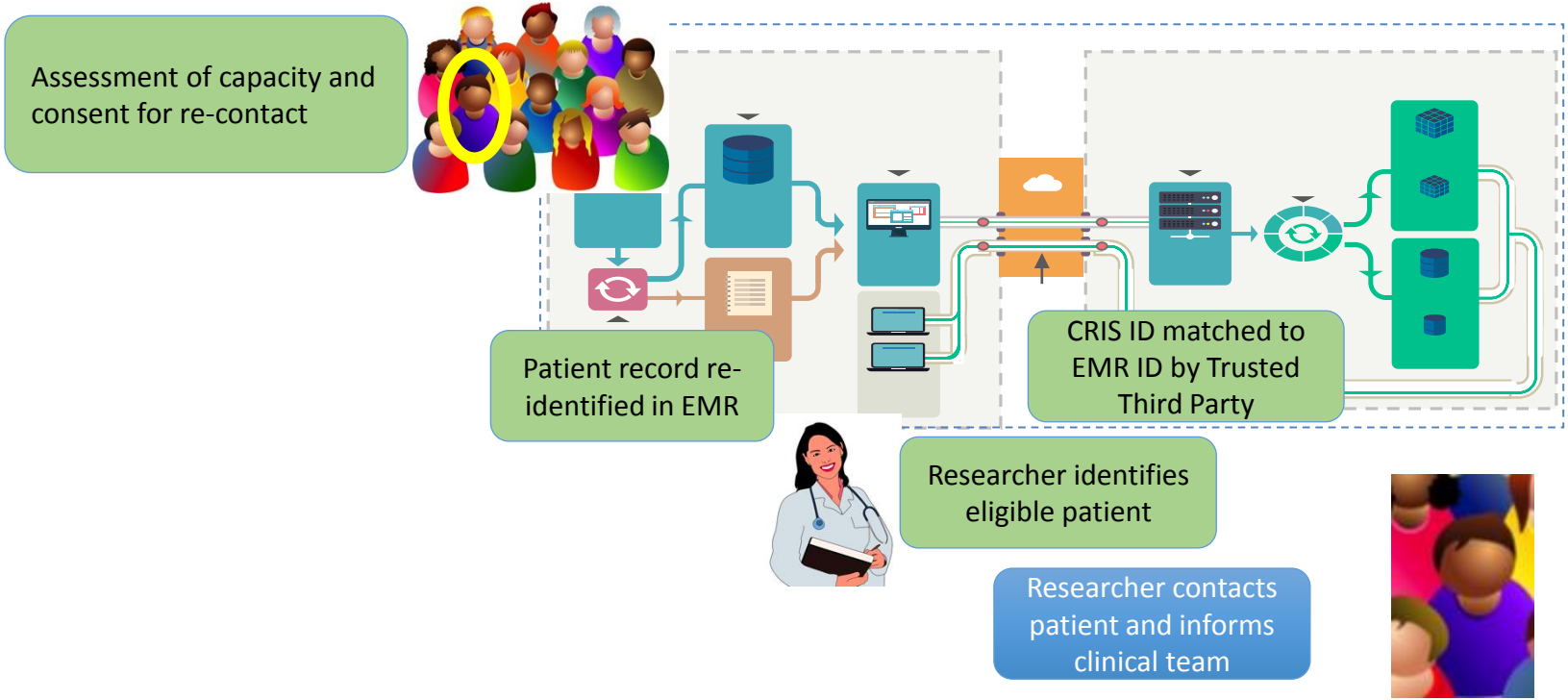
CRIS consent for contact model



Callard et al. Developing a new model for patient recruitment in mental health services: a cohort study using Electronic Health Records. BMJ open. 2014;4:e005654.

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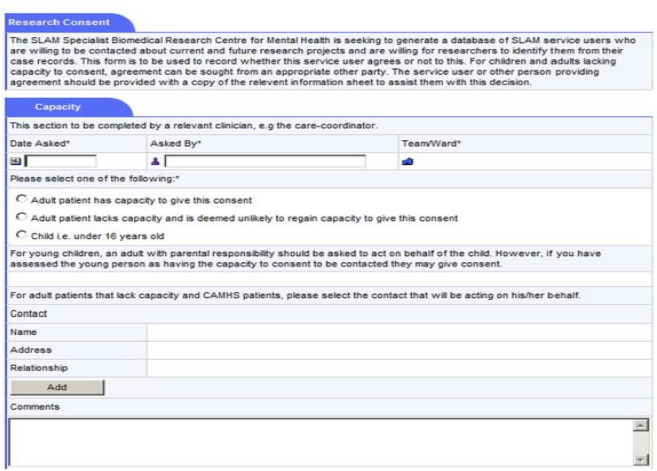
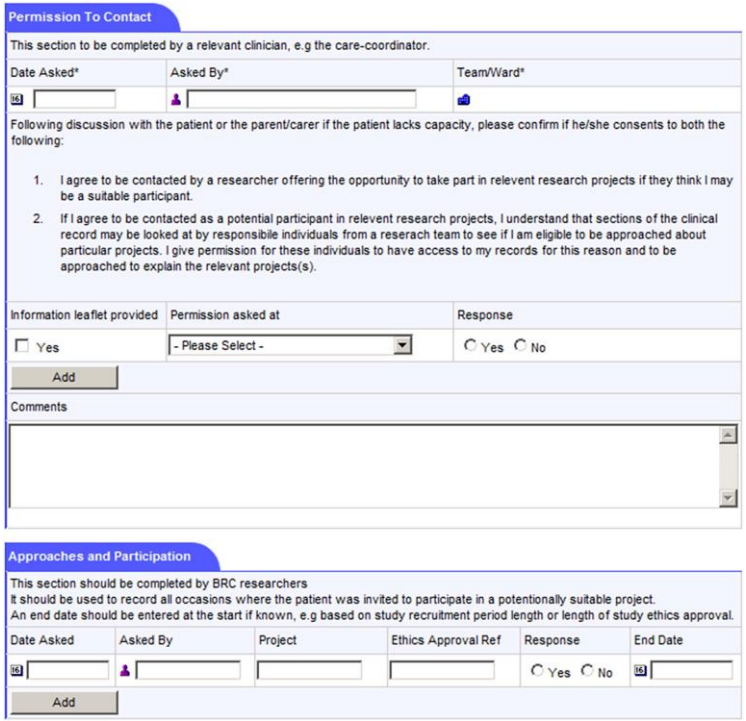
CRIS consent for contact model



74% agreement

20,000 consents and samples in 3 years



Callard et al. Developing a new model for patient recruitment in mental health services: a cohort study using Electronic Health Records. BMJ open. 2014;4:e005654.

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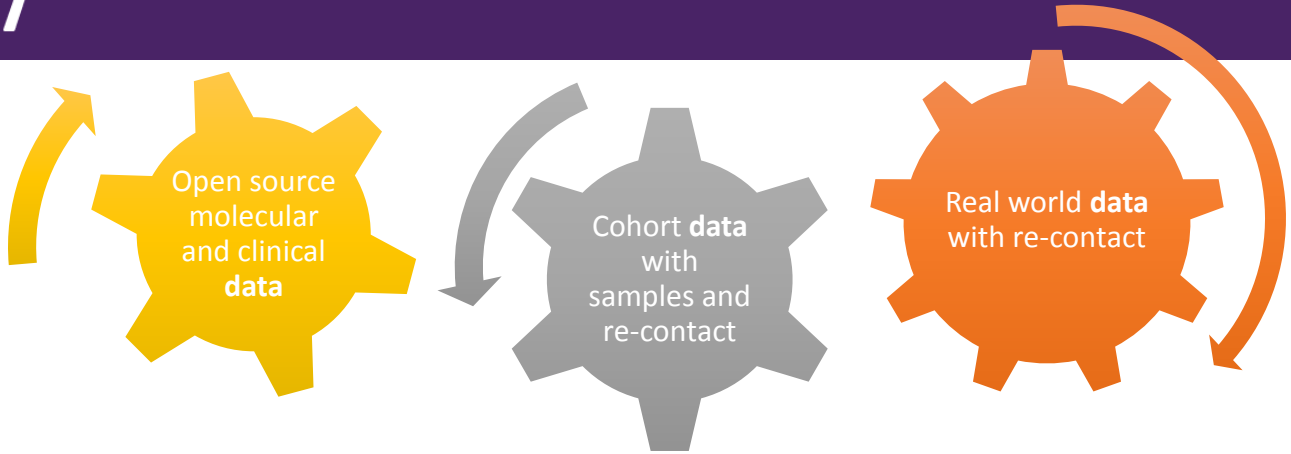
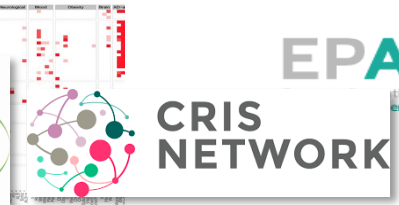
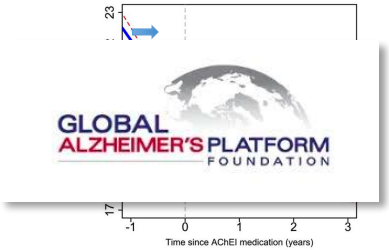
Platforms for dementia research

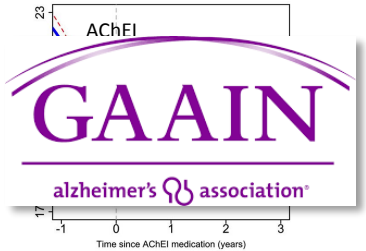


Target identification → Proof of concept clinical trials → Efficacy trials – feasibility to recruitment → Regulatory and payer approval → Phase IV



EPAD





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acknowledgments

- CRIS
  - Mike Denis (Oxford)
  - Rob Stewart (KCL)
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  - Chris Hinds
  - Ivan Koychev
  - Lynn Rochester (Newcastle)

MRC Medical Research Council

NHS National Institute for Health Research

Alzheimer's Research UK

imi Innovative Medicines Initiative

Alzheimer's Society

wellcome trust

DataParasites

DataPhilanthropists

DataSavesLives