EHDEN and the Oxford Study-a-thon

Peter Rijnbeek\textsuperscript{1}, Dani Prieto Alhambra\textsuperscript{2}

\textsuperscript{1}Erasmus MC The Netherlands
\textsuperscript{2}Oxford University, UK
Vision
The European Health Data & Evidence Network (EHDEN) aspires to be the trusted observational research ecosystem to enable better health decisions, outcomes and care.

Mission
Our mission is to provide a new paradigm for the discovery and analysis of health data in Europe, by building a large-scale, federated network of data sources standardised to a common data model.
Innovative Medicines Initiative (IMI) Project

www.imi.europe.eu

Start date: 1 Nov 2018
End date: 30 Apr 2024
Duration: 66 months

22 partners

Almost €29 million
EHDEN IS ABOUT ...

**Federation**
Creation of an EU-wide architecture for federated analyses of real world data

**Harmonisation**
Harmonise more than 100 million anonymised health records to the OMOP common data model

**Outcomes**
Enabling outcomes driven healthcare at a European level

**Community**
Establish a self-sustaining open science collaboration in Europe, supporting academia, industry, regulators, payers, government, NGOs and others

**Education**
The establishment of an EHDEN Academy, webinars and face-to-face training sessions to train all stakeholders
CALL PROCESS FOR DATA PARTNERS AND SMALL TO MEDIUM-SIZED ENTERPRISE (SMEs)

Data Partners

- Tailored for project objectives and sustainability

Open calls

- Evaluated via a pre-defined set of criteria by the Data source prioritisation committee

Grant Awarding

- Data sources can choose the SME from the pool of EHDEN certified SMEs

Harmonisation fund

Data Partners

- Supporting SMEs

Open calls

- Focusing on SMEs able to support mapping and sustainability

Grant Awarding

- Open calls

Workshop

- Source Data Evaluation

- Share of Mapping Process

- Mapping Audit

- Mapping Cycle Evaluated via a pre-defined set of criteria by the Data source prioritisation committee

Harmonisation fund

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Payments are milestone-based

Mapped data sources are encouraged to be active members of the EHDEN community, participating in research studies.

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- Training & Certification

SME certification committee prioritises SMEs for training and certification

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**The EHDEN Academy**

**Aim**
To develop an e-learning environment to train all stakeholders in the project in the use of the tools and processes that are being adopted in EHDEN and OHDSI.

**Collaboration**
Course development on the OMOP Common Data Model and the rich set of OHDSI tools are developed in collaboration with the OHDSI community.

**Infrastructure**
The EHDEN Academy is developed in Moodle and is hosted in the Amazon AWS cloud.

- Academy Pilot running with approx. 50 users
- Planned to be opened to full OHDSI community end of this year!
SME Certification

Goal: to provide the SME all the skills to perform the data standardisation task to the OMOP-CDM and train them on the installation of the analytical infrastructure

Training

1) EHDEN Foundation: Introduction to IMI, EHDEN, OHDSI
2) OHDSI-IN-A-BOX Virtual Machine
3) OMOP CDM and Standardized Vocabularies
4) Extract, Transform and Load
5) Analytical Infrastructure

More course will be added in the EHDEN Academy in the near future.

Certification

- 28 SMEs signed up from X countries
- 11 currently following the e-learning curriculum

• Final certification will contain a two days face-to-face meeting at the Erasmus MC in Rotterdam with all SMEs in the current batch. Multiple persons per SME can participate.
• Final assessment will contain a mapping exercise and installation of the Analytical Infrastructure.
OPEN CALL FOR DATA PARTNERS

• Draft Call Description has been made available on the website for public review since July. Pilot call opened Sept 1st and closed Sept 15th. Multiple Calls during the project for a total amount of 17 Million Euro financial support.

• Different types of grants (max 100.000 Euro):
  - Create new Data Transformation and Analytical Infrastructure
  - Revise Existing Data Transformation and Analytical Infrastructure
  - Inspect Completed Data Transformation and Analytical Infrastructure

• Data Partners from EU Member States and H2020 countries can apply through online application portal.

- X Data Partners showed interest in mapping
- X Applications Submitted
- X Countries
- Inpatient, Outpatient, Registry, etc.
- X number of patient records

For more information about the Open Calls see the EHDEN website: www.ehden.eu
<table>
<thead>
<tr>
<th>WP1: Evidence Workflow Development</th>
<th>WP2: Outcome Driven Healthcare</th>
<th>WP3: Personalized Medicine</th>
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<tbody>
<tr>
<td>Incorporating the use cases for supporting development and validation of the EHDEN socio-technical approach, inclusive of BD4BO projects</td>
<td>Related to all activities specific to e.g. BD4BO projects outcome focus, and ICHOM standards incorporation</td>
<td>Focusing on the support of outcomes/value based healthcare, inclusive of clinical prediction models, with the incorporation of ‘novel’ patient data</td>
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<tr>
<th>WP4: Technical Implementation</th>
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<td>Key priority is socio-technical development of the EHDEN federated framework and relevant services</td>
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<tr>
<th>WP5: Data Workflow Implementation &amp; Service Deployment</th>
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<tr>
<td>Development, oversight and evaluation of the ecosystem development from SME qualification/certification to data source engagement, OMOP CDM mapping and evaluation</td>
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<th>WP6: Outreach and Sustainability</th>
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<td>Ensuring the development of value propositions for key stakeholders, and developing the sustainable operational model for EHDEN during and post IMI phase</td>
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<th>WP7: Project Management and Dissemination</th>
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<td>Concentrating on intra-project project management, internal communications and external dissemination, and responding to IMI deliverables</td>
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QUICK UPDATES

• Data Quality Tool Development

• Portal Development to bring together multiple tools, e.g. Database Catalogue, Arachne Central, Atlas, EHDEN Academy

• Database Catalogue containing extrinsic and intrinsic meta data and visualisation on Database and Network level (see Forum Post)

• QueryLibrary developments for community training (200+ queries): https://github.com/OHDSI/QueryLibrary

• Tantalus vocabulary comparison tool: https://github.com/OHDSI/Tantalus

• Mapping of the Article 57th Database of European Medicines Agency (X % of codes currently mapped)

• Methods Research, e.g. Heterogeneity of Treatment Effect Package: https://github.com/OHDSI/XXXX (see poster and Shiny App)
Oxford Study-a-thon

EHDEN and OHDSI in Action
The Oxford Study-Athon
(based on true events)
Our journey with OHDSI and EHDEN to real-world useful evidence

Important clinical question

Data partners standardized to OMOP CDM: Iqvia Janssen

Standardized analysis tools from OHDSI

Reliable evidence

Valuable clinical answers disseminated to medical decision-makers
What we needed in the mix ...

**Hands-on knowledge**

- **of 1+ data source/s**, including its structure and content, the provenance of the underlying population and data capture process, data quality issues and temporal variability, so that you can responsibly use the data to generate reliable evidence and recognize its limitations.

- **knowledge in designing studies and executing statistical methods** to generate aggregate summary statistics from patient-level data. Different expertise required for clinical characterization, patient-level prediction, and population-level effect estimation.

**Direct knowledge of the diagnosis, treatment, and management of severe knee OA**, including healthcare delivery, natural history and patient prognosis.
Expertise required

- Clinical knowledge in knee OA/arthroplasty?
- UK electronic health records (THIN)?
- US claims (MarketScan, Optum, PharMetrics)?
- OHDSI tools?
- R programming?
- Literature review?
- Publication writing?

Who has all of these prerequisites?
“To compare the risk of post-operative complications (infection, venous thromboembolism, mortality) and long-term implant revision between unicompartmental vs total knee replacement.”
What we knew before we started ...

- N = 60 acceptable quality studies
- From 1998 to 2018 (20 years of research!!)
- Reduced risk of VTE with UKR
What we knew before we started (2) ...

- Possibly a reduction in post-operative mortality ...
- [although little data available on this]
What we knew before we started (3) ...

- Loads of data on pain and function and PROMs
- Most pointing towards a further improvement with UKR vs TKR
What we knew before we started (4) ...

• ... BUT

• An increase in long-term revision risk
What we knew before we started (5) ...

- Caveats with quality of these 60 papers (and 20y) of data (mostly observational and from different sources)

- NIHR UK-funded
  - 1 surgical RCT (TOPKAT)
  - 1 observational study (UTMOST)
MOTIVATION

“We need less research, better research, And research done for the right reasons”

Ie, CAN WE DO IN A WEEK AND 1 STUDY WHAT HAS TAKEN SO FAR 20+ YEARS, 60+ PAPERS AND LOADS OF CASH?
RATIONALE

• Surgical/Device RCTs are rare, costly, and difficult:
  – Logistics (eg “blinding”)
  – Ethics (placebo/sham surgery)
  – Not always required (by regulators)

• New US and EU regulation will increase the need for observational data in this field
RATIONAL (2)

- Methodological challenges in the area of surgery/device observational research
  - *Confounding due to patient characteristics*
  - *... but also due to surgeon/centre features*
  - *Modelling difficulties (propensity score building to include surgeon/hospital characteristics)*

- Little experience/investment to date ...
- EHDEN provides an unprecedented opportunity
BACKGROUND – UKR vs TKR

• **UKR** is a less invasive, partial replacement, of the knee

• **TKR** is an established procedure with excellent results in terms of safety and effectiveness

• *(Some)* surgeons prefer UKR in younger, fit patients
• But research to date suggests UKR leads to:
  – Less complications
  – More revision/s

• So maybe best for older patients with complex medical history
BACKGROUND (3) – UKR vs TKR

• An on going surgical RCT comparing UKR vs TKR is reporting 5-year data published **NOW in the Lancet!!!** [Beard D et al. Lancet]

• As usual in RCTs, they have excluded old complex patients with co-morbidity etc (ASA 3+) ...

• Also as usual, they are not powered for safety (complications)

• And the trial will be run in specialized treatment centres ...
OUR AIMS!

• Can we ‘predict’ the TOPKAT results (on complications) before they publish?

• And more:
  – can we report on the results of UKR (vs TKR) in the older, more complex patients, excluded from TOPKAT?
  – Can we predict who is likely to have a post-operative complication following knee replacement surgery
WE CAN DO THIS IN ONE WEEK (STUDY-A-THON)??

“To compare the risk of post-operative complications and mortality between unicompartmental vs total knee replacement.”

**Monday**
- Group consensus on the problem
- Draft cohort definitions

**Tuesday**
- Review clinical characterisation
- Draft patient-level prediction design

**Wednesday**
- Review patient-level prediction results
- Externally validate prediction model

**Thursday**
- Draft population-level effect estimation design
- Review population-level effect estimation diagnostics

**Friday**
- Review of results
- Plan for completing publications

(EHDEN 1st Study-a-thon, Oxford, December 2018)
“To compare the risk of post-operative complications (infection, revision, and venous thrombo-embolism) and mortality between unicompartmental vs total knee replacement.”
Let’s start collaborating!

• Open the shared group notes:
  https://docs.google.com/document/d/17Valb33sl64laDq307PpoMZd4drIsVoja0zpYE6ZXe8/edit?usp=sharing

• Ground rules:
  – During group exercises, take all your notes here together
  – During breakout exercises, assign one person in your team to make sure notes are recorded so other groups can learn from our experience
Let’s start writing our papers!

• Patient-Level Prediction:
  
  https://docs.google.com/document/d/13GlkduIRmU2nbrqM58G2neWPV0U4PoTh8w13UihLgLc/edit?usp=sharing

• Population-Level Effect Estimation:
  
  https://docs.google.com/document/d/1BC6-cBR1by0GNeRc4zatzdSkOOmtvWfMpZrePIn0XaE/edit?usp=sharing
Let’s start learning ATLAS!

• Public version from OHDSI (v2.6, simulated data), go to: http://ohdsi.org/web/ATLAS

• Private version from Iqvia (v2.4, THIN data), go to: https://training.atlasplus.imshealth.com
SO WHAT DID WE LEARN (by Friday!!)

• Population-level effect estimation:
  http://data.ohdsi.org/UkaTkaSafetyEffectiveness/

• Patient-level prediction
  http://data.ohdsi.org/oxfordMortalityExternalValidation/
OUR WEEK vs 20y of research
OX Study-a-thon vs BMJ Syst Rev

• VTE
  • RR 0.49 [0.20 to 1.17] (20 y)
  • vs HR 0.62 [0.36-0.96] (1 week)

• Long-term revision
  • RR 1.68 [1.07 to 2.64] (20y)
  • vs HR 1.51 to 2.16 (1 week)
OUR WEEK vs a £3m trial
[D Beard et al. Lancet 2019]

• Small improvement in pain/function with UKR in TOPKAT vs Small reduction in opioid/s use in Study-a-thon

• No power for safety in TOPKAT vs findings compatible w 20y of data in Study-a-thon

• ... Yet revision not significantly increased!! [vs all previous papers]
  • WAS IT ALL A WASTE??!!
Revision risk: confused vs confounding
Insights from UTMOST

- All methods well balanced in patient-level covariates
- All methods had extremely small $\tau^2$ & $I^2$; non-significant p-values
Surgeons’ experience (1): effect modifiers
Surgeons’ experience in trials vs The real world

What matters the most?

- Higher risk for TKR
  - TOKPAT: 1.37 (0.49, 4.00)
  - 1.42 (0.94, 2.15)
  - 1.58 (1.17, 2.13)
  - 1.93 (1.65, 2.25)
  - 2.16 (1.92, 2.43)

- Higher risk for PKR
  - >=10 outputs: IPW 1.93 (1.65, 2.25)
  - >=30 outputs: 2.16 (1.92, 2.43)
  - >=50 outputs: 1.58 (1.17, 2.13)
Prediction...
Predicting post-op mortality
3. Prediction...

Predicting post-op mortality

THE MODEL

Model Table

<table>
<thead>
<tr>
<th>Covariate Name</th>
<th>Value</th>
<th>Outcome Mean</th>
<th>Non-outcome Mean</th>
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<tbody>
<tr>
<td>index month: 1</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Charlson index - Romano adaptation</td>
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<td>3.81</td>
<td>2.16</td>
</tr>
<tr>
<td>Diabetes Comorbidity Severity Index (DCS)</td>
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<tr>
<td>CHADS2</td>
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<tr>
<td>CHADS2ASC</td>
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<tr>
<td>visit_occurrence concept count during day -1095 through -1 concept_count relative to index</td>
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</tr>
<tr>
<td>index month: 3</td>
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</tr>
<tr>
<td>index month: 4</td>
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<td>0.08</td>
<td>0.08</td>
</tr>
</tbody>
</table>
3. Prediction... Predicting post-op mortality

**DISCRIMINATION**

**CALIBRATION**
AND WHAT DID I LEARN (by Friday too!!)
The Oxford Study-Athon

“Why had we not joined the journey earlier?”

Finished in 1430

Finished in the 1600s
Tradition?

Scotch egg

Or laziness?
Or maybe we’re not as good as some think..
Or maybe we’re not as good as some think..

Oxford top of global university rankings

By Sean Coughlan
BBC News family and education correspondent

© 11 September 2019
It’s always hard to start a journey ...
But once you find a good boat ...

“As you set out for Ithaka

hope your road is a long one,

full of adventure, full of discovery…”

Ithaka, by G Cavafis
**AN EXCITING JOURNEY AHEAD**

The uptake of the OMOP-CDM and success of OHDSI enables the EHDEN project to build the European eco-system that brings reliable evidence quicker to our patients.

Expanding the Data Network, Community, and the support system with SMEs, will drive the sustainability of the eco-system.

The EHDEN project will continue the collaboration with OHDSI and will invest in further development of the CDM, Vocabularies, ETL tools, analytical tools, DQ tools.
All this work would not have been possible without the contribution of many collaborators in EHDEN and OHDSI.

Thanks for this great adventure!

www.ehden.eu

@IMI_EHDEN

IMI_EHDEN

github.com/EHDEN

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