MHRA and the use of RWE
Why an OHDSI study-a-thon?

Katherine Donegan, Head of Epidemiology
23 January 2024
MHRA: Who are we?!  

We are the regulator of medicines, medical devices and blood components for transfusion in the UK.

Our responsibilities include:
• ensure medicines and medical devices meet applicable standards of safety, quality and efficacy
• educate the public and healthcare professionals about the risks and benefits of medicines and medical devices and blood components, leading to safer and more effective use
• enable innovation and research and development that is beneficial to public health
• collaborate with partners in the UK and internationally to support our mission to enable the earliest access to safe medicines and medical devices and to protect public health

### Scientific Research and Innovation
- Innovation accelerator
- Clinical investigations and trials
- Research and development

### Healthcare Quality and Access
- Enabling access to innovative medicines and devices
- Population health

### Safety and Surveillance
- Robust vigilance
- Implementation of evidence-based risk mitigation
- Public health
Transforming vigilance: our ambitions

- Engaging and transparent
- Fully integrated into the healthcare system
- Prediction and risk minimization through pharmaco-genomics
- Latest tools, innovation and improved data
- Proactively monitoring and acting on insights across the product full lifecycle

Better use of data to provide insight to inform decisions on medical products but also to improve the efficiency of our operational processes.
Other drivers for increasing access to RWE

• Promoting innovation
  - Real world evidence to support authorisation
  - Innovative Licencing and Access Pathway – early identification of RWE needs
  - Early access to medicines scheme – requirements for proactive vigilance

• Recognised data gaps and opportunities
  - Independent medicines and medical devices safety review
  - Life sciences vision
  - Opportunity to build around the Clinical Practice Research Datalink

• Evolving landscape
  - Improvements to data particularly for medical devices
  - Advancing analytical methodologies and pipelines
  - COVID-19 experience
  - Role of regulators promoting robust use of RWE
Aims:

- Characterise use of fluoroquinolones in UK to monitor impact of RMMs
- Increase understanding on epidemiology of rectal prolapse & rectopexy (& associated outcomes).

- Increase understanding of utility of OMOP CDM
- Understand implications of CDM on robustness, timeliness, & availability of data
- Understand contribution to data gaps – particularly devices
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The names, images and logos identifying the Medicines and Healthcare products Regulatory Agency are proprietary marks. All the Agency’s logos are registered Trademarks and cannot be used without the Agency’s explicit permission.
Use of systemic fluoroquinolones in primary care and hospital settings in the UK: a drug utilisation study
Background

• Fluoroquinolone antibiotics have been approved decades ago
• They are commonly prescribed in primary care and hospitals to treat different types of infections, e.g. respiratory and urinary tract infections.
• More recently, they have been associated with an increased risk of severe adverse events
• MHRA issued Risk Minimisation Measures in March 2019
  • no fluoroquinolone prescriptions for self-limiting, mild or moderate infections
  • avoid use in patients who have previously had serious adverse reactions
  • special caution for people ≥60 years, renal impairment or solid-organ transplants
  • avoid use of a corticosteroid with a fluoroquinolone

 Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects

Disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems have been reported very rarely with fluoroquinolone antibiotics. Fluoroquinolone treatment should be discontinued at the first signs of a serious adverse reaction, including tendon pain or inflammation.

From: Medicines and Healthcare products Regulatory Agency
Published: 21 March 2019
Research question and Objectives

Objectives

Population-level drug utilisation:
To estimate the incidence and prevalence of use of fluoroquinolones in the UK stratified by setting, calendar term/year, and age for the period 2012-2022.

Additional analysis: Interrupted time series analyses

Patient-level drug utilisation
To characterise new users and calculate the duration, indication and dose of fluoroquinolone use in the UK, stratified by setting, calendar term/year, and age.

Additional stratifications for characterisation:
• before/after RMM intervention
• age groups 18-59, >60
• Comorbidities/comedication as suggested as by MHRA
• Previous use of other antibiotics
Methods

Study population

Population-level drug utilisation
All people in database
- recorded between 01/01/2012 and 31/12/2022
- at least 30 days of previous database visibility.

Patient-level drug utilisation
New users of any fluoroquinolone
- not using the same index medicine for 30 days
- between 01/01/2012 and 31/12/2022
- at least 30 days of visibility prior to therapy initiation
**Methods**

### Diagnostics and Study Code

**Feasibility checks**
- DrugExposureDiagnostics
- CohortDiagnostics

**R-Packages used for study**

<table>
<thead>
<tr>
<th>Package</th>
<th>CRAN Link</th>
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<tbody>
<tr>
<td>CodelistGenerator</td>
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<tr>
<td>DrugUtilisation</td>
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Population-level drug utilisation before/after RMM

Primary care databases (CPRD GOLD + AURUM) + Primary/secondary care data from Scotland (HIC)
Interrupted time series analyses

\[ Y_t = \alpha + \beta_1 \cdot \text{time} + \beta_2 \cdot \text{intervention} + \beta_3 \cdot \text{time since intervention} + \varepsilon \]
Population-level drug utilisation before/after RMM

Hospital databases (Barts Health) 2013-2021 [Great Ormond Street Hospital and Lancashire data 2019 onwards]
## New user characterisation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Format</th>
<th>Primary care databases</th>
<th>Primary/Secondary care</th>
<th>Hospital databases</th>
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<td></td>
<td>CPRD Aurum</td>
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<td>HIC Dundee</td>
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<td>Number of subjects</td>
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<td>384,744</td>
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<td>Number of records</td>
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<td>1,621,106</td>
<td>606,683</td>
<td>113,740</td>
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<tr>
<td>Sex: Female</td>
<td>N (%)</td>
<td>807,037 (50%)</td>
<td>305,647 (50%)</td>
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<tr>
<td>Comedication</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antibiotics 30 days prior</td>
<td>N (%)</td>
<td>512,815 (32%)</td>
<td>205,629 (34%)</td>
<td>NA</td>
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<tr>
<td>Glucocorticoids 1 year prior</td>
<td>N (%)</td>
<td>256,745 (16%)</td>
<td>100,620 (17%)</td>
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</tr>
<tr>
<td>Comorbidities</td>
<td></td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>N (%)</td>
<td>190,944 (12%)</td>
<td>73,448 (12%)</td>
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</tr>
<tr>
<td>Solid organ transplant</td>
<td>N (%)</td>
<td>6,128 (0%)</td>
<td>2,297 (0%)</td>
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<tr>
<td>Trauma</td>
<td>N (%)</td>
<td>405,076 (25%)</td>
<td>132,508 (22%)</td>
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<td>Stroke ischemic hemorrhagic</td>
<td>N (%)</td>
<td>21,187 (1%)</td>
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<td>COPD</td>
<td>N (%)</td>
<td>140,878 (9%)</td>
<td>52,072 (9%)</td>
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<td>Heart valve disorder</td>
<td>N (%)</td>
<td>140,878 (9%)</td>
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<tr>
<td>Hypertension</td>
<td>N (%)</td>
<td>441,640 (27%)</td>
<td>121,405 (20%)</td>
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<td>Hyperlipidemia</td>
<td>N (%)</td>
<td>139,987 (9%)</td>
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<td>Ischemic heart disease</td>
<td>N (%)</td>
<td>128,943 (8%)</td>
<td>44,761 (7%)</td>
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</table>
Indication for fluoroquinolones before/after RMM

Conditions recorded within 7 days before treatment start was used as proxy for indication
Drug utilisation: DrugExposure Diagnostics

<table>
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<tr>
<th>Parameter</th>
<th>Median [IQR]</th>
<th>CPRD AURUM</th>
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<td>Duration</td>
<td>7 days [5-10]</td>
<td>5 days [5-7]</td>
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<tr>
<td>Initial dose</td>
<td>1000mg [1000 – 1000mg]</td>
<td>1000mg [1000 – 1400mg]</td>
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<tr>
<td>Cumulative dose</td>
<td>7000mg [5000 – 1000mg]</td>
<td>7000mg [5000mg – 1000mg]</td>
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</table>
Conclusion

✓ **RMM was effective** in reducing population-level incidence of fluoroquinolones prescriptions

✓ Slightly **stronger effect in people ≥60 years**

✓ Substantial proportion of new users received different antibiotic the immediate time before “second-line” use

✓ Proportion of **prescriptions for urinary tract infections and respiratory tract infections decreased** after RMM relative to the time before
Thank you very much!

Katherine, Helen, Stephanie, John, Patrick, Allison
Ed and Dani
OHDSI UK Data Partners
Oxford team

It's been a great week!
Rectopexy & the search for devices

Jennifer Lane MD
NIHR Academic Clinical Lecturer
Trauma & Orthopaedic Surgery
Aims of the surgical question

- Epidemiology of Rectal prolapse
- Epidemiology of Rectopexy
- Rectopexy (surgical) coding incl subtypes
- Rectopexy (surgical) complications
- Can we really identify device use?
- Is the device data useful?
Studyathon as a Data Partner

5 hospitals across East London, UK = 2.6M patients, 15y horizon

Specialist services
Cardiac/Cancer/Renal/Paediatrics

Level 1 Trauma Centre
Ortho/ICU/Major trauma
Ortho:
100,000 patients per year
10,000 procedures

QMUL University
Barts & the London Medical (& Dental) School
Prolapse, Rectopexy & subtypes

Based upon phenotyping work pre-studyathon (props to Albert Prats Uribe & team!)

יפור Knowledge expert – identify prolapse, rectopexy incl those with and without device use
יפור Focus on OPCS -> SNOMED
יפור Outcome measures- complications 30d, 90d, 1y, 2y

-> CodelistGenerator; PatientProfiles; DrugUtilisation; IncidencePrevalence
-> +/- device identifier
What happens in surgery?

From the OR to Oxford
SEARCH RESULTS FOR: 1363-44-000 (1 result)

Company Name: DEPUY ORTHOPAEDICS, INC.

NA - 10603295032762
MODULAR CATHCART FRACTURE HEAD HIP BALL 44mm OD +6mm

Company Name: DEPUY ORTHOPAEDICS, INC.

Version or Model: 1363-44-000
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SEARCH RESULTS FOR: UPA31015 (1 result)

ULTRAPRO ADVANCED - 10705031236998
Macroporous Partially Absorbable Mesh

Company Name: Johnson & Johnson International Inc.

Version or Model: UPA31015
Device Progress

What did we achieve?

- Discovered specific implants in our cohorts
- Generated device specific cohort – future use
- 1,200,000 implantable device serial numbers found in Barts Data during Studyathon
- Identification of devices in other UK Node partners
Learning Points

- Consistency of data entry
- Formats of UDI vary internationally (but predictable)
- Understanding UDI format in our data
- Developing infrastructure to analyse data related to these devices
What’s next?
Taking the work forward

01 Identify approved devices
02 Re-format data within our CDM for devices
03 Check consistency of data entry
04 Generate device specific cohorts
05 Develop longitudinal surveillance of specific devices
06 Build infrastructure and capacity + local community
Big Thanks to Collaborators

- Lancashire Teaching Hospitals NHS trust
- CPRD
- University of Dundee
- University of Oxford
Thank you

@jennifercelane
@usamarahman
@xlgriffin
BARTS

BONE JOINT HEALTH

W bonejointhealth.ac.uk
E boneandjointhealth@qmul.ac.uk
<table>
<thead>
<tr>
<th>Issuing Agency/Entity</th>
<th>Qualifier</th>
<th>Identifier</th>
<th>Data type</th>
<th>Human Readable Field Size</th>
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ex: (01)09506000117843(11)141231(17)201231(10)1234AB(21)5678CD

* See Table 7.11.1 of the GS1 General Specifications: https://www.gs1.org/docs/barcodes/GS1_General_Specifications.pdf