Medicines & Healthcare products Regulatory Agency

MHRA and the use of RWE

Why an OHDSI study-a-thon?

Katherine Donegan, Head of Epidemiology

23 January 2024

MHRA: Who are we?!

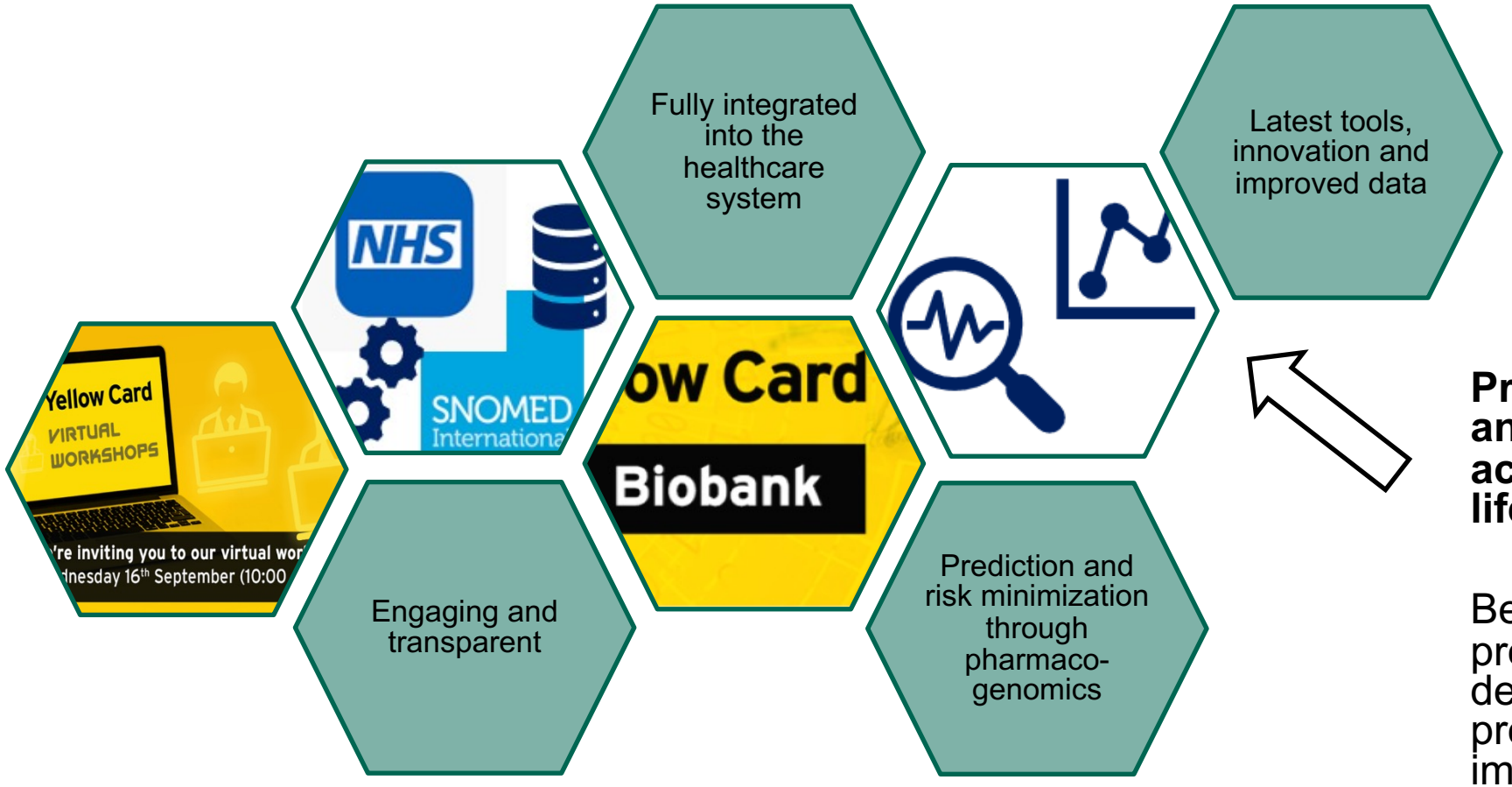
We are the regulator of medicines, medical devices and blood components for transfusion in the UK.

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	Healthcare Quality and Access	Safety and Surveillance
• Innovation accelerator • Clinical investigations and trials • Research and development	• Enabling access to innovative medicines and devices • Population health	• Robust vigilance • Implementation of evidence-based risk mitigation • Public health

Transforming vigilance: our ambitions



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

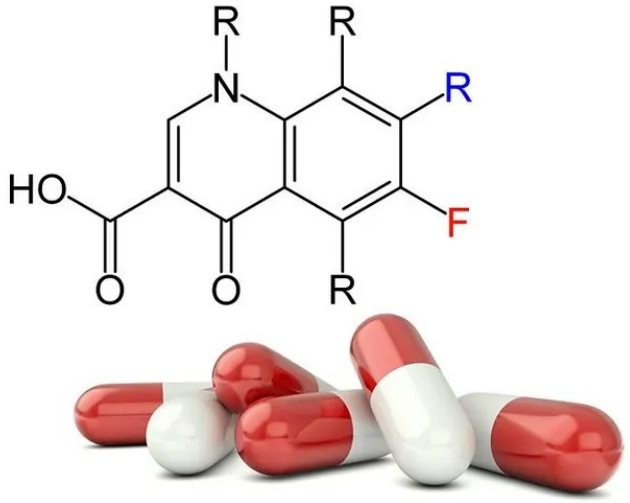
- Recognised data gaps and opportunities
  - Independent medicines and medical devices safety review
  - Life sciences vision
  - Opportunity to build around the Clinical Practice Research Datalink

- 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

MHRA Study-a-thon: **Fluoroquinolones & Rectopexy Mesh**

Aims:

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



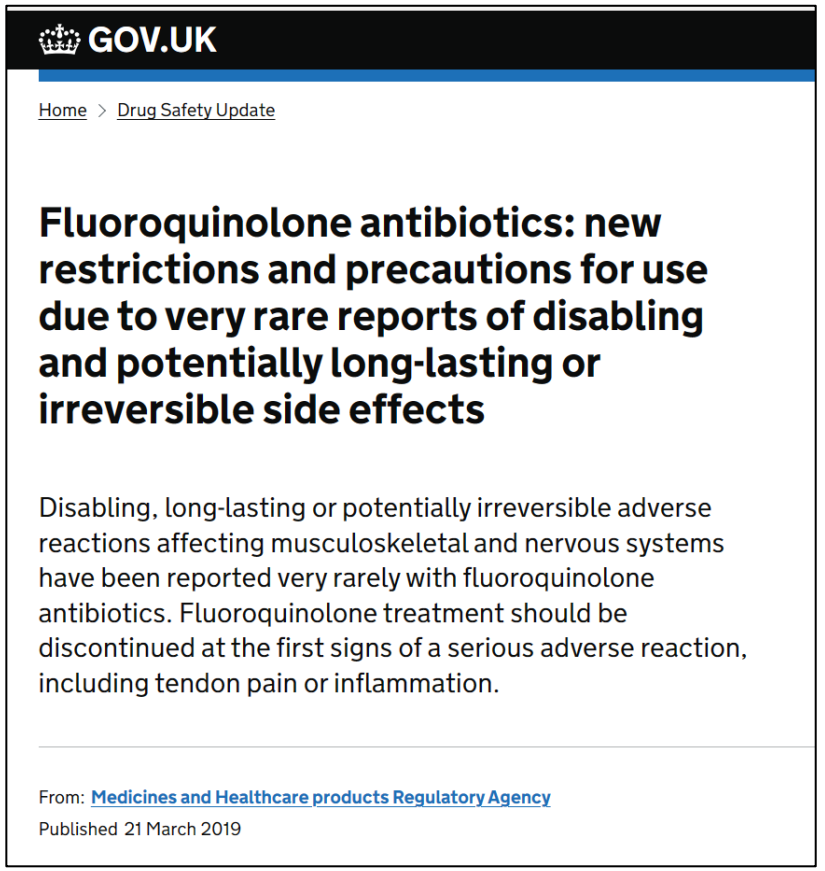
- Increase understanding of utility of **OMOP CDM**
- Understand **implications of CDM** on robustness, timeliness, & availability of data
- Understand contribution to **data gaps** – particularly **devices**

Copyright information

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



GOV.UK

Home > Drug Safety Update

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.

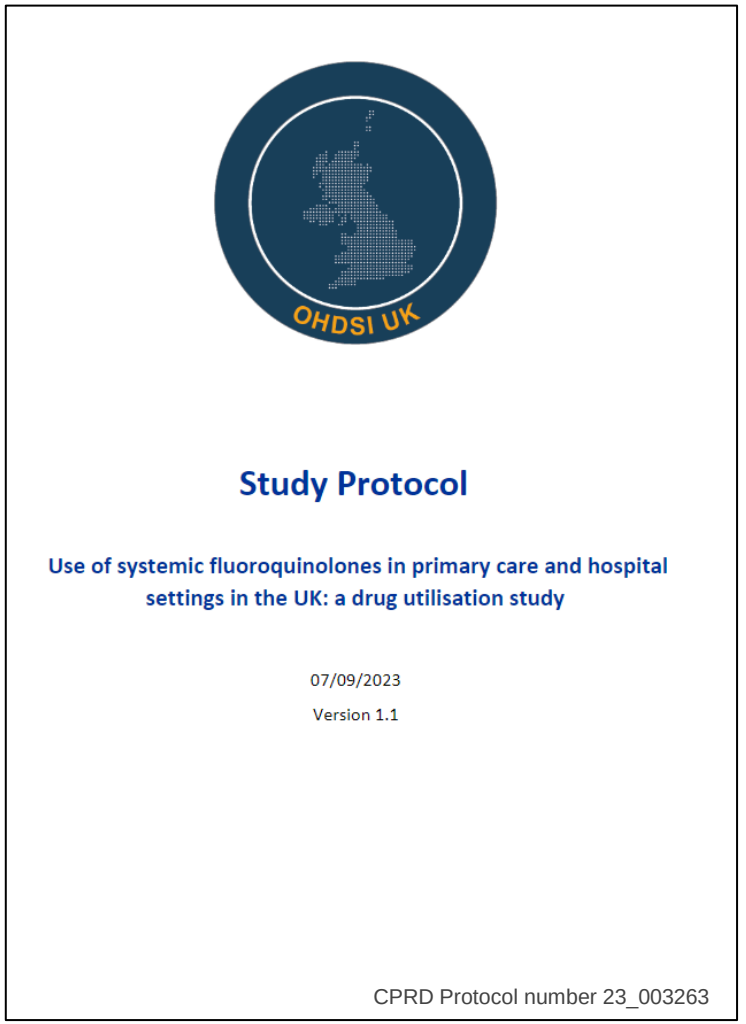
Additional analysis: Interrupted time series analyses

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.

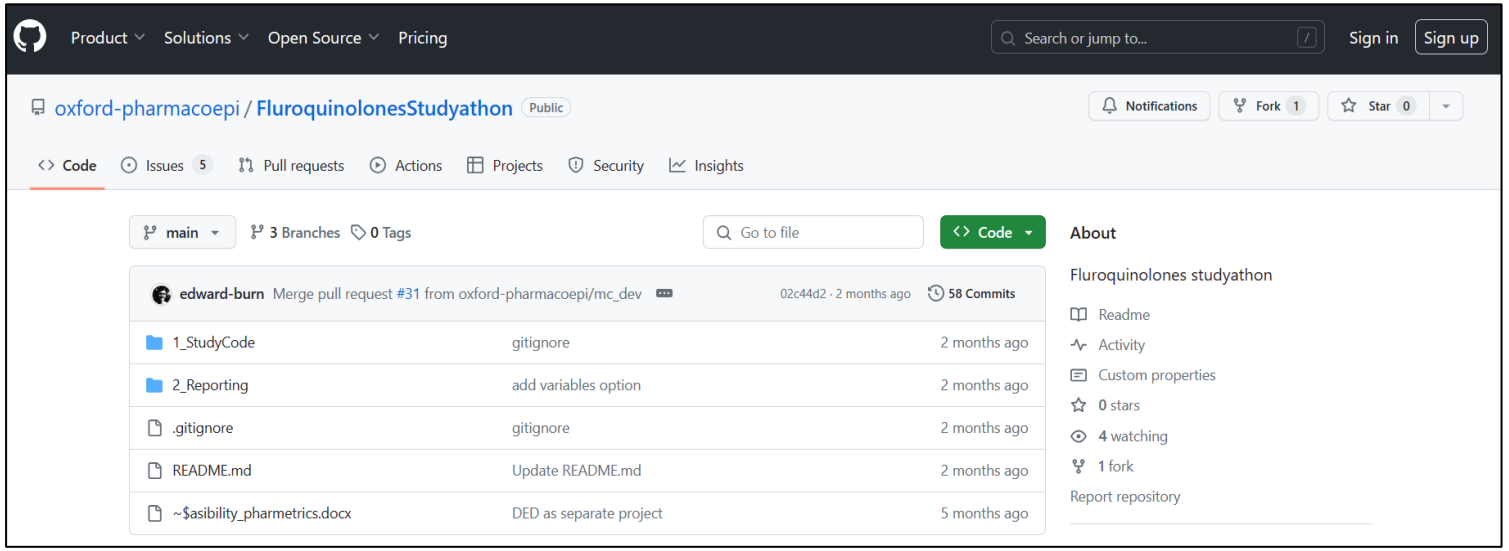
Patient-level drug utilisation

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

CodelistGenerator

CRAN - Package CodelistGenerator (r-project.org)

IncidencePrevalence

CRAN - Package IncidencePrevalence (r-project.org)

PatientProfiles

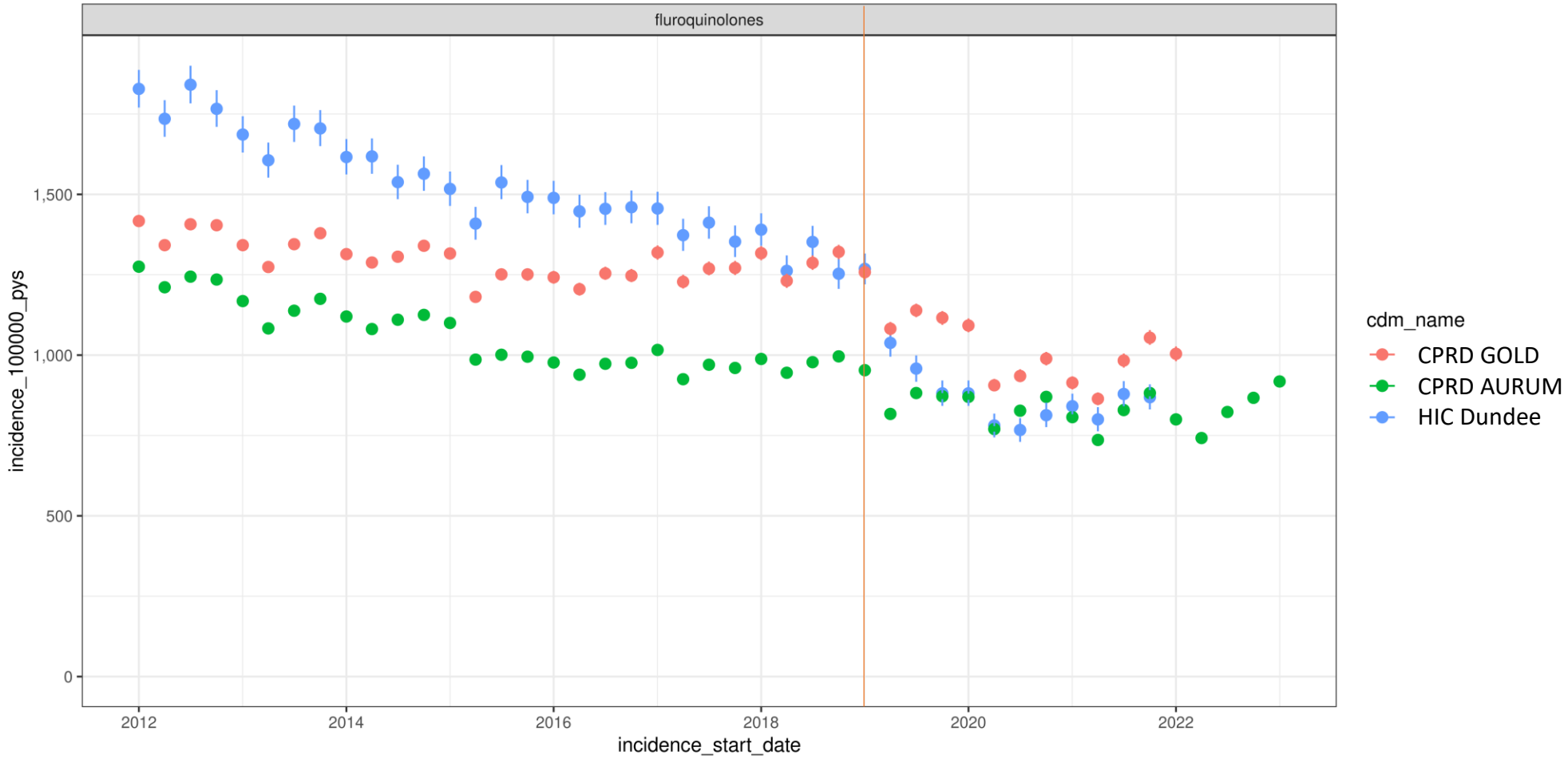
CRAN - Package PatientProfiles (r-project.org)

DrugUtilisation

CRAN - Package DrugUtilisation (r-project.org)

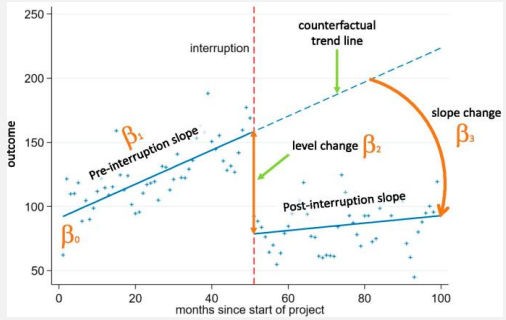
Population-level drug utilisation before/after RMM

Primary care databases (CPRD GOLD + AURUM) + Primary/secondary care data from Scotland (HIC)



Interrupted time series analyses

Interrupted time series analyses



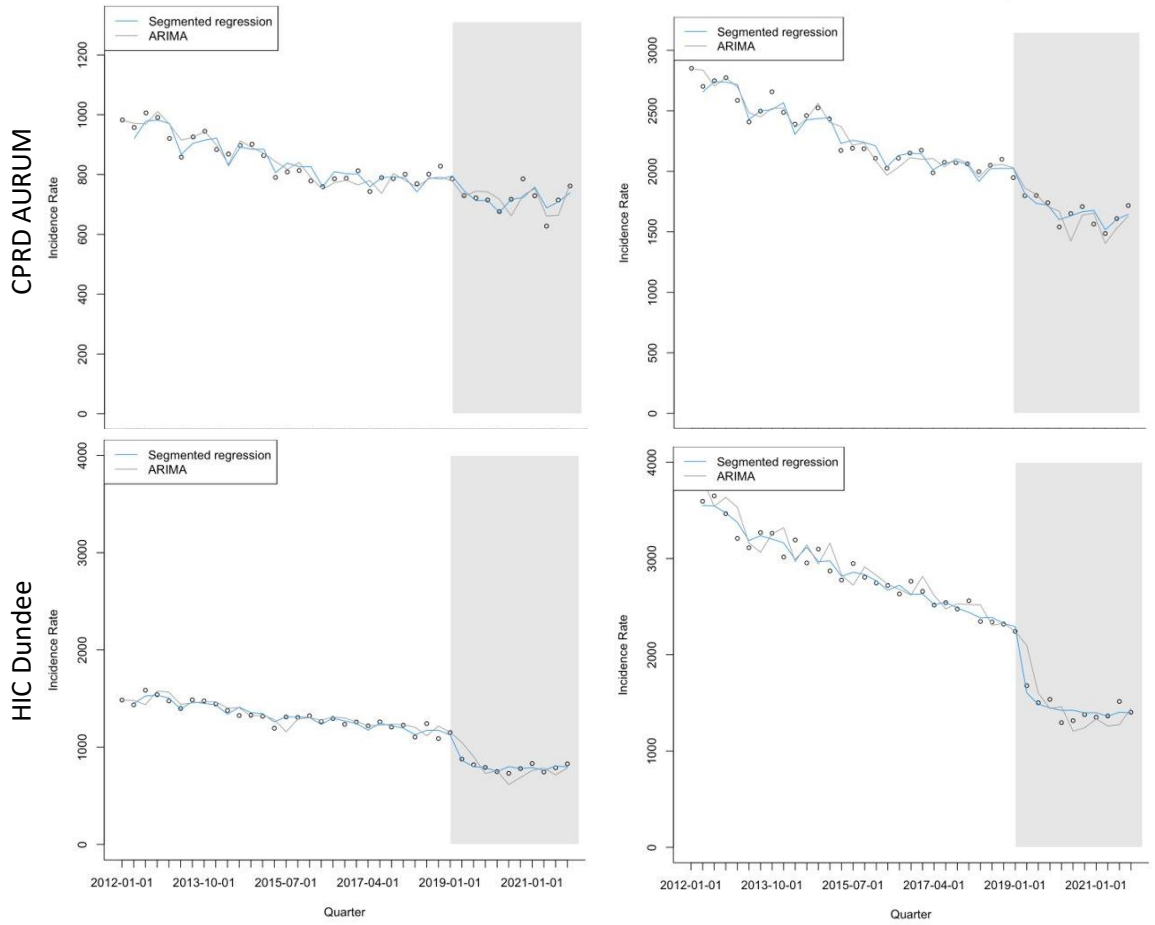
$$Y_t = \alpha + \beta_1 \cdot time + \beta_2 \cdot intervention + \beta_3 \cdot time\ since\ intervention + \varepsilon$$

Age group 19-59

Age group >60

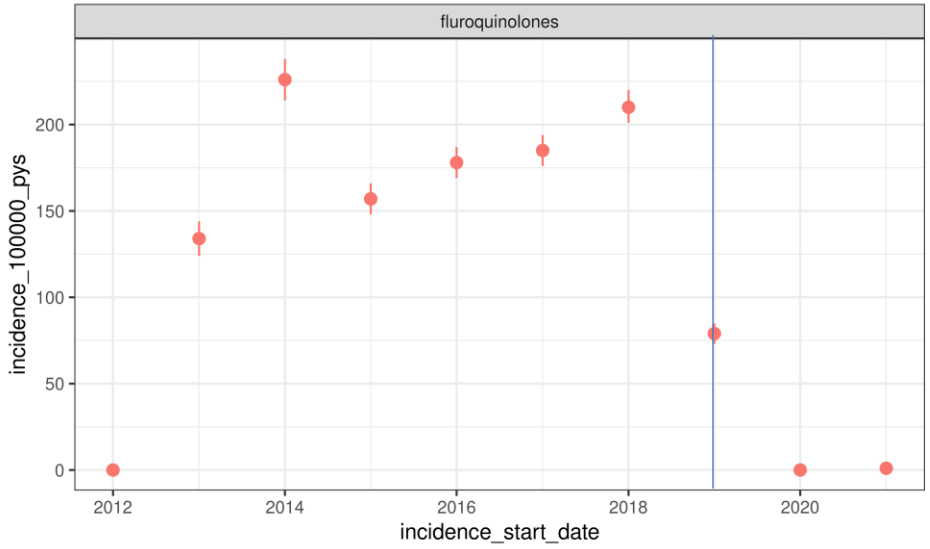
CPRD AURUM

HIC Dundee

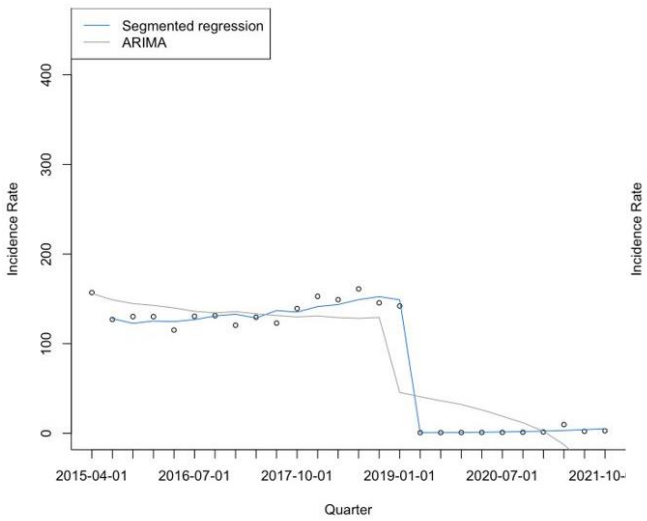


Population-level drug utilisation before/after RMM

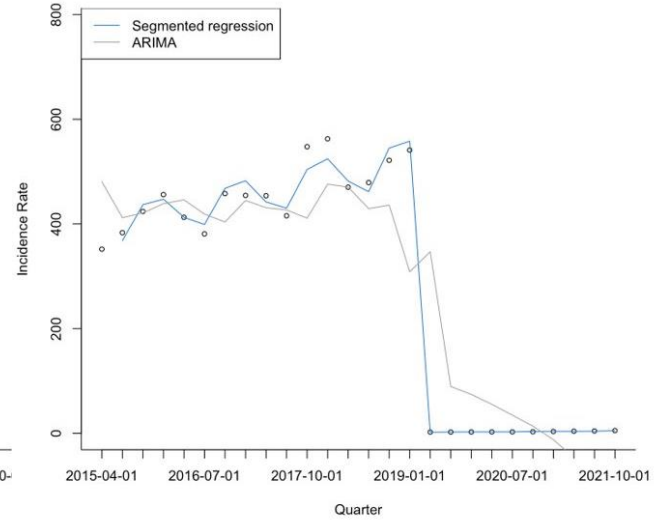
Hospital databases (Barts Health) 2013-2021 [Great Ormond Street Hospital and Lancashire data 2019 onwards]



Age group 19-59



Age group >60



New user characterisation

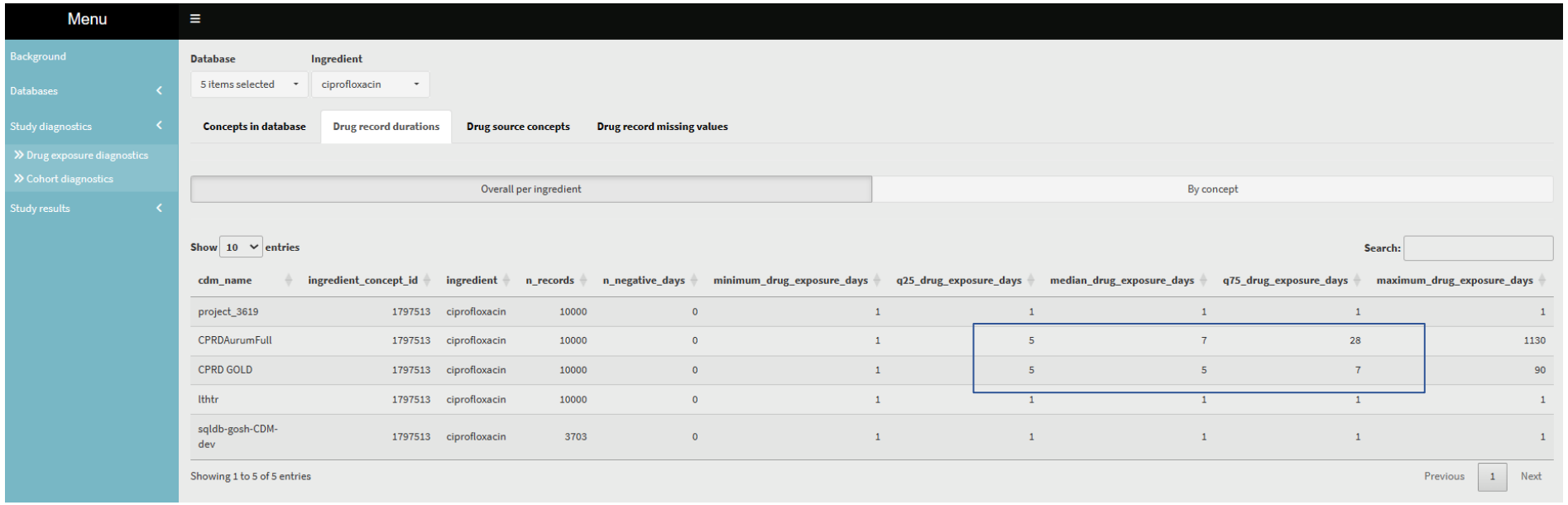
		Primary care databases		Primary/Secondary care	Hospital databases		
Variable	Format	**CPRD Aurum**	**CPRD GOLD**	**HIC Dundee**	**Barts Health**	**Lancashire**	**GOSH**
Number of subjects	N	1,044,142	384,744	67,394	7,007	2,287	46
Number of records	N	1,621,106	606,683	113,740	8,680	2,527	192
Age	median [IQR]	58 [39 - 73]	59 [41 - 73]	58 [41 - 72]	57 [37 - 71]	70 [55 - 80]	6 [1 - 10]
Sex: Female	N (%)	807,037 (50%)	305,647 (50%)	55,397 (49%)	4,000 (46%)	1,236 (49%)	96 (50%)
Comedication							
Antibiotics 30 days prior	N (%)	512,815 (32%)	205,629 (34%)	NA	2,528 (29%)	NA	NA
Glucocorticoids 1 year prior	N (%)	256,745 (16%)	100,620 (17%)	NA	NA	NA	NA
Comorbidities							
Chronic Kidney Disease	N (%)	190,944 (12%)	73,448 (12%)	NA	1,632 (19%)	NA	NA
Solid organ transplant	N (%)	6,128 (0%)	2,297 (0%)	NA	275 (3%)	NA	NA
Trauma	N (%)	405,076 (25%)	132,508 (22%)	NA	252 (3%)	NA	NA
Stroke ischemic hemorrhagic	N (%)	21,187 (1%)	7,362 (1%)	NA	538 (6%)	NA	NA
COPD	N (%)	140,878 (9%)	52,072 (9%)	NA	1,649 (19%)	NA	NA
Heart valve disorder	N (%)	140,878 (9%)	52,072 (9%)	NA	1,649 (19%)	NA	NA
Hypertension	N (%)	441,640 (27%)	121,405 (20%)	NA	3,869 (45%)	NA	NA
Hyperlipidemia	N (%)	139,987 (9%)	46,181 (8%)	NA	2,339 (27%)	NA	NA
Ischemic heart disease	N (%)	128,943 (8%)	44,761 (7%)	NA	1,595 (18%)	NA	NA

Indication for fluoroquinolones before/after RMM

Conditions recorded within 7 days before treatment start was used as proxy for indication

Drug utilisation: DrugExposure Diagnostics

DrugExposureDiagnostics



		CPRD AURUM	CPRD GOLD
Duration	Median [IQR]	7 days [5 -10]	5 days [5-7]
Initial dose	Median [IQR]	1000mg [1000 – 1000mg]	1000mg [1000 – 1400mg]
Cumulative dose	Median [IQR]	7000mg [5000 – 1000mg]	7000mg [5000mg – 1000mg]

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!

BARTS

BONE JOINT HEALTH

Rectopexy & the search for devices

Jennifer Lane MD

NIHR Academic Clinical Lecturer

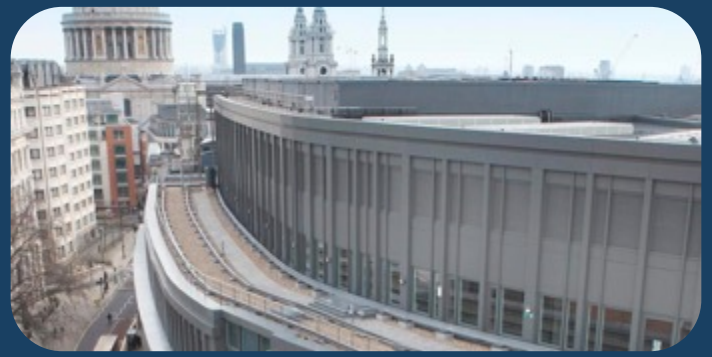
Trauma & Orthopaedic Surgery

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!)

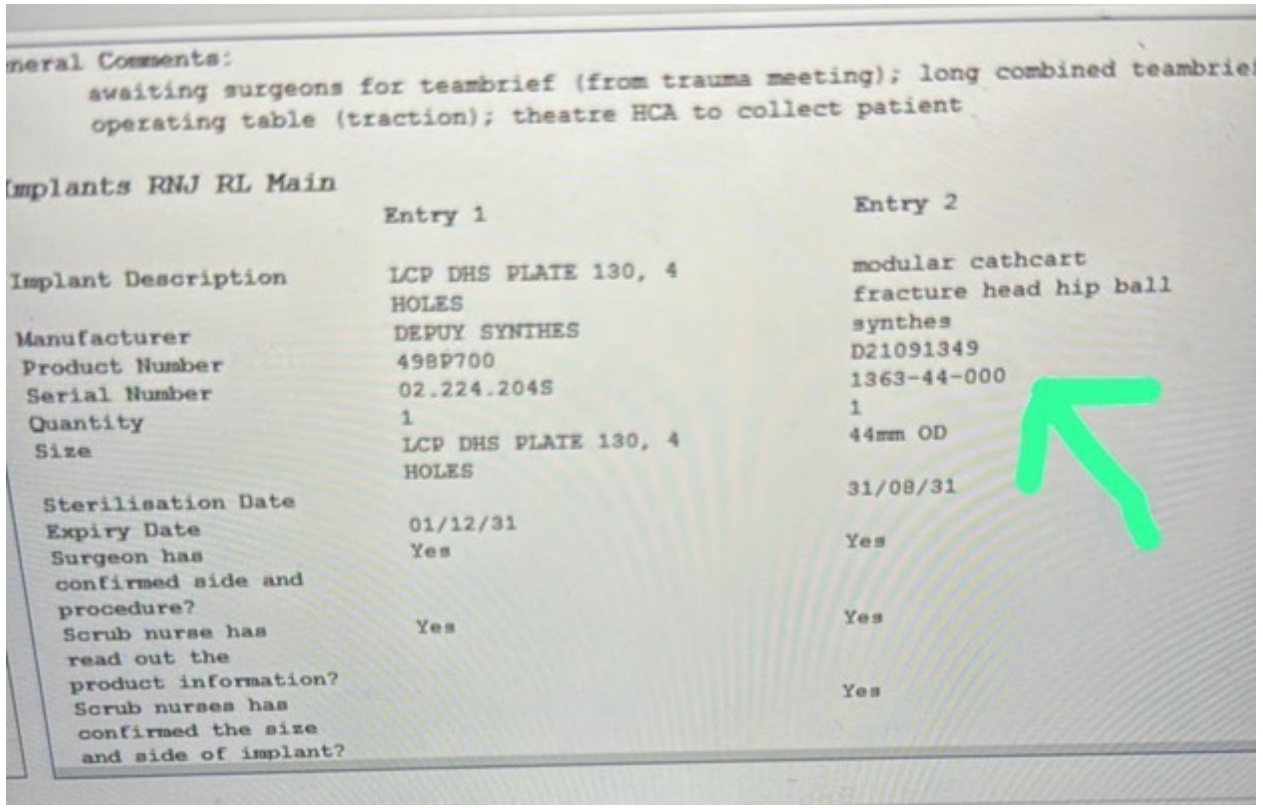
- Knowledge expert – identify prolapse, rectopexy incl those with and without device use
- Focus on OPCS -> SNOMED
- Outcome measures- complications 30d, 90d, 1y, 2y

-> CodelistGenerator; PatientProfiles; DrugUtilisation; IncidencePrevalence

-> +/- device identifier

What happens in surgery?

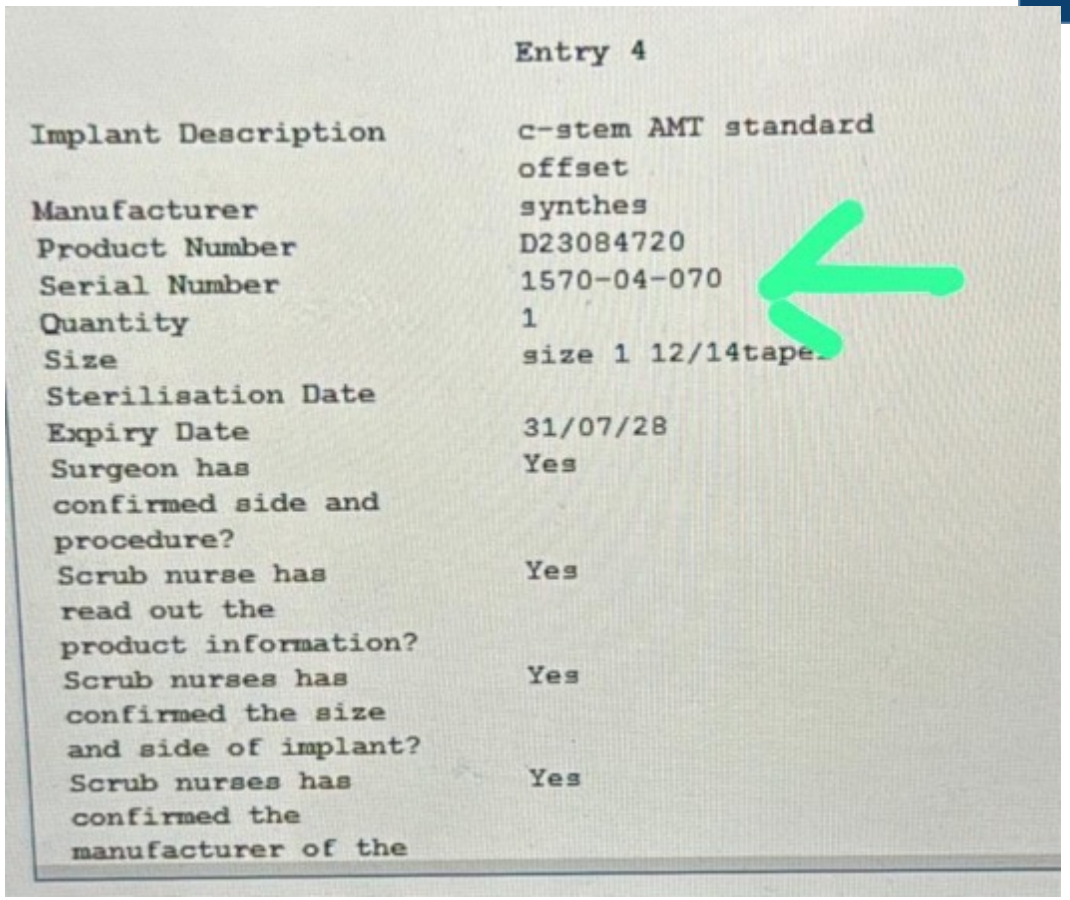
From the OR to Oxford



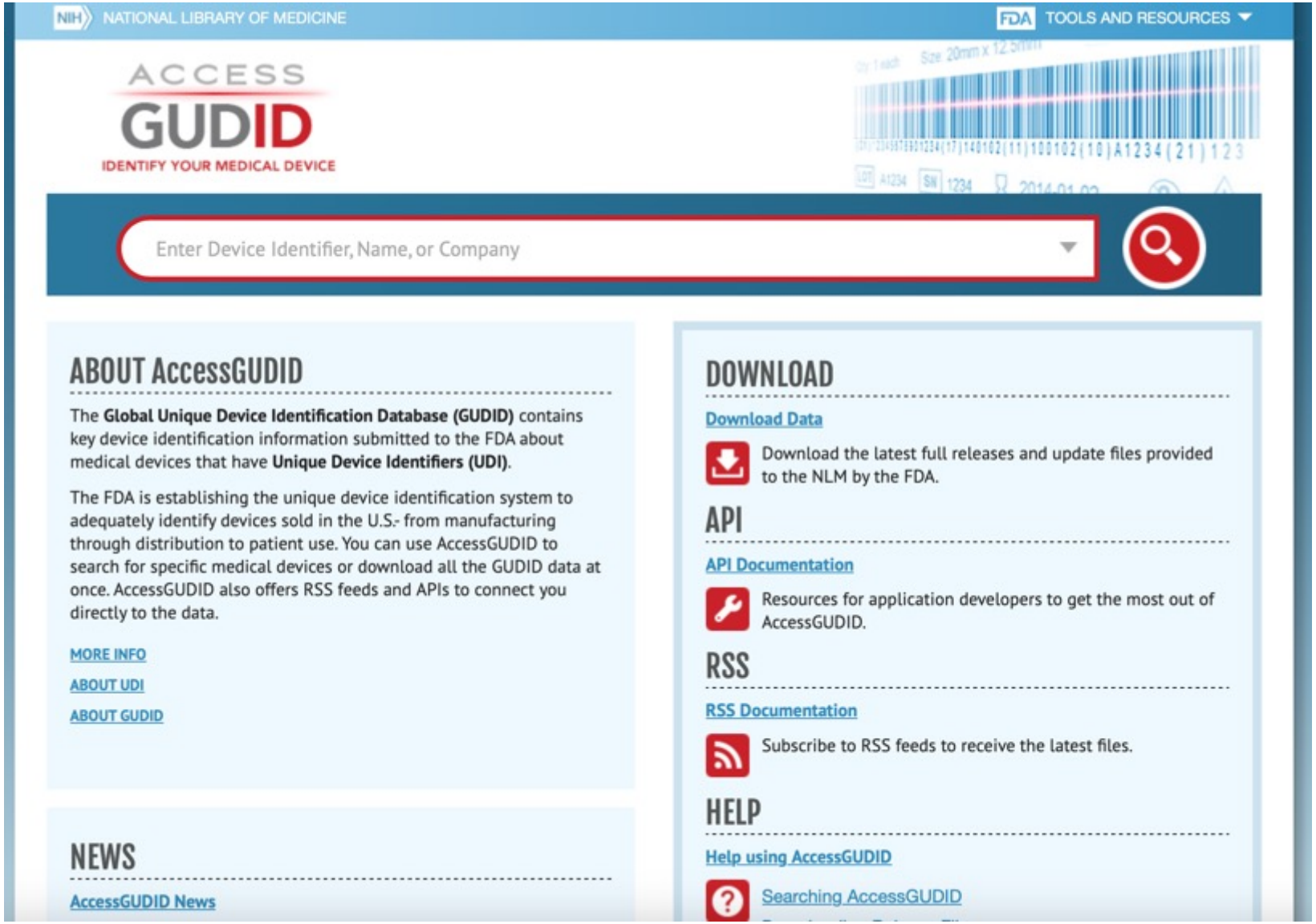
neral Comments:
awaiting surgeons for teambrief (from trauma meeting); long combined teambrie
operating table (traction); theatre HCA to collect patient

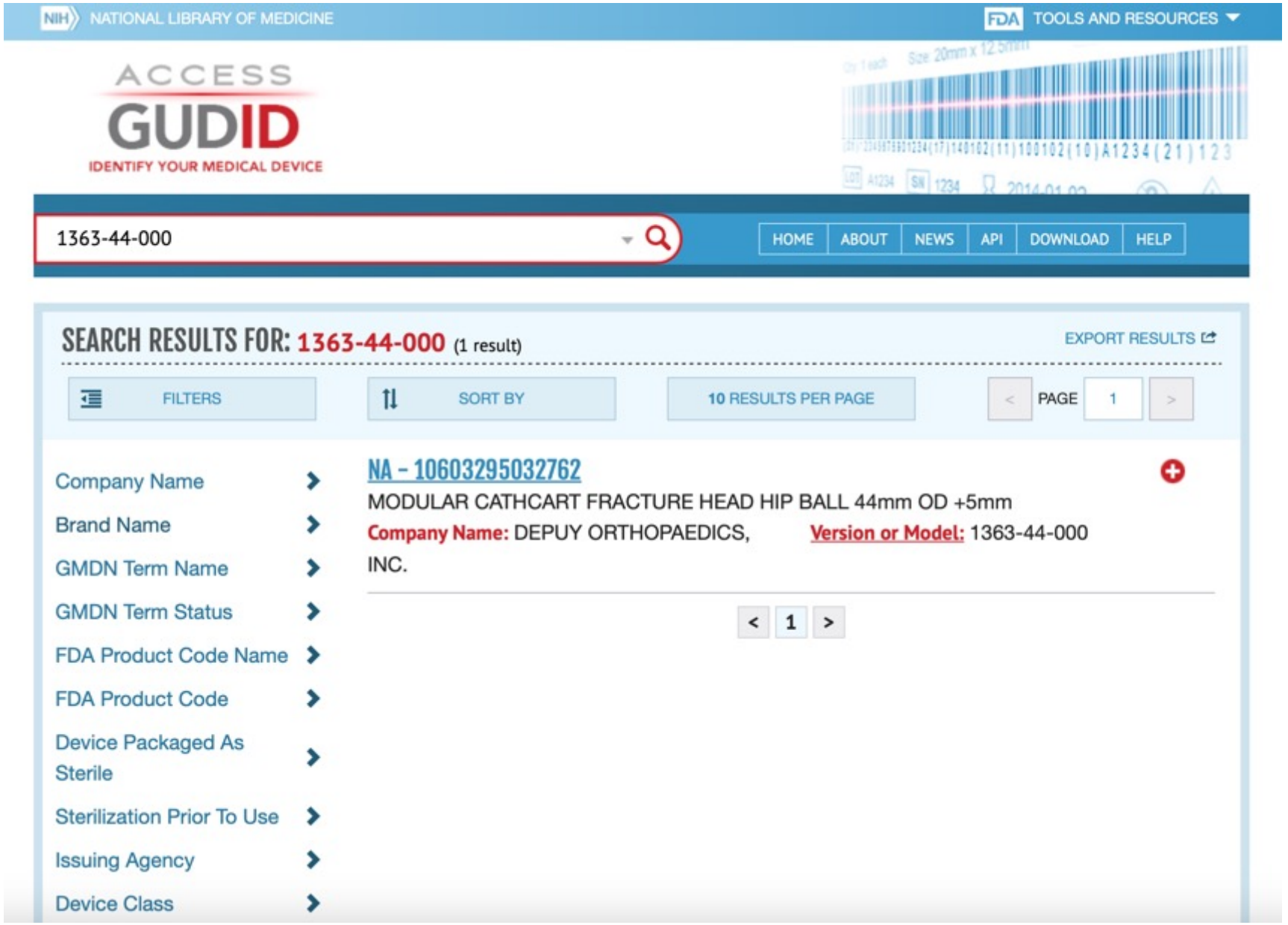
Implants RNJ RL Main

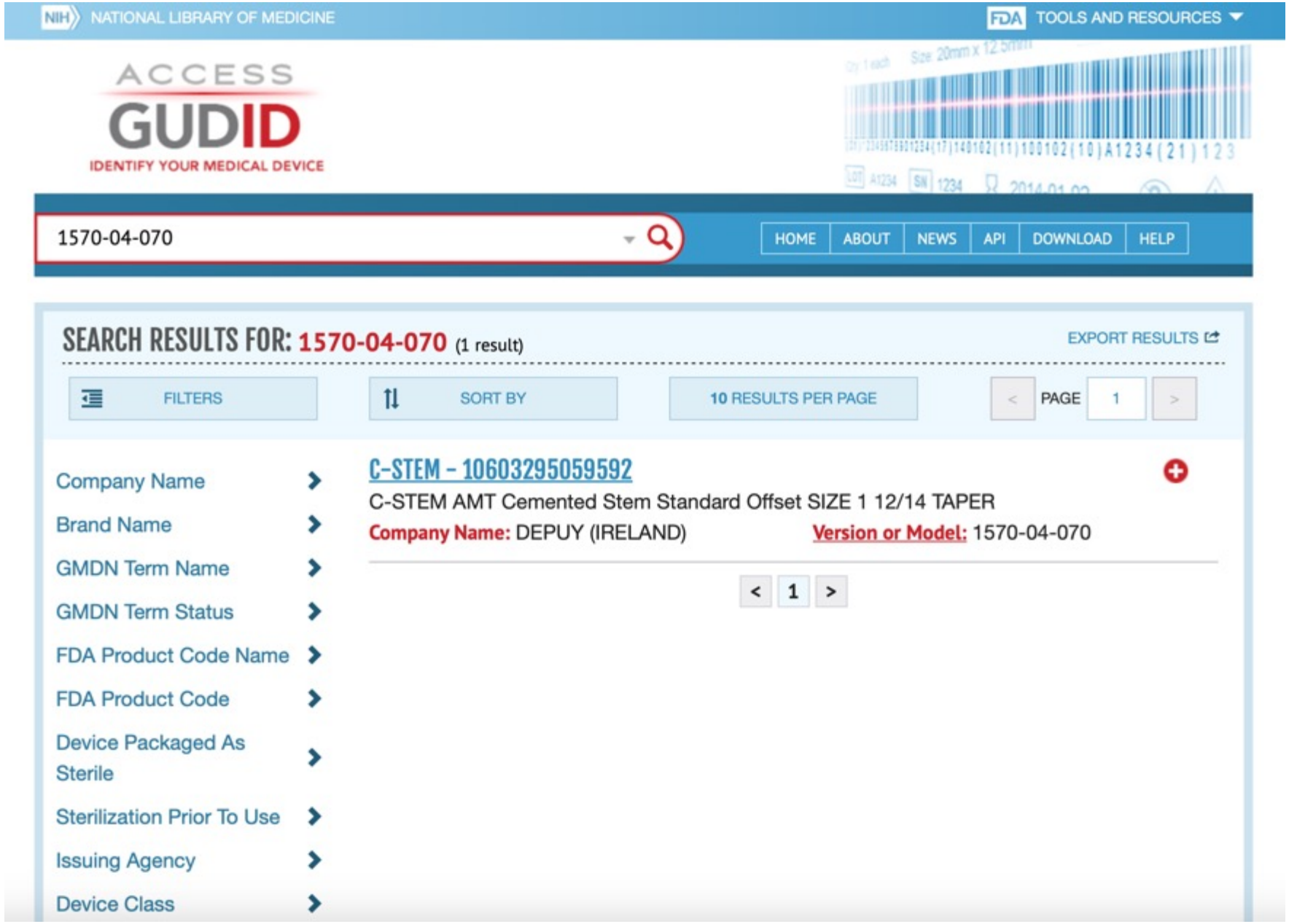
	Entry 1	Entry 2
Implant Description	LCP DHS PLATE 130, 4 HOLES	modular cathcart fracture head hip ball
Manufacturer	DEPUY SYNTHES	synthes
Product Number	498P700	D21091349
Serial Number	02.224.204S	1363-44-000
Quantity	1	1
Size	LCP DHS PLATE 130, 4 HOLES	44mm OD
Sterilisation Date		31/08/31
Expiry Date	01/12/31	
Surgeon has confirmed side and procedure?	Yes	Yes
Scrub nurse has read out the product information?	Yes	Yes
Scrub nurses has confirmed the size and side of implant?		Yes



	Entry 4
Implant Description	c-stem AMT standard offset
Manufacturer	synthes
Product Number	D23084720
Serial Number	1570-04-070
Quantity	1
Size	size 1 12/14tape
Sterilisation Date	
Expiry Date	31/07/28
Surgeon has confirmed side and procedure?	Yes
Scrub nurse has read out the product information?	Yes
Scrub nurses has confirmed the size and side of implant?	Yes
Scrub nurses has confirmed the manufacturer of the	Yes


NIH NATIONAL LIBRARY OF MEDICINE
FDA TOOLS AND RESOURCES
ACCESS GUDID
IDENTIFY YOUR MEDICAL DEVICE
Enter Device Identifier, Name, or Company
ABOUT AccessGUDID
The Global Unique Device Identification Database (GUDID) contains key device identification information submitted to the FDA about medical devices that have Unique Device Identifiers (UDI).
The FDA is establishing the unique device identification system to adequately identify devices sold in the U.S.- from manufacturing through distribution to patient use. You can use AccessGUDID to search for specific medical devices or download all the GUDID data at once. AccessGUDID also offers RSS feeds and APIs to connect you directly to the data.
MORE INFO
ABOUT UDI
ABOUT GUDID
NEWS
AccessGUDID News
DOWNLOAD
Download Data
Download the latest full releases and update files provided to the NLM by the FDA.
API
API Documentation
Resources for application developers to get the most out of AccessGUDID.
RSS
RSS Documentation
Subscribe to RSS feeds to receive the latest files.
HELP
Help using AccessGUDID
Searching AccessGUDID

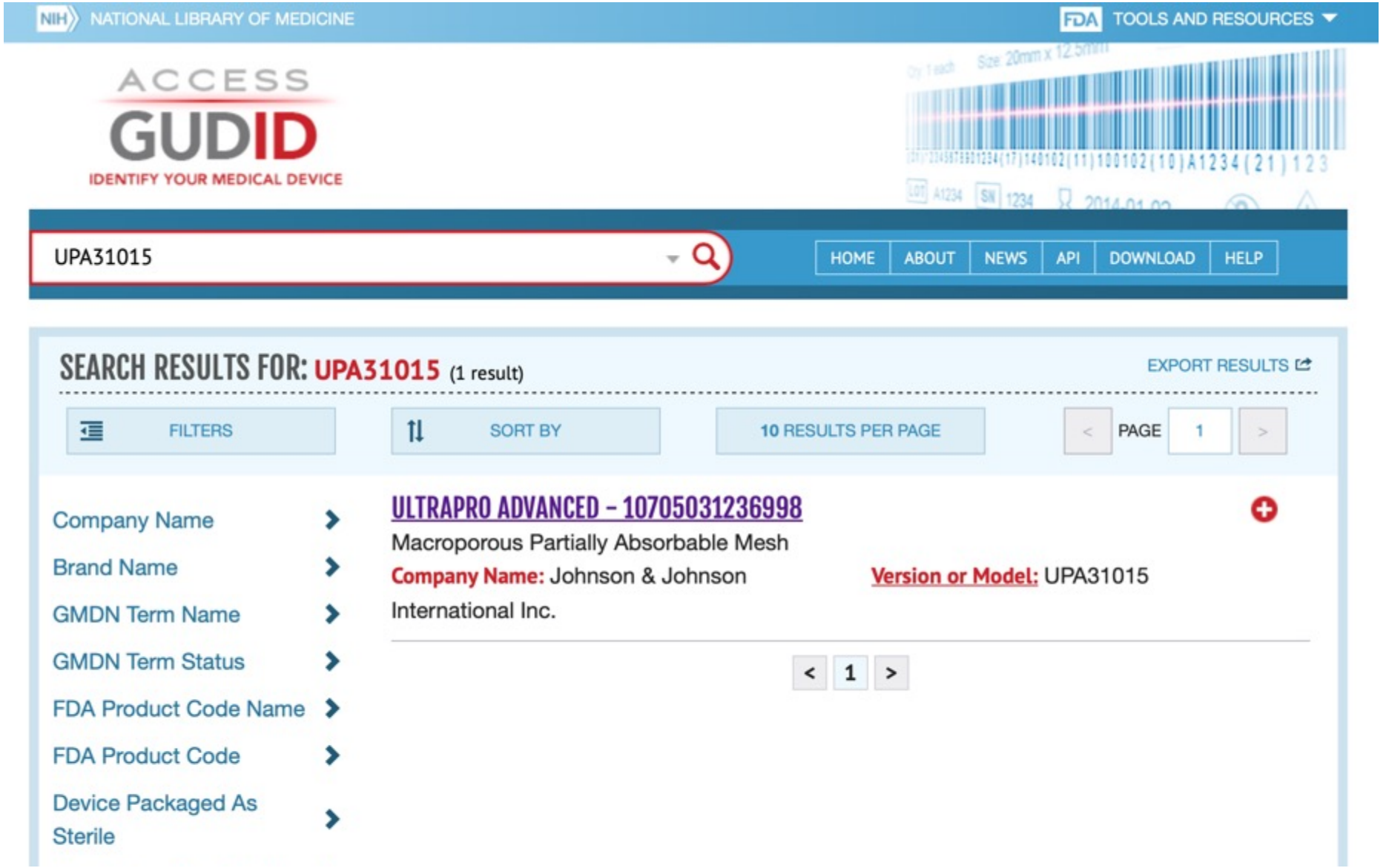

NIH NATIONAL LIBRARY OF MEDICINE
FDA TOOLS AND RESOURCES
ACCESS
GUDID
IDENTIFY YOUR MEDICAL DEVICE
1363-44-000
HOME
ABOUT
NEWS
API
DOWNLOAD
HELP
SEARCH RESULTS FOR: 1363-44-000 (1 result)
EXPORT RESULTS
FILTERS
SORT BY
10 RESULTS PER PAGE
PAGE 1
Company Name
Brand Name
GMDN Term Name
GMDN Term Status
FDA Product Code Name
FDA Product Code
Device Packaged As Sterile
Sterilization Prior To Use
Issuing Agency
Device Class
NA - 10603295032762
MODULAR CATHCART FRACTURE HEAD HIP BALL 44mm OD +5mm
Company Name: DEPUY ORTHOPAEDICS, INC.
Version or Model: 1363-44-000
< 1 >


NIH NATIONAL LIBRARY OF MEDICINE
FDA TOOLS AND RESOURCES
ACCESS
GUDID
IDENTIFY YOUR MEDICAL DEVICE
1570-04-070
HOME
ABOUT
NEWS
API
DOWNLOAD
HELP
SEARCH RESULTS FOR: 1570-04-070 (1 result)
EXPORT RESULTS
FILTERS
SORT BY
10 RESULTS PER PAGE
PAGE 1
Company Name
Brand Name
GMDN Term Name
GMDN Term Status
FDA Product Code Name
FDA Product Code
Device Packaged As Sterile
Sterilization Prior To Use
Issuing Agency
Device Class
C-STEM - 10603295059592
C-STEM AMT Cemented Stem Standard Offset SIZE 1 12/14 TAPER
Company Name: DEPUY (IRELAND)
Version or Model: 1570-04-070
< 1 >

Studyathon – Rectopexy - Devices

Finding the associated device

Equipment serial number	Equipment serial number	80511303	4594507	4231843	08/05/2018	NULL	32817	NULL	UPA31015
Equipment serial number	Equipment serial number	80572832	4604634	4231843	31/01/2018	NULL	32817	NULL	UPA31015
Equipment serial number	Equipment serial number	87243359	49306379	4231843	01/02/2018	NULL	32817	NULL	UPA31015
Equipment serial number	Equipment serial number	88835959	50655593	4231843	16/01/2019	NULL	32817	NULL	UPA31015
Equipment serial number	Equipment serial number	89117294	50890772	4231843	31/07/2019	NULL	32817	NULL	UPA31015


NIH NATIONAL LIBRARY OF MEDICINE
FDA TOOLS AND RESOURCES
ACCESS
GUDID
IDENTIFY YOUR MEDICAL DEVICE
UPA31015
HOME
ABOUT
NEWS
API
DOWNLOAD
HELP
SEARCH RESULTS FOR: UPA31015 (1 result)
EXPORT RESULTS
FILTERS
SORT BY
10 RESULTS PER PAGE
PAGE 1
Company Name
Brand Name
GMDN Term Name
GMDN Term Status
FDA Product Code Name
FDA Product Code
Device Packaged As Sterile
ULTRAPRO ADVANCED - 10705031236998
Macroporous Partially Absorbable Mesh
Company Name: Johnson & Johnson International Inc.
Version or Model: UPA31015
< 1 >

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

@bartsbonejoint @boneandjointhealth @...

Issuing Agency/Entity	Qualifier	Identifier	Data type	Human Readable Field Size	Database Field Size
GS1	(01)	DI (GTIN)	Numeric	18 (incl. identifier + data delimiter)	. 14 digits . digit characters '0' to '9'
GS1	(11)	Manufacturing/ Production Date	numeric [YYMMDD]	10 (incl. identifier + data delimiter)	. 6 digits . digit characters '0' to '9'
GS1	(17)	Expiration Date	numeric [YYMMDD]	10 (incl. identifier + data delimiter)	. 6 digits . digit characters '0' to '9'
GS1	(10)	Batch/Lot Number	alphanumeric	24 (max) (incl. identifier + data delimiter)	. 20 (max) . GS1 AI encodable character set 82*
GS1	(21)	Serial Number	alphanumeric	24 (max) (incl. identifier + data delimiter)	. 20 (max) . GS1 AI encodable character set 82*
GS1		***Maximum Base UDI***	***alphanumeric***	86	***66***
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