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Pharmacovigilance in 2020 - Future horizons and efficiencies in data acquisition, evaluation and risk management

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9th International Conference and Exhibition on Pharmacovigilance and Drug Safety
July 2017

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- **The authors of the presentation are identified as:**
  - Flic Gabbay, Managing Partner, TranScrip

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What is the future?

A time of rapid change



Dr June Raine
Director, Vigilance & Risk Management of Medicines, MHRA

- Growing public and patient expectations
- Changing demographics and disease patterns
- Unlocking the power of the human genome
- Digital transformation

Presentation DIA 29th Annual EuroMeeting, Glasgow 30 March 2017

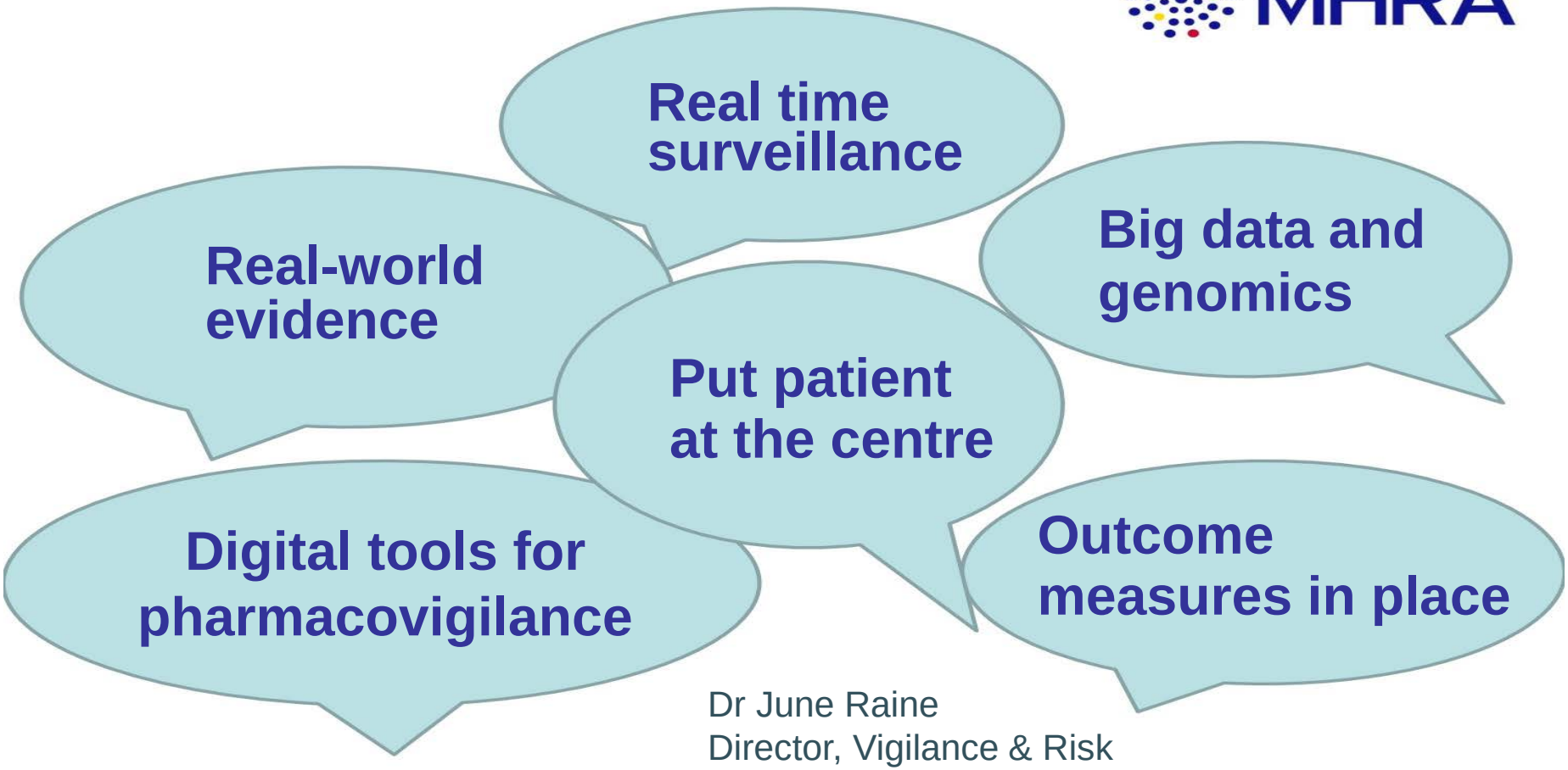
Data is at the heart

Maximising benefit, minimising risk



FDA Web Site, 2017

What's the key to success



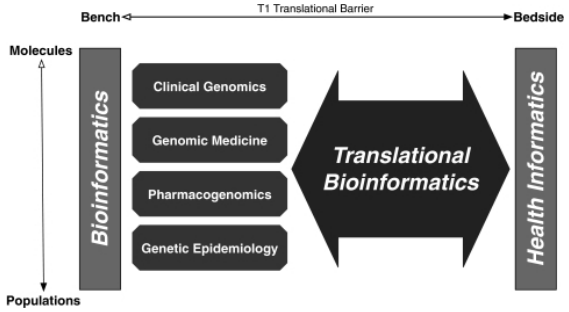
Dr June Raine
Director, Vigilance & Risk Management of Medicines, MHRA

Future challenges

- **Less data**
  - Earlier registration – PRIME- EMA



- **More data**
  - More depth and personalisation
  - More volume



Sarker et al, 2011

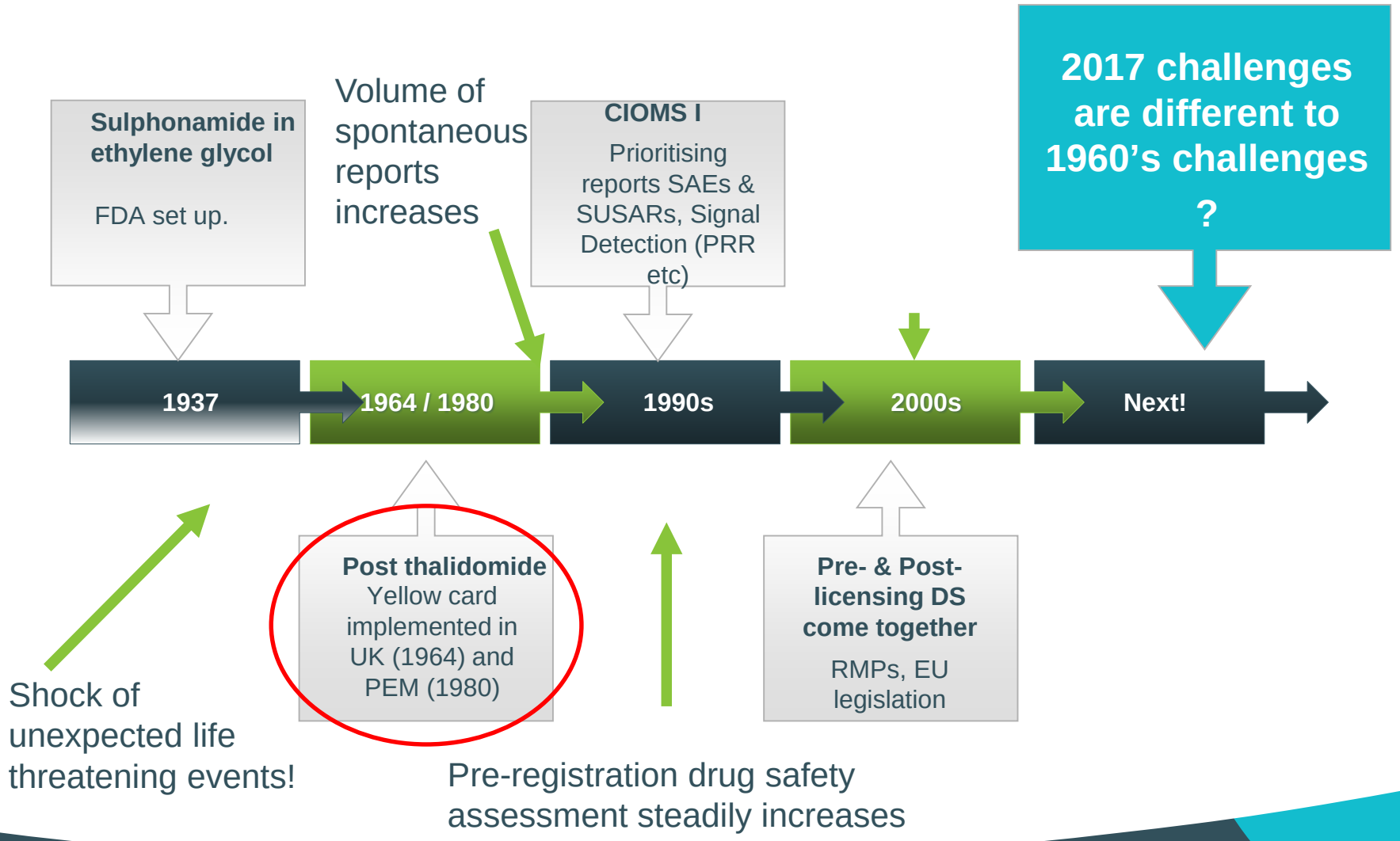
Larger trials – Clinical Trial Networks

More trials

Observational data

Early PASS

Collecting ICSRs for over 50 years!



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Drug Safety Burden to Health

The Burden

- **Admissions to two hospitals**
  - 18,820 patients aged > 16 years admitted over six months assessed for cause of admission
  - Patients were categorised as having an ADR
  - Excluded deliberate or unintentional overdose or non-compliance
- **Results**
  - 6.5% (1225) of admissions were related to ADRs (28 deaths) .
  - 72% of the ADRs were considered avoidable

Pirmohamed et al, BMJ 2004

Commonest Events

No unexpected ADRs were seen. The ADRs were almost all known events

Table 4 Drugs causing adverse drug reactions

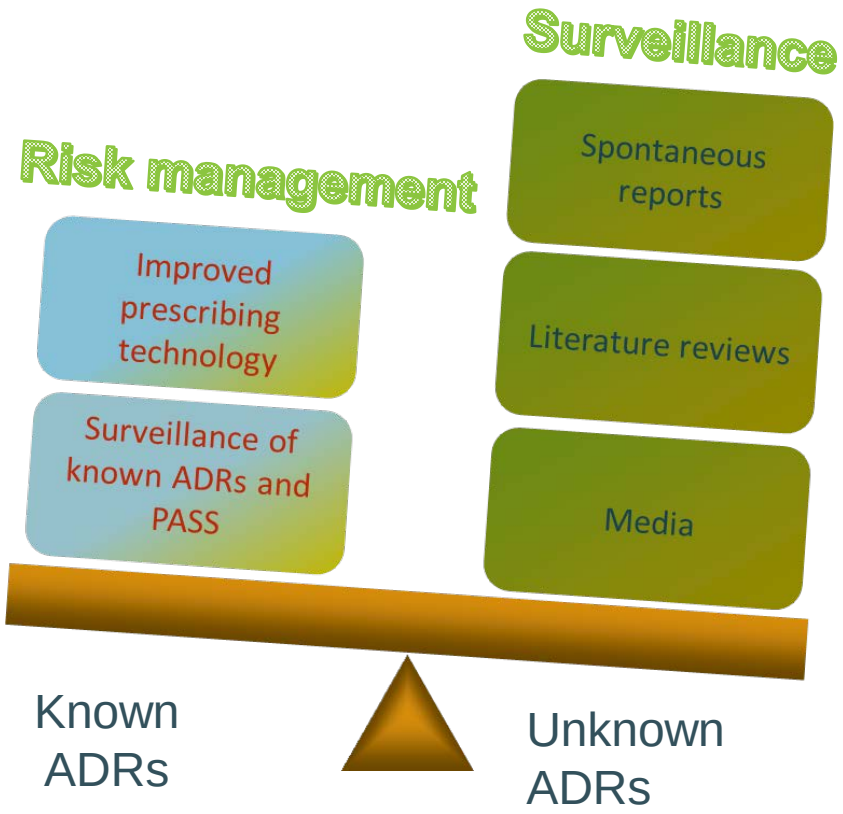
Drug group/drug	No (%) of cases	Individual drugs	Adverse reactions
NSAIDs	363 (29.6)	Aspirin (218), diclofenac (52), ibuprofen (34), rofecoxib (33), celecoxib (8), ketoprofen (6) naproxen (5)	GI bleeding, peptic ulceration, haemorrhagic cerebrovascular accident, renal impairment, wheezing, rash
Diuretics	334 (27.3)	Furosemide (128), bendroflumethiazide (103), bumetanide (43), spironolactone (37), amiloride (19), metolazone (11), indapamide (6)	Renal impairment, hypotension, electrolyte disturbances, gout
Warfarin	129 (10.5)	—	GI bleeding, haematuria, high INR, haematoma
ACE inhibitors/ AII receptor antagonists	94 (7.7)	Ramipril (28), enalaparil (25), captopril (12), lisinopril (9), irbesartan (6), losartan (5), perindopril (4)	Renal impairment, hypotension, electrolyte disturbance, angioedema
Antidepressants	87 (7.1)	Fluoxetine (17), paroxetine (14), amitriptyline (13), citalopram (9), lithium (8), venlafaxine (8) dosulepin (7),	Confusion, hypotension, constipation, GI bleed, hyponataemia
β blockers	83 (6.8)	Atenolol (69), propranolol (6), sotalol (3), bisoprolol (2), metoprolol (2), carvedilol (1)	Bradycardia, heart block, hypotension, wheezing
Opiates	73 (6.0)	Morphine (20), dihydrocodeine (20), co-codamol (8), tramadol (8), co-dydramol (6), fentanyl (5)	Constipation, vomiting, confusion, urinary retention
Digoxin	36 (2.9)	—	Symptomatic toxic digoxin levels
Prednisolone	31 (2.5)	—	Gastritis, GI bleeding, hyperglycaemia, osteoporotic fracture
Clopidogrel	29 (2.4)	—	GI bleeding

GI=gastrointestinal, INR=international normalised ratio.

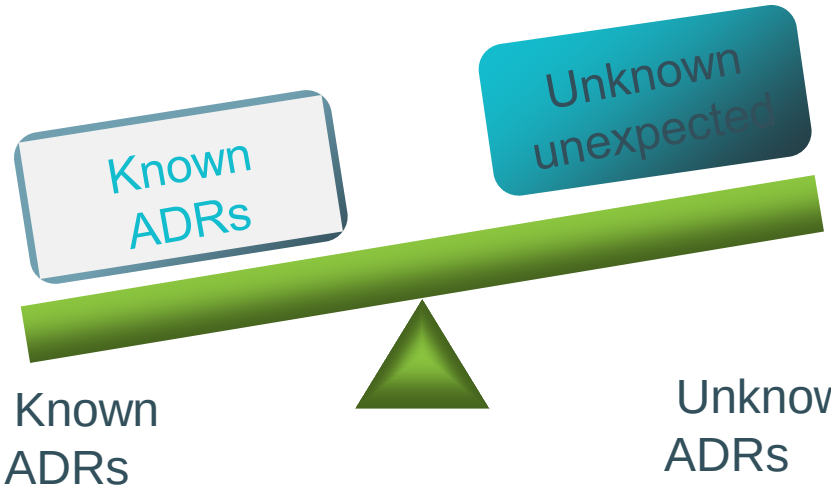
Pirmohamed et al, BMJ 2004

Risk Management vs Surveillance

What we spend in resource



Burden to health



Regulatory Emphasis Shifting

- **Risk management**
  - Effectiveness check of risk mitigation PV legislation

> Guideline on good pharmacovigilance practices (GVP)
> Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)

- **Shortcomings Report European Commission 2015**
  - SmPC
  - PIL

- *Article 59(4) Directive 2001/83/EC*
  - **"an assessment report on current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals."**
- *Two external study reports*
  - **Readability of PIL/SmPC and possible 'key information' section**
  - **Literature search and stakeholder surveys**
- *Consultation of Member States (Pharmaceutical Committee)*
  - **Summarised in the background document**
  - **Published on the Commission website, together with the external study reports**

Now - Eudravigilance 2016

- **Cumulatively, 10.8 million ADR reports from 6.7 million individual cases from December 2001 till 31 December 2016**
- **1.23 million ADR reports from 804,558 670,000 medicines in 2016.**

ADRs received at EVPM & EVCTM	Individual cases
Total received	804,558
Received from MAHs/ sponsors	650,571
Received from NCAs	190,272
Received from EEA	241,800
Received from NON EEA	562,758
Literature reports from EMA	5,595

Eudravigilance Annual Report, 2016

Referred for PRAC Review

- **673, 137 medicines Eudravigilance database**
- **22,429 electronic Reactions Monitoring Reports issued**
  - 94 confirmed signals, 48 signals from Eudravigilance - 46 by MS

Outcome of signal	Number
Label change	25
DHPC (and RMP 1)	3
Referral procedure	4
PSUR /PSUSA FU	9
PASS requested	1
RMP change (& DHPC 1)	2
Routine PV	30
Ongoing review	21

Eudravigilance Annual Report, 2016

Economic Pressure by 2020 plus

- **Pharma total revenue estimated to be $1.4 trillion dollars by 2020 (IMS/Reuters 2015)**
  - PV outsourcing to be ~ $8 bn by 2024 (gminsights 2016)
  - Regulatory Affairs outsourcing to be $5.7bn by 2023 (Manufacturing Chemist 2016)
- **Total spend > $13.7bn plus internal spend of about >0.1% of revenue**
- **R&D in comparison is ~10-18% of turnover**

- **Price pressures will be felt … but price may not be as much of a pressure as we think…**
- **However, agencies are very aware of resource redundancy and are innovating efficiency**

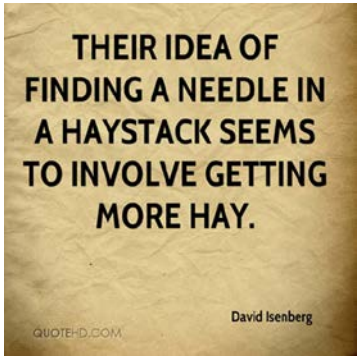
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How Surveillance and Drug Safety Might Change in 2020 plus

Reduce Cost and Risk

2020 Plus Target: Increasing value of surveillance

- **Much outsourced spend in pharmacovigilance is**
  - reporting, signal evaluation, label changes and related processes…
  - Individual Case Study Reporting - challenges well known
    - **BUT some individual reports provide really useful data**



- **2020 plus will see much better use of pharmacoepidemiology style real time big data from better sources than ICSRs**
- **2020 plus will see better use of technology**

2020 Plus Target: Improve SmPC & PIL

- **1. Room for improvement of PIL rather than of SmPC**
- **2. Consider revising Amendments of Guidelines and QRD templates to enhance readability of PIL**
- **3. Improving patient input in developing and testing of PILs**
- **4. Promotion and exchange of best practice**
- **5. Electronic SmPC and PIL format**
- **6. Potential "key information" section in the SmPC and PIL**

Study on the Package Leaflets and the Summaries of Product Characteristics of Medicinal Products for Human use. **PIL-S study.**

Liset van Dijk, Susana PatrícioMonteiro, Marcia Vervloet, Jolanda de Bie, and DK Theo Raynor

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Impact of Technology

World Outside – 2020

- Internet of Things
- Artificial Intelligence
- Augmented reality / Virtual reality
- Robotics – dispensing?
- 3D printing will transform devices
- Next generation security

All will change drug safety & pharmacovigilance!



Driverless cars are here!

Geneva motor show – demonstrating arguing about TV channels in the car!

Connecting 50bn Devices

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Cloud
Hospitals
BPOs
Regulators
Pharmacy
Carers & family
Academia
Patients
Med info - pharma
Reps - pharma
Insurance companies
Doctors
TV - media
PV - Pharma
Laboratories



The Way We Do PV Now!

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Pharmacy



Patient /doctor



Regulatory authority



Literature /academia



Medical information



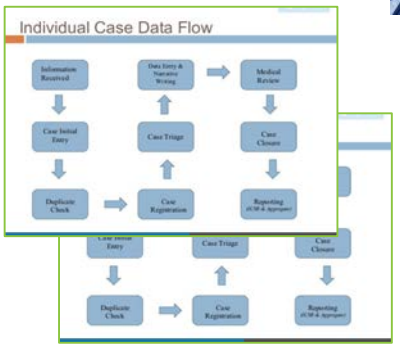
Clinical trial CRO





Pharmas

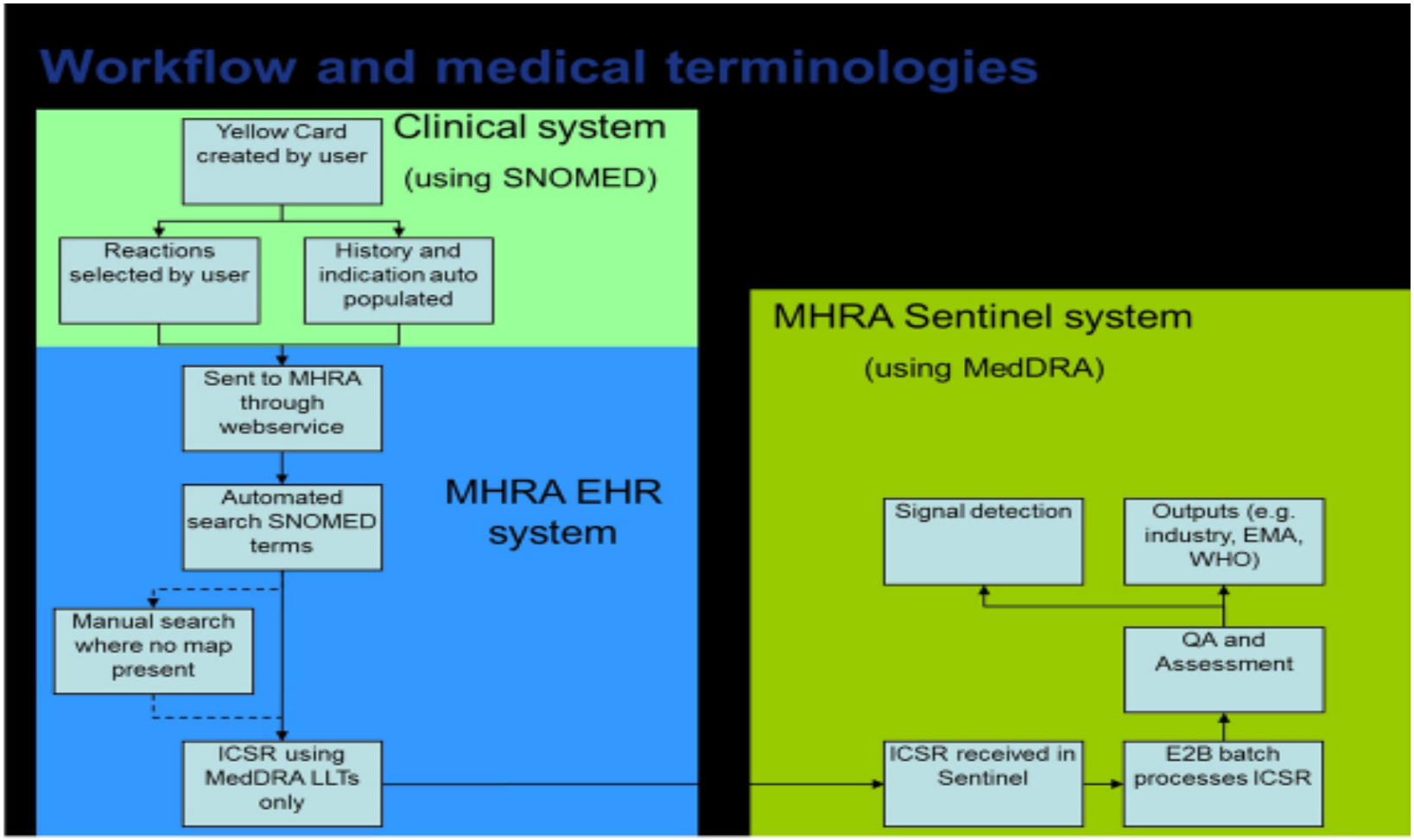
BPOs



Agencies are innovating

- **Screening literature for ADRs**
- **Mobile phone apps for reporting ICSRs (FDA and MHRA)**
- **Direct reporting from Electronic Health Records**
  - Could ICSR reporting be simplified with direct reporting from doctors
  - Challenges include coding (SNOMED)

The way it could be done

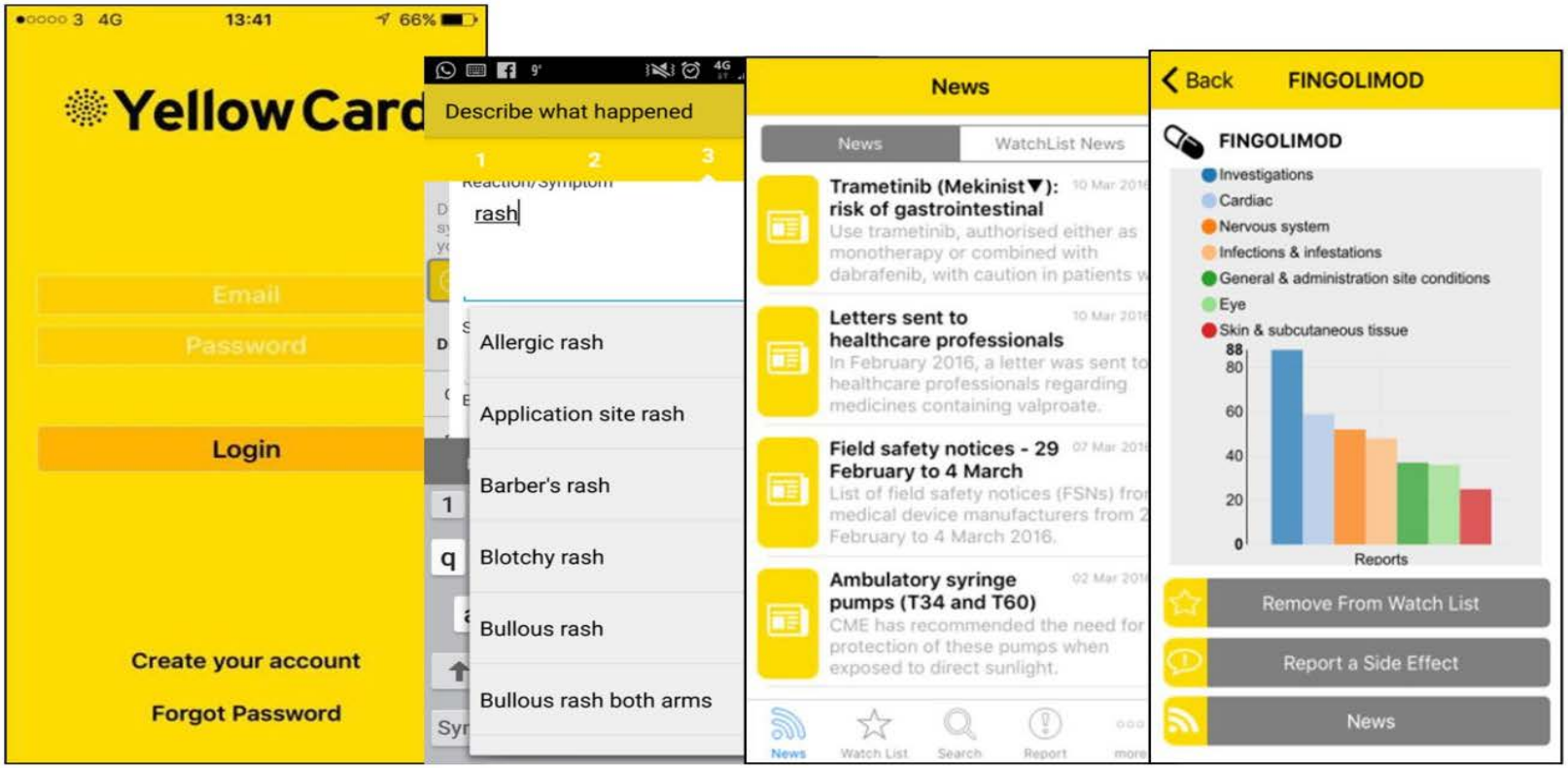


Mike Foy, MHRA, DIA Euromeeting March 2017

In 2020 plus - a trigger for ICSRs…?

- **A new prescription or a diagnosis for a patient on treatment would electronically flag whether:**
  - It is temporally related to taking the drug
  - The drug-event was known
- **Question would then be asked of the physician**
  - This is a known event of drug X, you might want to consider treatment adjustment
  - This is an unknown event of the drug but might be related to treatment. If you wish to report this as a possible event, does it meet the following SAE criteria.
  - “I do not wish to report” is still transmitted to obtain a denominator

Going Mobile, where we are now?

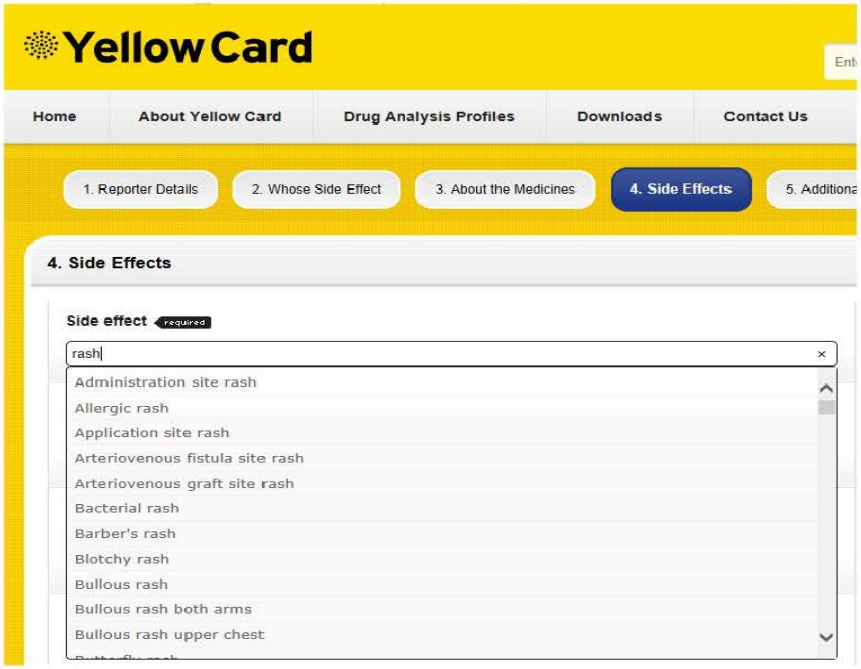


Mike Foy, DIA Euromeeting, March 2017

Patient Friendly MedDRA

- 76,468 MedDRA terms available at LLT level
- Great specificity but how to choose the best term
- <4000 unique terms coded from patient Yellow Cards in 2016

221 available terms for rash in MedDRA which the user could scroll through on our online YC form!



Mike Foy, MHRA Euromeeting, March 2017

Efficiencies in Reporting

- Reduction in resource and increase in accuracy
- Much closer to real time and there is a denominator
- Detailed narratives would be collected when appropriate
- Allow merging and variation of pharmacoepidemiology techniques
- Can be applied to websites, social media and other apps

Managing Risks in 2020 plus

- **Robotics – to reduce error rates in prescribing**
- **Digital measures to guide treatments for**
  - Hypertension, diabetes, asthma, NSAIDs
- **Test could be transmitted direct to the surgery by mobile!**
- **Artificial intelligence (machine learning) could monitor and adjust biomarkers for example, in pain management**

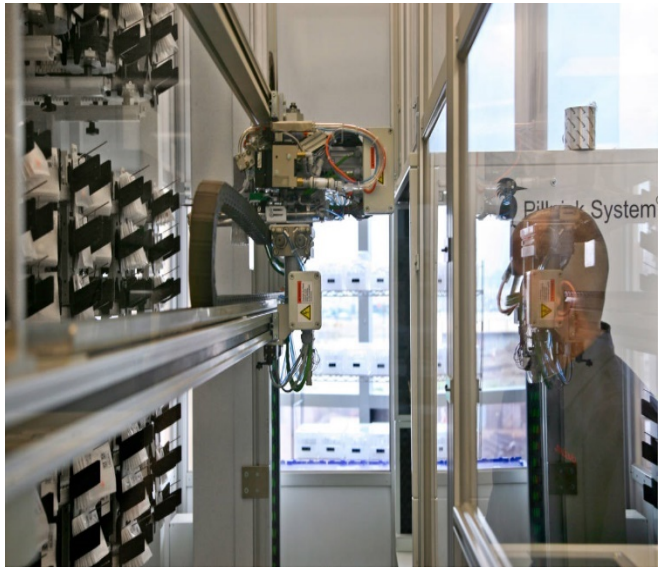


Faecal occult blood test

Could you identify and monitor faecal occult blood in patients on long term NSAIDs? (almost the commonest reason for ADR admission)

Pharmacy - Robots in Pharmacies

Robots are here in pharmacies in San Francisco!



UCSF April 2016

‘Automation has led to the ability for us to reinvent ourselves as a profession, and we need to take the challenge.’
— Dr. Marilyn Stebbins, UCSF

Natural Language Processing

- **Is ability to text mine information and highly sensitive for signals**
  - Literature reviews
  - Improving quality of non-coded reported but Identified ADRs
  - Electronic health records
  - ADR narratives
  - Social media
- **Challenges include**
  - Dictionaries, quality of original data, thinking differently but it will come

Pharmacovigilance through the development of text mining and natural language processing techniques.

Segura-Bedmar I and Martinez P. J Biomed Inform. 2015 Dec;58:288-91. Epub 2015 Nov 4.

Active Computerized Pharmacovigilance Using Natural Language Processing, Statistics, and Electronic Health Records: A Feasibility Study

Xiaoyan Wang, George Hripcsak, Marianthi Markatou, and Carol Friedman

J Am Med Inform Assoc. 2009 May-Jun; 16(3): 328–337.

2020 plus

- **Better use of science pre- and post- license with real time big data from better sources than ICSRs**
- **More integrated surveillance support between agencies, health care organisations and pharma**
- **Agency drive pharma to greater involvement in risk management**
- **Better use of technology**
  - ADR reporting apps
  - Direct reporting from doctors & patients
  - NLP from literature reporting
  - Pharmacy robots

Increased rate of change!

THANK YOU FOR YOUR KIND ATTENTION

