ORACLE Health Sciences

ICON

WORLD DRUGSAFETY CONGRESS

Preparing for the new world of safety: embracing cloud and AI

World Drug Safety Congress webinar

16 June 2020

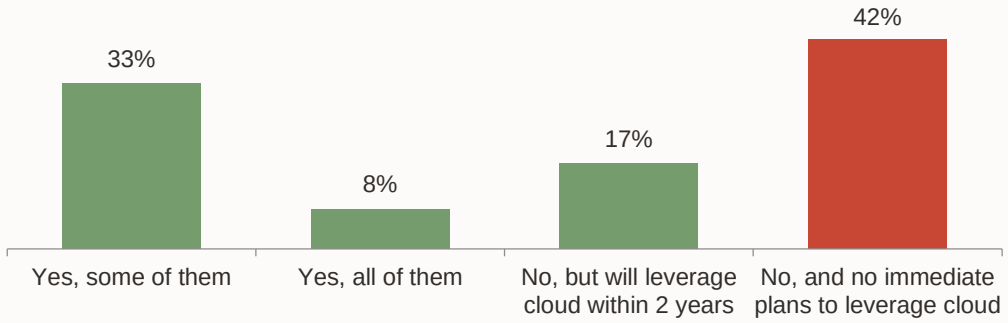
Moderator:
Michael Braun-Boghos
Senior Director Safety Strategy
Oracle Health Sciences

Increasing caseloads are driving the move to the cloud and AI

Although safety budgets have remained flat, safety caseloads are increasing by an average of 30-50% a year [1], so teams are looking for ways to process cases more quickly and efficiently as well as strategies to lower costs

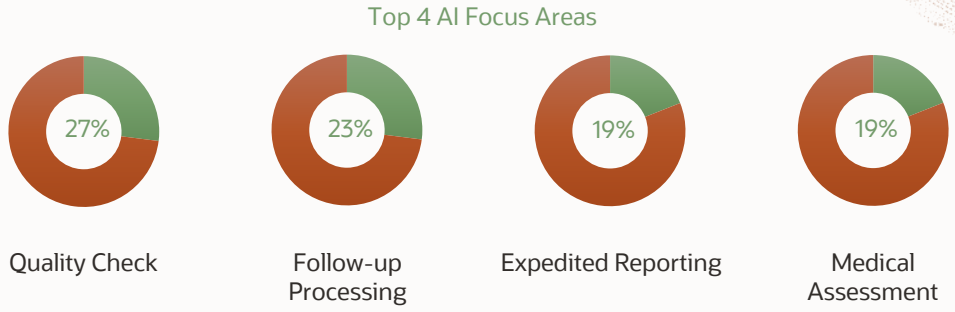
CLOUD

Almost 60% of companies already have safety solutions in the cloud or are planning to move there within the next two years [2]



ARTIFICIAL INTELLIGENCE

The majority of companies (62%) are actively implementing, or planning to implement, artificial intelligence in AE case processing [2]



1) IDC MarketScape: Worldwide Life Science Drug Safety Services 2019–2020 Vendor Assessment — Building for Innovation
2) Informa Engage Pharma Intelligence Survey of Pharmacovigilance — January 2018

Today's presenters from ICON plc

Quintin van Wyk, VP of Pharmacovigilance & Safety Reporting has 17 years of experience at ICON and in pharmacovigilance. He joined ICON as a Clinical Research Physician in 2003 and was involved in medical monitoring and drug safety since that time and also provided oversight of Global Regulatory Affairs, Medical Writing, and Publishing. Quintin has worked on a variety of indications across all phases of clinical trials. In his current role as Vice President, Quintin oversees Pharmacovigilance and Safety Reporting, including Safety Regulatory Intelligence.

Andy Garrett, EVP of Global Scientific Operations joined ICON in 2016 and is responsible for the strategic direction and operational execution of Global Scientific Operations for Pharmacovigilance, Regulatory, Medical Imaging, Medical Monitoring, Endpoint Adjudication, Interactive Technologies, and Clinical Supplies Management. Previously Andy spent 20 years at IQVIA and before that worked for Warner Lambert, American Cyanamid, and Parexel. Andy has worked extensively in the area of rare diseases and has published papers on non-inferiority trials, subgroup analyses, data transparency, and modelling and simulation.

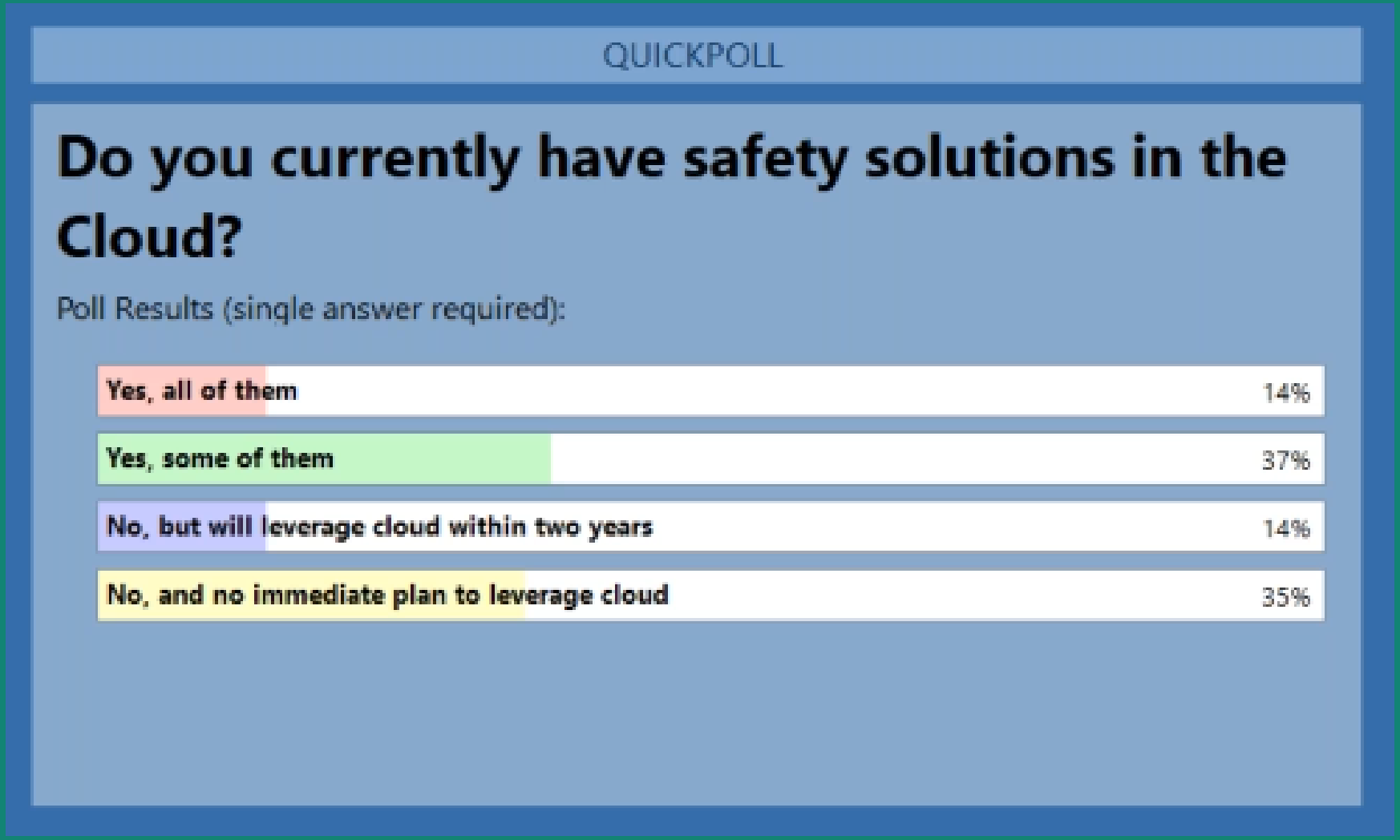
Agenda

- ICON’s journey to the cloud
  - History and the what
  - Why, how, who
  - Lessons learnt
- Artificial intelligence
  - Operating principles
  - Social media
  - ICON’s approach to automation
  - Evangelist or sceptic
  - Final thoughts
- Q&A

ICON’s Journey to the Cloud

Quintin van Wyk

Quick Poll


QUICKPOLL
Do you currently have safety solutions in the Cloud?
Poll Results (single answer required):
Yes, all of them
14%
Yes, some of them
37%
No, but will leverage cloud within two years
14%
No, and no immediate plan to leverage cloud
35%

ICON’s journey to the cloud

- History
  - Argus 7 hosted by Oracle partner (3rd party)
  - Acquisitions adding complexity with additional databases to consolidate
  - Complex and tired manual processes – we were serving the system
    - Costly inefficiencies

- What
  - Argus 8.1.2 Enterprise Edition
  - Hosted directly in the Oracle Cloud
  - Built around Best Practice CRO process, developed with Oracle Health Sciences Consulting
  - Enhanced support from Oracle Health Sciences with BCP in mind
  - Enhanced data analytics capability through data analysis tools
  - Resulting efficiency gains ≈25% (certain case processing tasks) / ≈50% (some submission tasks)

Why did we change?

- Regulations (E2B R3)
- Argus Enterprise Edition, including capability to scale further, e.g. signalling
- Analytics / listings
- Automation (e.g. narratives, workflow, scheduled listings output)
- Forward-looking, technology-enabled process
- Scalable – big organisation, broader deeper level of expertise
  - Previous low number of tenants, low case volume
- Direct support line to Oracle
- Cost effective solution to customers → growth
- Cloud vs. on-premises installation

The plan

- Reset internal expectations; expanded the team (Ops, IT, Oracle)

- Two-phase project:
  1. New enhanced Golden Tenant created with input from Oracle Health Sciences Consulting; industry best practice/standard, efficient
  2. Migrated all legacy data from Argus 7 to Argus 8.1.2; lift and shift
     - Keep familiarity with workflows, SOPs, training, etc.

- Why two phases?
  - New tenants benefit immediately to secure early wins
  - Enhancements subsequently applied to the migrated tenants
  - Some overlap of work for the two phases; not all in sequence

How did we manage the change?

- Intense project management
  - Very regular meetings
  - Working with affected customers
    - Considered critical time points around data lock points and regulatory filing
  - Risk around not lift and shift
    - Potentially had to leave one customer on old system with a custom migration script to follow later
  - Holding everybody accountable to deliverables
  - Concluded the project in 7 months

Who were involved?

- PV case processing ops
- PV case submission ops
- PV safety systems / technical
- PV QA and Data Privacy Officer
- IT PM
- IT safety systems support
- IT Validation
- IT Security
- IT/tech QA
- Document control
- Training department
- Oracle PM, IT, Consulting
- Source database vendor
- Senior level oversight

One team with common goals

Collegial behaviours

Win or lose as one team

Our experience / lessons learnt

- Collaboration (ICON and Oracle)
- *“Seamless”* upgrade from Argus 7 to Argus 8
  - It worked (eventually)!, on time, under budget
  - Innovated around data transfers (plane vs. e-migration)
    - Challenges with electronic transfer include systems hanging due to the volume of data in some tables. Had to split transfers into smaller chunks of data
  - Last-minute coding issue in Argus 7 which had to be fixed prior to cut-over
  - System security flagged – malware scanning was improved
  - Plan carefully and involve stakeholders incl. QMS – can’t release new tools without appropriate SOPs
- Industry standards / consulting
- Proof is in the outcome
  - Multiple client migrations since rollout with support from Oracle teams

Next steps with Argus

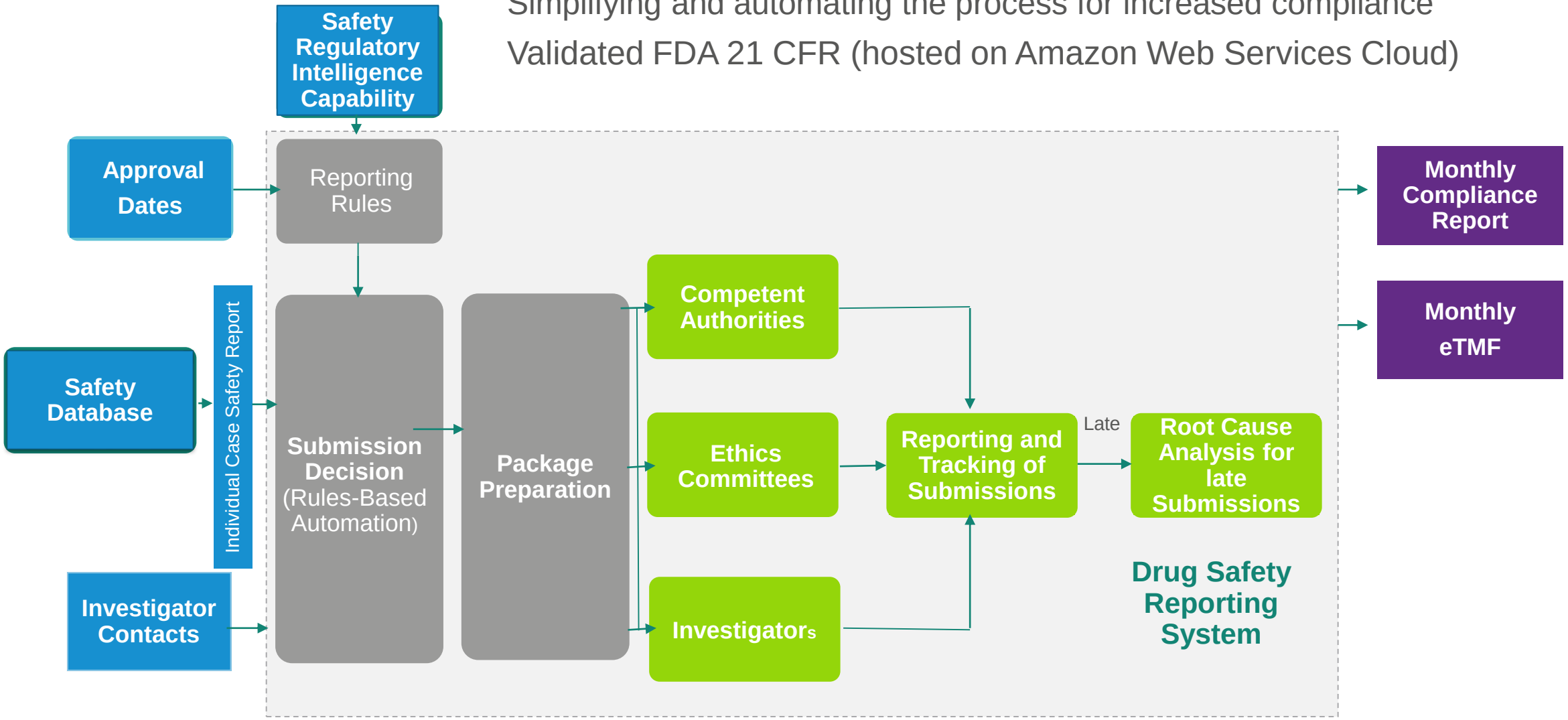
- Migrating recent acquisition into Argus 8.1.2
  - Argus to Argus
  - Cloud to Cloud

- Other Cloud-based PV systems

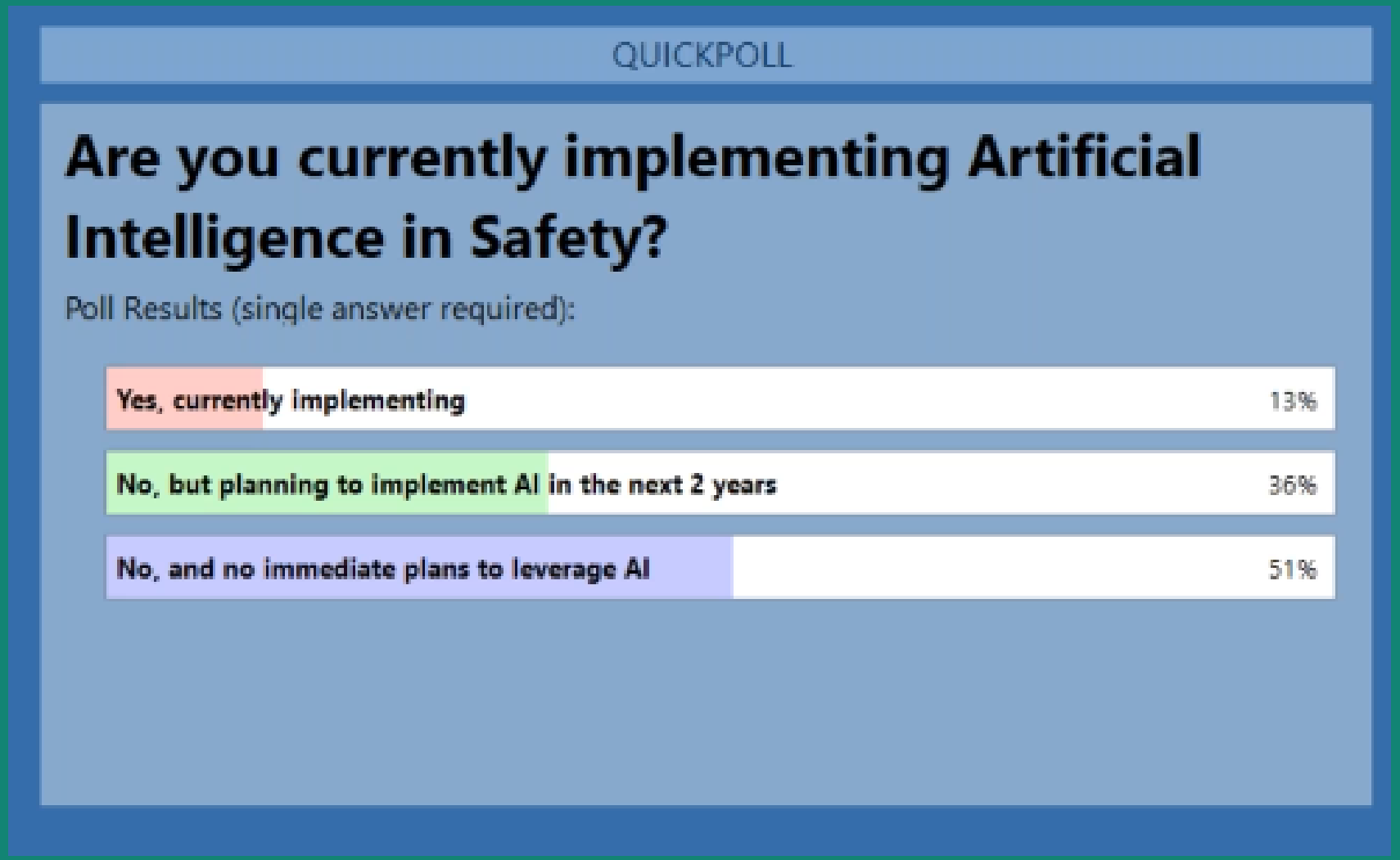
Drug safety reporting system

Simplifying and automating the process for increased compliance

Validated FDA 21 CFR (hosted on Amazon Web Services Cloud)



Quick Poll


QUICKPOLL
Are you currently implementing Artificial Intelligence in Safety?
Poll Results (single answer required):
Yes, currently implementing
13%
No, but planning to implement AI in the next 2 years
36%
No, and no immediate plans to leverage AI
51%

Artificial Intelligence

Andy Garrett

Some operating principles

- Data quality is key (increased volume does not compensate for poor quality)
- Standardise the soup before the nuts
- Don’t automate an inefficient process
- An automated process doesn’t have to match a human one
- Don’t be seduced by complexity, simple is best
- Rules-based (deterministic) will always beat data-driven (probabilistic)
- We don’t need 1000 unique solutions to the same problem
- Machine learning is classification based on correlation, not causation

Social media

Drug Safety
https://doi.org/10.1007/s40264-019-00858-7

SPECIAL ARTICLE

Check for updates

Recommendations for the Use of Social Media in Pharmacovigilance: Lessons from IMI WEB-RADR

John van Stekelenborg[1] · Johan Ellenius[2] · Simon Maskell[3,4] · Tomas Bergvall[2] · Ola Caster[2] · Nabarun Dasgupta[5] · Juergen Dietrich[6] · Sara Gama[7] · David Lewis[7,8] · Victoria Newbould[9] · Sabine Brosch[9] · Carrie E. Pierce[10] · Gregory Powell[11] · Alicia Ptaszyńska-Neophytou[12] · Antoni F. Z. Wiśniewski[13] · Phil Tregunno[12] · G. Niklas Norén[2] · Munir Pirmohamed[14,15]

Is it possible to find rare events and find events earlier than in other systems?

- Can you find your drug?
- If so, can you find an event?
- If so, can you assign the event to the drug?
- Potential for reverse causality (event → drug)
- Is it a duplicate?

"has the potential to negatively impact Signal Detection systems"

"had very low value in the given context"

Why “accuracy” can be misleading

Antibody testing example during a pandemic			
	Test +	Test -	All +
Infected	95%	5%	100%
Not infected	5%	95%	100%

False +

False -

What happens if **10,000** people are tested, but the unknown population prevalence is only **1%**?

What is probability of having been infected given the test is positive?

Antibody testing example			
	Test +	Test -	All +
Infected	95	5	100
Not infected	495	9405	9900
	590	9410	10000

1% Prevalence

P (true positive | test positive) = (95/590) = 16%

In other words, 84% of the positive tests are false positives!

PV surveillance is not immune to a similar issue

Social media

Twitter and looking for an AE with Drug			
	Tweet +	Tweet -	All +
AE w/ Drug	95	5	100
Not AE w/ Drug	495	9405	9900
	590	9410	10000

Assume Incidence of AE is 1% (uncommon, but neither rare nor very rare)

What is the probability of an AE given the tweet is positive?

P (true AE w/ Drug | tweet positive) = (95/590) = 16%

This is likely a highly optimistic scenario too

What if the underlying incidence is changed to 10%?

Twitter and looking for an AE with Drug			
	Tweet +	Tweet -	All +
AE w/ Drug	950	50	1000
Not AE w/ Drug	450	8550	9000
	1400	8600	10000

P (true positive | test positive) = (950/1400) = 68%

Now, 32% of the positive tests are false positives – not great, but better

ICON Pharmacovigilance / Safety Reporting Approach

- Maximise use of COTS functionality
- Make upgrading as simple as possible, and aim to do it quickly
- Adopt best practices, learn from others
- Build only if we have to
- Think beyond PV (interoperability)

- *Intake, Evaluation, Follow-up, Distribution*

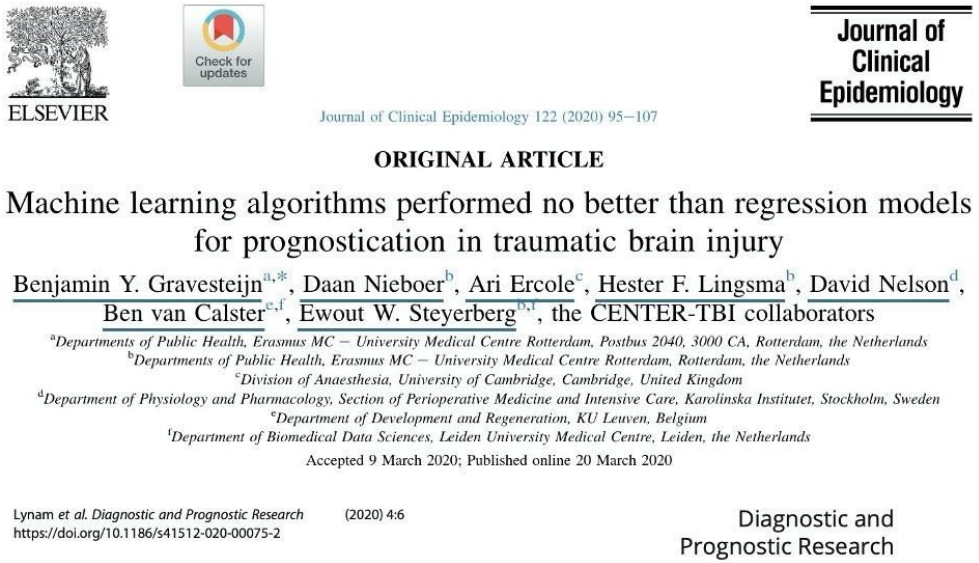
Maximise COTS functionality

- Argus 8 Enterprise Edition (Cloud) / Golden Tenant
  - Auto-narratives
  - Auto-query-letters
  - Automated listings
  - Reporting rules to “*Safety Reporting Tool*” and other destinations
  - etc.

Interoperability – extending the distribution model

- Safety letter management
- Delivers direct to sites from Safety Reporting Tool via FIRECREST portal
- Replaces email
- Provides structured tracking (audit trail) of investigator read/receipt (compliance)
- Enables remote monitoring checks – CRA efficiency

Evangelist or AI sceptic



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Journal of Clinical Epidemiology 122 (2020) 95–107

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Machine learning algorithms performed no better than regression models for prognostication in traumatic brain injury

Benjamin Y. Gravesteijn[a,*], Daan Nieboer[b], Ari Ercole[c], Hester F. Lingsma[b], David Nelson[d], Ben van Calster[e,f], Ewout W. Steyerberg[b,f], the CENTER-TBI collaborators

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[d]Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden
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[f]Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, the Netherlands

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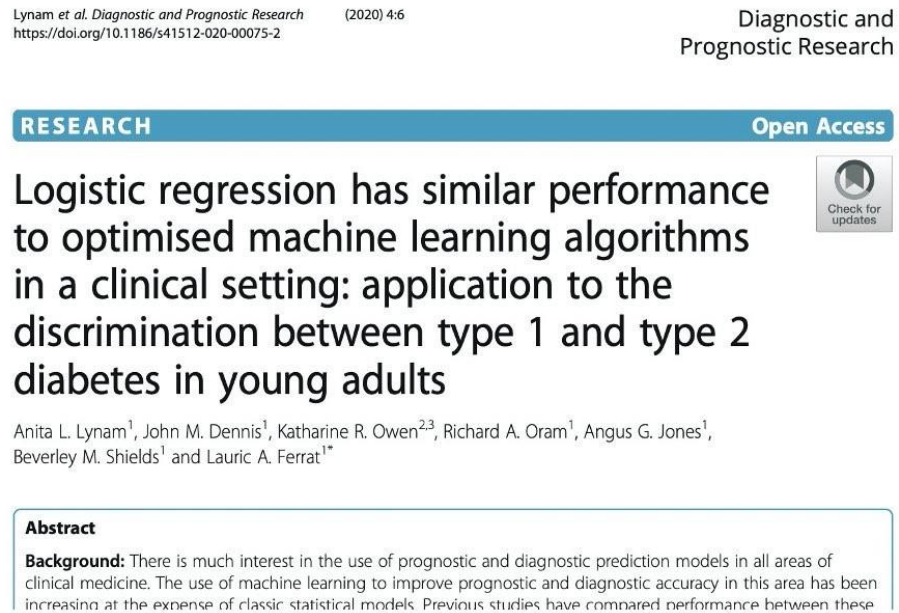

Lynam et al. Diagnostic and Prognostic Research (2020) 4:6
https://doi.org/10.1186/s41512-020-00075-2

Diagnostic and Prognostic Research

RESEARCH Open Access

Logistic regression has similar performance to optimised machine learning algorithms in a clinical setting: application to the discrimination between type 1 and type 2 diabetes in young adults

Anita L. Lynam[1], John M. Dennis[1], Katharine R. Owen[2,3], Richard A. Oram[1], Angus G. Jones[1], Beverley M. Shields[1] and Lauric A. Ferrat[1*]

Abstract

Background: There is much interest in the use of prognostic and diagnostic prediction models in all areas of clinical medicine. The use of machine learning to improve prognostic and diagnostic accuracy in this area has been increasing at the expense of classic statistical models. Previous studies have compared performance between these

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Journal of Clinical Epidemiology 122 (2020) 56–69

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Logistic regression was as good as machine learning for predicting major chronic diseases

Simon Nusinovici[a], Yih Chung Tham[a,c], Marco Yu Chak Yan[a], Daniel Shu Wei Ting[a,c], Jialiang Li[a,d], Charumathi Sabanayagam[a,c], Tien Yin Wong[a,b,c], Ching-Yu Cheng[a,b,c,*]

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[b]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
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Journal of Clinical Epidemiology 110 (2019) 12–22

Journal of Clinical Epidemiology

REVIEW

A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models

Evangelia Christodoulou[a], Jie Ma[b], Gary S. Collins[b,c], Ewout W. Steyerberg[d], Jan Y. Verbakel[a,e,f], Ben Van Calster[a,d,*]

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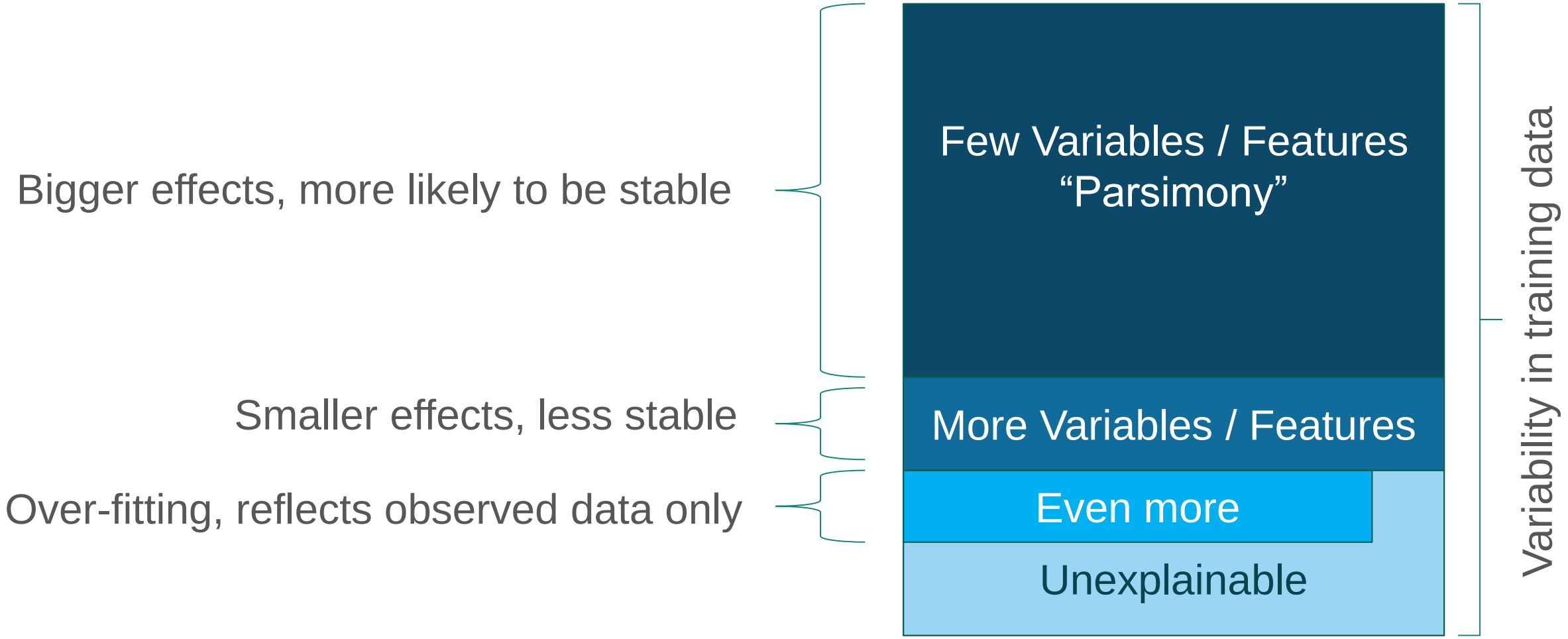
Accepted 5 February 2019; Published online 11 February 2019

Modelling / machine learning (probabilistic classification)



Hand DJ. (2006). Classifier Technology and the Illusion of Progress. *Statistical Science* **21**(1) 1-14

Algorithm challenges

Algorithmic transparency

- Representativeness (bias input)
- Fairness (bias output)
- Understanding
- Maintenance
- Privacy, security, and malevolence

- Non-rules-based systems (like deep learning) can be fooled, in mysterious ways…..
  - Subtle changes to images can have big impacts
  - Adversarial challenge needed

Considerations

- There is scope for data-driven solutions, but not 1000 of them
- Work with technology partners to develop a common solutions framework
- Be unrelenting in the push for standardisation (the input)
  - Easier for CT, but harder for CROs
  - CT focus on process, post-marketing focus on data
- Scope for OCR and NLP tools – as components of wider solution
- Never underestimate the benefits arising from solid technology solutions, particularly where there is a clear, forward-looking roadmap

Exposure required to observe at least one AE

AE incidence	Subjects exposed to drug	Probability of at least 1 AE
Common (10%)	50	99.5%
Uncommon (1%)	50	39.5%
	500	99.3%
Rare (0.1%)	50	4.9%
	1,000	63.2%
	3,000	95.0%
Very Rare (0.01%)	50	0.5%
	1,000	9.5%
	10,000	63.2%
	30,000	95.0%

Final thoughts: Post-mkt “spontaneous” surveillance by design

- UK Biobank and ONS COVID-19 infection survey
  - Broad and deep data from consenting de-identified individuals

- Could we create a global network of EMR-enabled sites where detailed post-marketing surveillance could be done?

- Is it better to have fewer “rich” quality data (and denominator), OR
- high-volume, but under-reported, unrepresentative, poor quality data?

- Privacy and security (accredited processors and researchers)

Thank You!
Questions?