Symposium

From the NHS Research & Development Forum

NHS

Research and Development Forum

Non-Commercial Research Sponsors Symposium for Health & Care

19th November 2019

Non Commercial Sponsors
2nd Annual Symposium

NHS
Research and
Development Forum

Housekeeping

#noncomsponsors

Keeping the conversation going

A connected noncom sponsors community

NEW closed group

https://www.linkedin.com/groups/10494496/

Don’t forget REX

Sponsor & Set Up Research

Hide Categories

- Capacity and Capability Assessment and Confirmation
- Computer Systems Validation
- Confirming Research Categories
- Data Analysis Plans
- Data Collection Tools and CRF Design
- Deciding if a Project is Research, Audit, Service Evaluation or Quality Improvement
- Developing a Research Idea
- Finding New Studies
- Indemnity
- Laboratory Systems
- Monitoring Plans (Data and Safety)
- Open Access Data Platforms
- Peer Review Systems

Assure Quality, Safety & Integrity

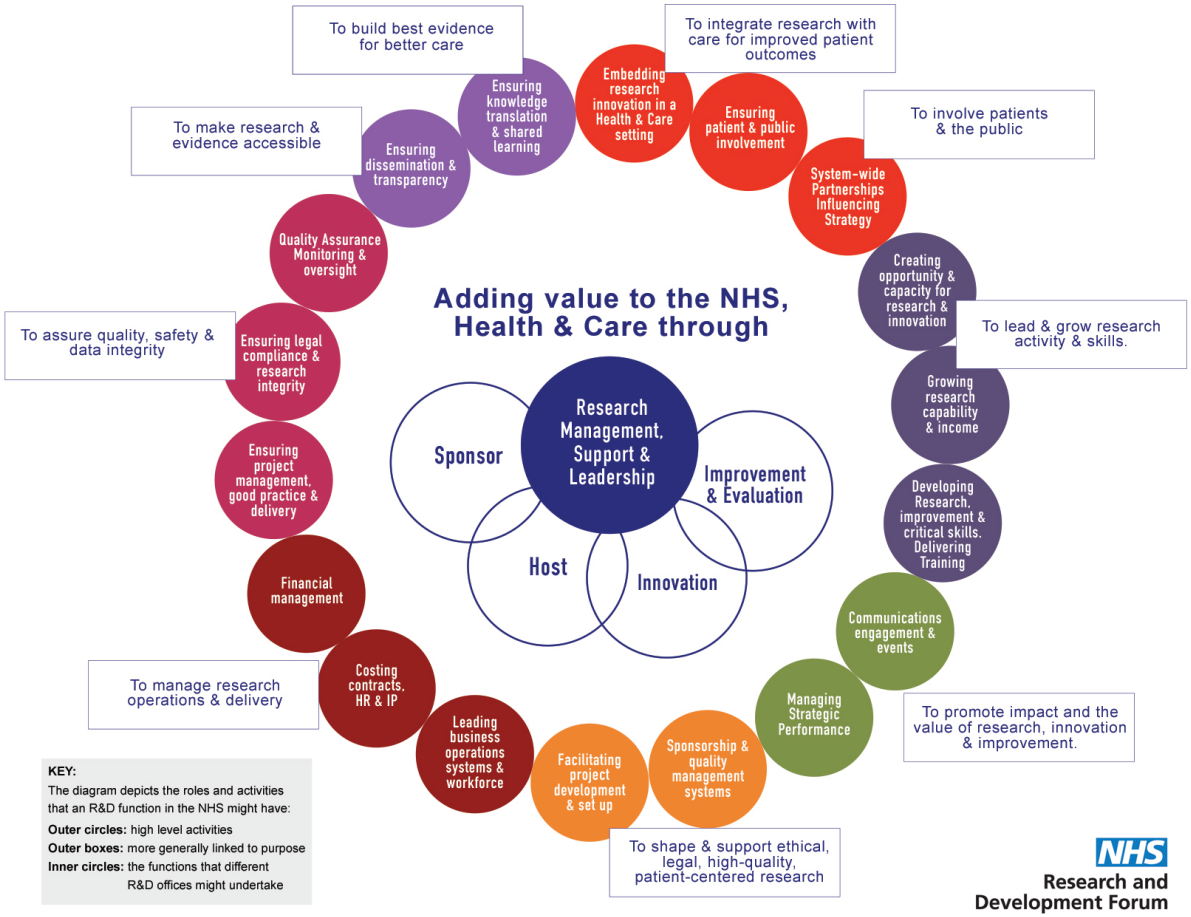
Hide Categories

- Archiving
- Audit
- GCP and Clinical Trials Regulations
- Information governance and the information governance toolkit
- Managing Inspections
- Mental Incapacity and Research Regulation
- Monitoring
- Regulation of Data, Tissue and Regenerative Medicine
- Regulatory Approvals
- Research Ethics Favourable Opinion
- Responsible Research and Research Integrity

Manage Research Operations & Delivery

Hide Categories

- Amendments
- Close Out/End of Study Management
- Competencies and Induction for RD Management Staff
- Consent
- Contracts and Agreements
- Cost Attribution
- Costing Tools and Templates
- Data Management and Integrity
- Delegation of Responsibilities
- Deviations, Incidents and Serious Breach
- Excess Treatment Costs and Savings
- Financial Management



Your Forum

Research Management Group
Chair Sally Humphreys

HRA Noncom Sponsors Reference Group
Chair Angela Williams

Forum newsletter
News, policy, calls, jobs, resources, events, training

Twitter: @NHSRDFORUM

NHS Research and Development Forum

Thank you

Forum Sponsorship Work Stream

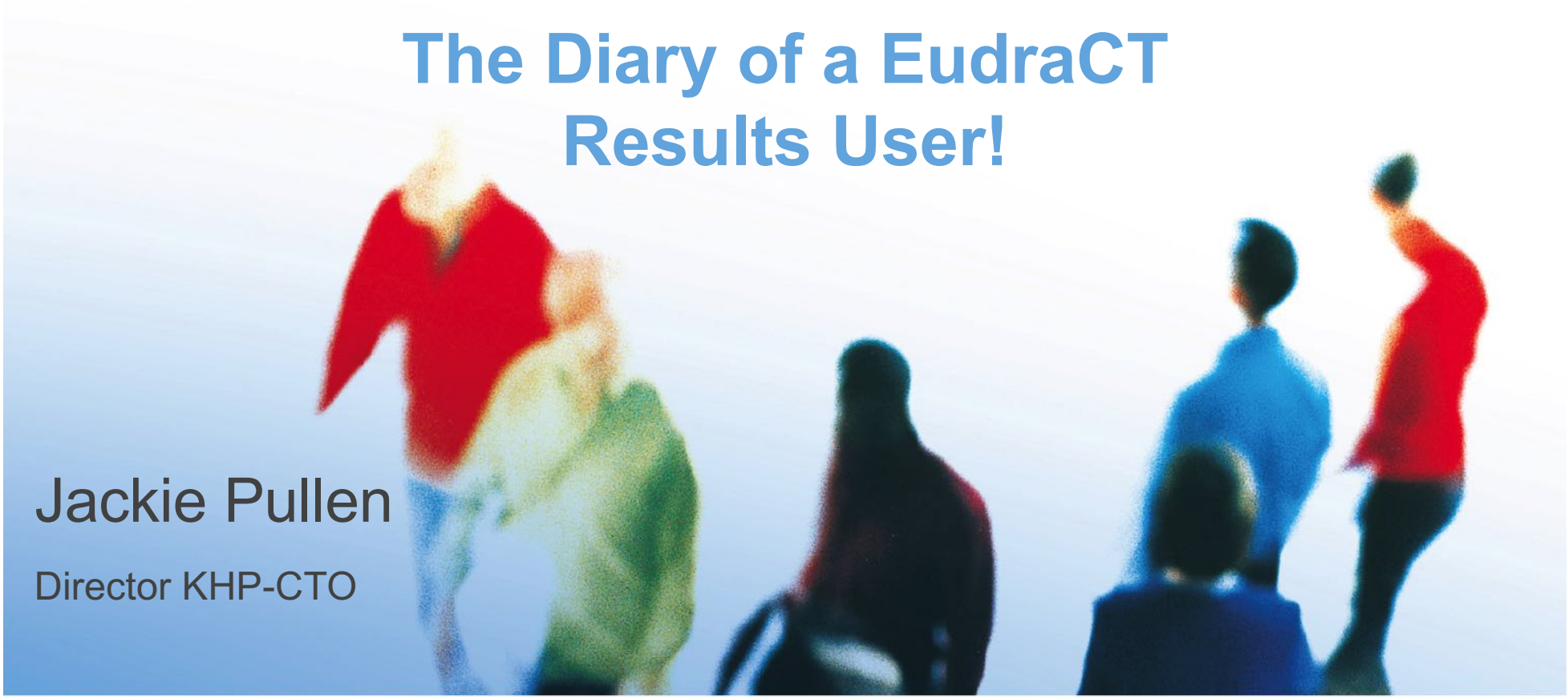
- Heather Rogers
- Gemma Jones
- Mikayala King
- Sean Scott
- Birgit Whitman
- Heidi Nield
- Sarah Townsend
- Jess Bisset
- Angela Williams
- Jen Harrison
- Kate Greenwood

KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

The Diary of a EudraCT Results User!



Jackie Pullen

Director KHP-CTO

KING'S College LONDON

Guy's and St Thomas' NHS Foundation Trust

King's College Hospital NHS Foundation Trust

South London and Maudsley NHS Foundation Trust

What we shall cover……

- EudraCT & FDA Reporting Timeframes
- Challenges with EudraCT post 2014 trial results using academic publications.
- Tips and “Work arounds” to enable posting of these results.
- Trials that have Clinical Trial Authorisation but were abandoned prior to recruitment.

Requirements regarding trial results…..

FDAAA 801 and the Final Rule (42 CFR Part 11).

Came into force in January 2017

- **Responsible Party (sponsor) must register all trials within scope on clintrials.gov**
- **Trial Results must be posted no later than 1 year after the Primary Completion Date.**
- **Primary completion date defined as date final patient examined or received intervention.**

Requirements regarding trial results…..

EudraCT

- **Non-paediatric trials results must be published ≤ 12 months after the end of the trial.**

- **Paediatric trials results must be published ≤ 6 months after the end of the trial,** *(exceptionally ≤ 12 months after the end of the trial if justified and if trial not sponsored by marketing authorisation holder for involved product(s))*

EudraCT Requirements for Pre & Post 2014

- Acceptable to upload end date & academic publication for trials completing before and during 2013.
- Since 21st July 2014 mandated that the FULL trial DATA SET is uploaded into EudraCT results system.
- A Summary attachment or publication may also be posted – this is optional.
- Additional results tables/documents can be uploaded within the “End points” section.

Post 2014 key information & challenges!

- Results User must set up an account within the EudraCT system.
- Assignment of Trials to Results User, either by:- protocol information or letter
- It is not possible to progress through the system if :-
  - Any fields are left blank
  - Participant recruitment is entered as 0

NB EudraCT take 14 days to publish trial results once posted.

Challenges Posting results for post 2014 Trials

Scenario

Trial has completed and academic publication written and accepted for publication to International Journal.

However, published data is not in the format required in order to complete results data fields within EudraCT database.

Challenge

Academic has no resource or desire to re-visit raw dataset and provide sponsor with data in EudraCT friendly form……..

Tips - Uploading Results

Trial Information

Complete all fields, remember those marked with a * are mandatory, add in other registry numbers where applicable plus number and ages of trial participants.

*Tip –**Don't be too concerned if the age ranges listed do not match your trial exactly, you can amend the age ranges further on in the process.***

Tips – End Points

End Points

Add as many end points as you require and indicate whether primary or secondary.

If you are able to complete the statistical analysis within this section - do so. However if you are taking data from an academic publication it may not be possible to upload in the required format.

Tips! The Save Button

Tip – Don't forget to keep hitting the save button at the top of the screen as you move through the fields and pages!

Tips – End Points & Statistical Analysis

End Points

Select the arms that the endpoints apply to and select "**ready for collecting values**"

Click **"Done – start collecting values"**

Tip - in the "Charts" section upload the statistical data section from your publication! Leave the "subject analysis set" and "statistical analyses" sections blank.

Tips – Adverse Events

Adverse Events

Perfect way to complete this section is to upload data via .xml file.

Not possible when working from a publication, so must be entered individually by event and system organ class!

Tip – The SAVE button does NOT WORK within the individual SAE event page. Save when on the Adverse Event main page only!!

Biggest Tip! – Adverse Events

Adverse Events

If you have a list of 1000's of AE's upload this list with the Charts on the previous "End Point" section and leave the AE entries blank.

Biggest Tip! – Adverse Events

Serious Adverse Events

SAE's must be entered by system organ class, per event and by treatment.

Uploading Results – Validate Full Data Set

Validate Full Data Set

Use this tool to check data completion – posting is not permitted with data validation errors.

Tip – Don't forget to hit save after changes and before re-checking validation

Tips – Validate Full Data Set

Validate Full Data Set

Warning message will appear under End Points stating

No statistical analyses have been specified……

Tip - Click "justification" next to warning message and enter "see attached chart/documents for results"

Uploading Results – Validate Full Data Set

Validate Full Data Set

Warning message will appear under Adverse Events stating

No non-serious adverse events recorded……

Tip - Click "justification" next to warning message and enter "see attached chart/documents for results"

Posting Results

Results will not be publicly accessible until they are marked published.

Phase I trials will not be available on the public facing system.

Trials with Zero Recruitment

Index

Upload a statement detailing that the trial was abandoned/closed prior to any participant recruitment activity taking place.

Tip – call this document "Cancelled Before Active Statement". This will then be seen immediately by any results viewers.

Trials with Zero Recruitment

Subject Disposition

In “recruitment” field enter :-

99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants enrolled in the trial

Trials with Zero Recruitment

Enter 99999 in the participants recruited section of Trial Information

Enter 99999 in the Number Analysed section of End Point values

Enter 99999 in the Subjects Exposed of Adverse Event Section and any other section where number of subjects MUST be entered

Trials with Zero Recruitment

End Points

In “end point description” field enter :-

99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants enrolled in the trial

Trials with Zero Recruitment

Validate Full Data Set

In the warning fields Justification for End Point enter:

99999 is "Not applicable" value or 0 participants, this trial was discontinued with no participants. No statistical analyses for this end point

Trials with Zero Recruitment

Validate Full Data Set

In the warning fields Justification for Adverse Events enter:

No subjects were enrolled in the trial hence results are not available

POST RESULTS!!

EudraCT Documentation Webpage

https://eudract.ema.europa.eu/result.html

I think that the Most Useful documents are:-

- Details and template letter for Results User assignment

- PDF document with details of validation rules for each data point within the system. (45 pages).

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Introduction to Sponsorship

NHS
Health Research Authority

Dr Janet Messer
Director of Approvals Service, HRA
10 November 2010

What is a sponsor?

Health Research Authority

An individual, company, institution, organisation or group of organisations that takes on responsibility for initiation, management and financing (or arranging the financing) of the research.

What is a sponsor's role?

Health Research Authority

- Organisational role
- Ongoing responsibility
- Not just a signature on the IRAS submission.

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Health Research Authority

Sponsor's role

- Research quality
- Suitable sites and research teams
- Clear responsibilities and delegation
- Adequate insurance and indemnity

NHS
Health Research Authority

Sponsor's role

- Manage money and risk
- Agree start
- Oversee progress and reporting
- Monitor delivery

Health Research Authority

What makes a good sponsor?

Be visible

Be proportionate

Be helpful

Health Research Authority

What makes a good sponsor?

Confidence to say **no** to researchers or amend research if the study is poorly designed or poor quality or is overambitious

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Health Research Authority

Sponsoring Student Research

- Sponsor = university unless NHS **wants** to
- Ensure supervisors can and do fulfil their roles
- Students should not normally be Chief Investigator

Frequent feedback

Health Research Authority

Lack of understanding of time takes to set up

Not appropriately supported

Over ambitious

Poor quality applications

Comes too late in the day (site)

Magic fairies make it happen

Sponsoring student research

NHS
Health Research Authority

- Train supervisors
- Understand educational objectives
- Ensure projects are achievable
- Be creative!

Top three reasons for delay in HRA & HCRW Approval

Health Research Authority

1. Missing Organisation Information Document/ Costing Template or Contract
2. No response to favourable opinion with conditions
3. Lack of clarity about site activity/ site types

Health Research Authority

Thank you for listening

Contact information:

- **Dr Janet Messer**
- Hra.approvalprogramme@nhs.net

Follow us on Twitter **@HRA_Latest**
Sign up for our monthly newsletter at **www.hra.nhs.uk**

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How We Make the Decision to Sponsor

Dr Mikayala King
R&D QA Manager

NHS
University Hospital Southampton
NHS Foundation Trust

So you want to sponsor?

Why?

- Feel you should
- Support local investigators
- Increase research activity
- Improve research reputation
- Increase revenue
- Other reasons?

Responsibility of Sponsoring

The sponsor is the individual, organisation or partnership that takes on overall responsibility for proportionate, effective arrangements being in place to set up, run and report a research project.

An individual, company, institution, organisation or group of organisations that takes on responsibility for initiation, management and financing (or arranging the financing) of the research.

UK policy framework for health and social care research

University Hospital Southampton NHS Foundation Trust

Things to Consider

- Grant Applications
- Template Protocols
- Investigator suitability
- Training courses
- Multi-site studies
- Contracting
- Insurance
- Governance
- Finance
- Monitoring
- Reporting
- Study Types

Set your Rules

What you can do

- CI experienced
- CI employed by Organisation
- Fully Funded
- Insurance
- Trial Management
- Organisation Type

What you can't do

- Multicentre
- ATIMP
- International
- Under/Non Funded
- Unusual Study Design

Assess the Study

- Do you understand what the study is about?
- Does it meet your rules?
- Formal Risk assessment

- Data Protection
- Tissue
- Reporting
- Inspection
- Monitoring
- Data Management
- Archiving

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University Hospital Southampton
NHS Foundation Trust

Make your Decision

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The End of the Story?

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The Christie
Research

The Christie

Benita Hallewell-Goodwin

R&D Sponsor Coordinator

Risky Business

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Defining risk

Risk (/rɪsk/)

verb

‘To expose to a hazard or danger’

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Sponsor Risk Assessment

Vital 

Proportionate 

Dynamic 

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Risk and Research

Participants

Researchers

The integrity of the study

The organisation

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Sponsor Risk Assessment


Risk Areas


Assigning Risk


Risk management


Risk assessment tool

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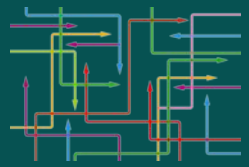
Risk Areas

Study management

Research team

Vendors



Study design

Data

IMP management

Finances & Contracts

Publication & dissemination

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Assigning Risk

Impact

Likelihood

Detectability

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Risk Management

Proportionate

Achievable

Measurable

Oversight

Accountability

Living Document

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Research

Case Study






An investigator for a study spanning multiple tumour types has proposed survival follow-up every month until patient death.

For two of the disease areas involved (Glioblastoma and colorectal cancer) median survival is a few months. For the other disease area (pancreatic neuroendocrine tumours) the median survival is around 2 years.

The primary end point relates to median survival.

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Research

Case Study

Impact: Patients will find the follow-up period too burdensome, leading to patients leaving the study. Patients may also be unwilling to enter the study

Mediu
m

Likelihood: We can reasonably expect some patients to leave the study and/or for the study to experience recruitment difficulties due to this frequency of follow-up

High

Detectability: It will be clear if a patient leaves the study or if recruitment is difficult, but patients are under no obligation to tell us why they refused the study or why they left it

Mediu
m

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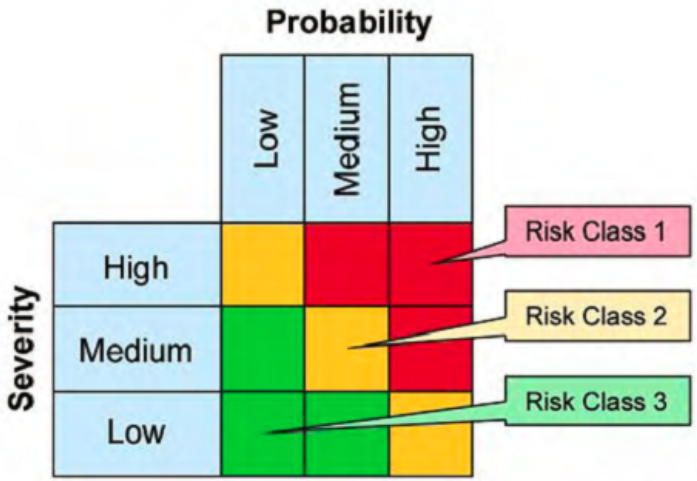
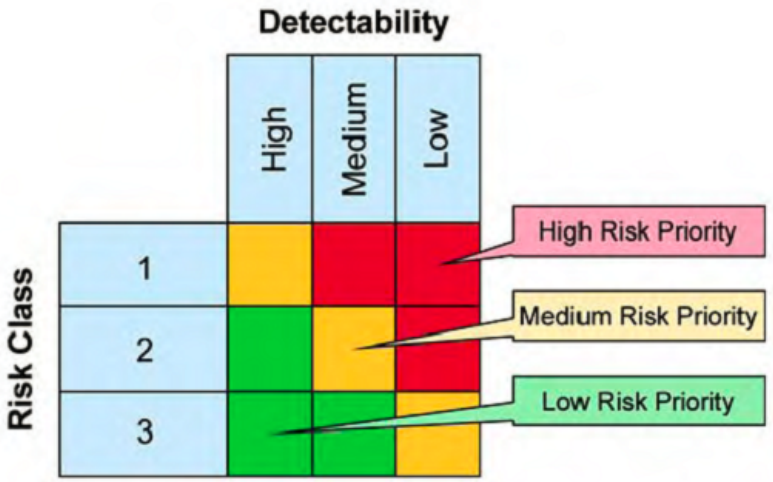
Case Study





Severity = Impact on patient safety, product quality and data integrity (or other harm)

Probability = Likelihood of the fault occurring

Risk Class = Severity x Probability

Detectability = Likelihood that the fault will be noted before harm occurs

Risk Priority = Risk Class x Detectability

Acknowledgment: Risk Assessment Method from GAMP 5, Appendix M3, Science Based Quality Risk Management.

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Case Study

High Risk Priority

Management plan: The Chief Investigator will consider changing the frequency of follow up prior to submission to regulatory bodies

Proportionate ✓

Action is required in order to mitigate the risk to study integrity, recruitment and the comfort of the patient

Achievable ✓

Survival should be able to be assessed with less frequent follow-ups and the CI has the requisite knowledge to make this decision

Measureable ✓

We know what the action is and can measure it against a target timeframe

Accountability ✓

CI is name as the responsible person and they have agreed to do this prior to a specific time-point

Oversight ✓

Sponsor authorisation for submission will only be given once the issue has been addressed – this will be monitored through the risk assessment and the sponsor's pre-submission checks

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Your Risk Assessment Tool

Risk statements

Information gathering

Usability

Functionality

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What we wish we'd known

"How important it is to revisit and update the risk assessment"
Deanna, R&D Sponsor Coordinator

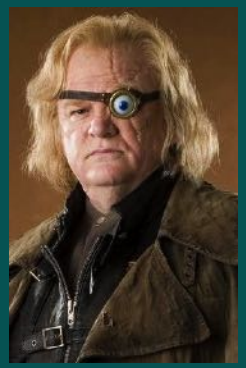
"That, if well designed and well completed, they confer the power to predict the future!"
Clare, Research Integrity & Governance Manager

"How broad the scope of the risk assessment is and the amount of detailed information required"
Steven, R&D Sponsor Coordinator

"How much trouble and time you can save later on by being really, really thorough at the start"
Holly, R&D Sponsor Coordinator

What we wish we'd known

Be prepared



Constant vigilance

Save time

Get in touch

ChristieSponsoredResearch@Christie.nhs.uk

The Christie

Research

Experimental

Pioneering

Life Changing

The Christie NHS Foundation Trust, Wilmslow Road , Manchester, M20 4BX

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Liverpool University Hospitals
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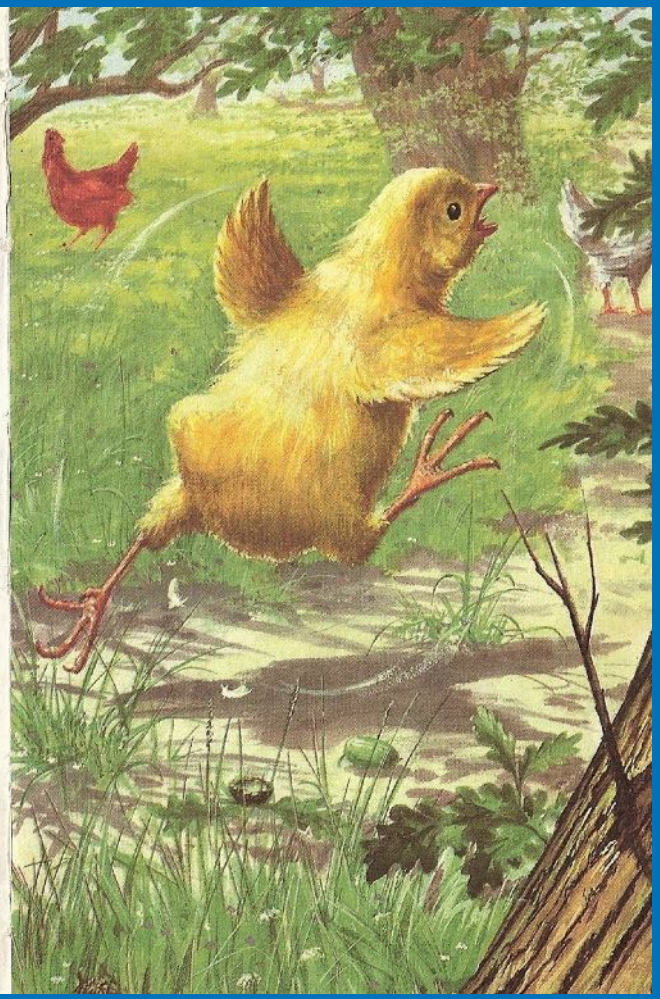
Keep calm and carry on : dealing with the unexpected

Lara Lavelle-Langham – University of Liverpool
Heather Rogers – Liverpool University Hospitals NHS Foundation Trust

Chicken Licken thought that the sky was falling down. So he ran off to tell the King.



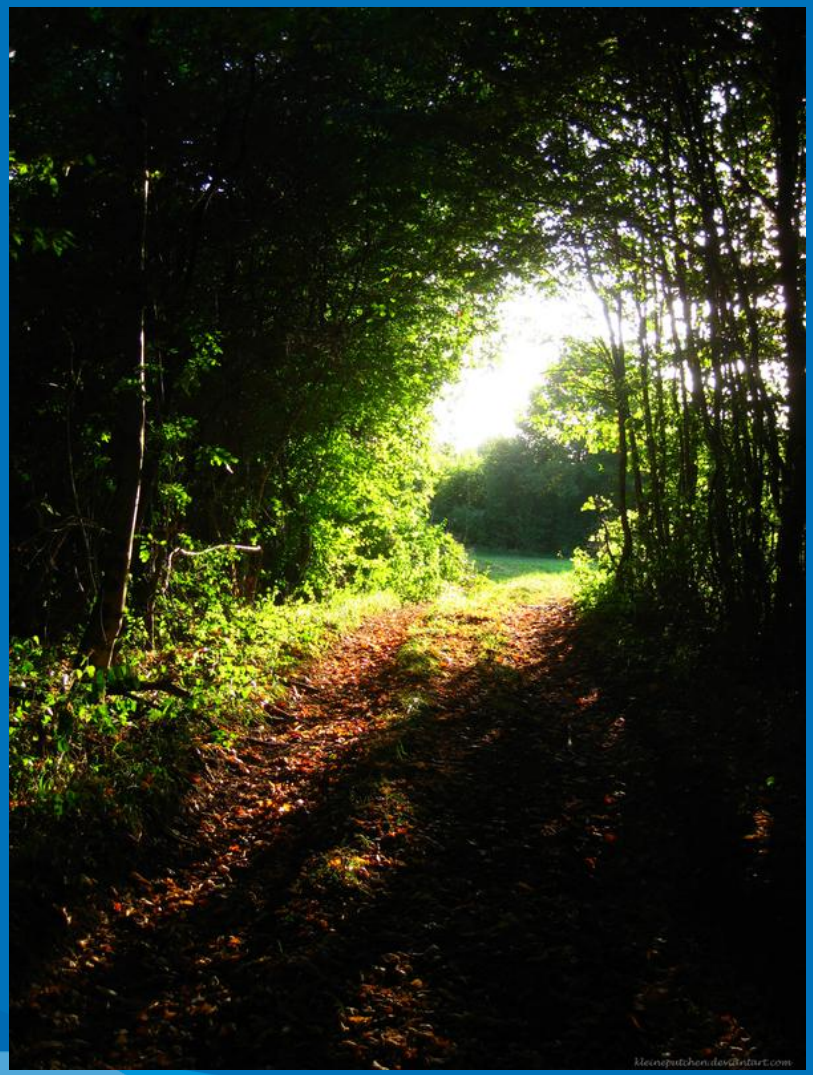
Pre-emptive : Gap analysis

- What are your limits?
- Have you got an SOP for it?
- Training v. competency

MIND THE GAP

Knowing your unknowns

- Transparency with an open an honest learning culture
- Near miss reporting
- Trending


kleuneputchen.deviantart.com

Fact finding

- Has a patient been injured?
- Has tissue integrity been lost
- Has there been a data protection breach?
- Will it impact on scientific integrity?
- Is it a near miss

Containment

Don’t forget Containment

- Safety first
- Have a plan
- Communication and Escalation

UNIVERSITY OF LIVERPOOL

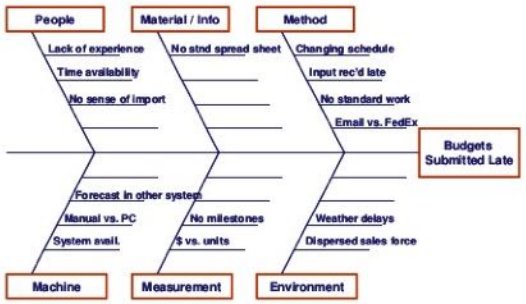
Root Cause Analysis

There are countless tools available…

5 Why's

Why?
Why?
Why?
Why?
Why?

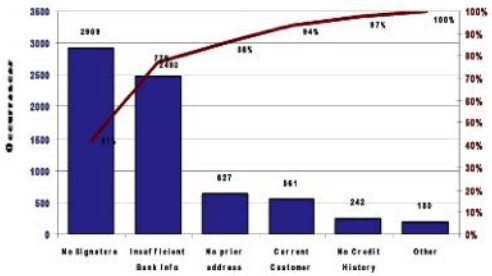
Cause-and-Effect Diagram



Check Sheets Quantify Occurrences

Reason	Tally
Material shortage	IIIII II
Quality issue requiring rework	IIIII
Staffing/absenteeism	III
Order entry error	IIIII IIIII
Changing customer requirements w/ no adjustment to expected delivery	IIIII IIIII III
Equipment failure	I

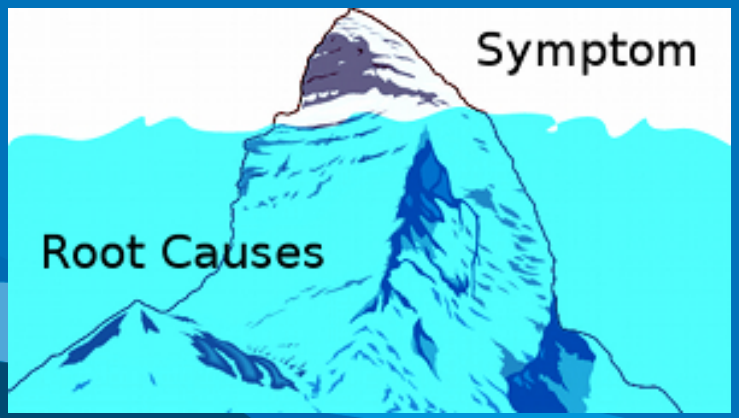
Pareto Chart
Credit Application Delays



The 8D Methodology

Root Cause Analysis

- Have the right investigation team – cross-functional and multidiscipline
- Correctly Define the issue(s)
- Identify the causes – be open and reflect honestly
- Understand that there can be contributory factors



CAPA

There are important differences in types of CAPA

Corrective action – correct or address the nonconformity that has occurred

Preventative action – Prevent the nonconformity from occurring again

Make them achievable, agree them, plan their implementation and successfully deploy them.

Above all, they must address the root cause!

Liverpool University Hospitals
NHS Foundation Trust

Thank you.

For more details please contact:

SPARK

enquries@lhpspark.nhs.uk

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UKRI
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Welcome

Medical Research Council

Research Data Sharing

Rachel Knowles & Sarah Dickson

NHS R&D Forum
19 November 2019

Current landscape in clinical trials transparency

Increased pressure for transparency in clinical trial results and data sharing

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

NHS
Health Research Authority

+AllTrials

ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

Findable Accessible Interoperable Reusable

UKRI Medical Research Council

Benefits of sharing data

Key benefits identified

- Increases the impact and value from public funding
- Potential to synthesise data across trials to generate new insights
- Avoids duplication of research effort
- Supports transparency – open and accessible research
- Permits assessment of reproducibility

UKRI Medical Research Council

Challenges of sharing data

Key concerns identified

- Patient privacy and preventing re-identification of participants
- Concerns about misuse of data by other researchers
- Restrictions on disclosure in consent, e.g. to industry sponsors
- Resources required to prepare data and manage access
- Lack of credit for researchers who share data

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Trial participants views of data sharing

Survey of 771 participants in US trials

- 93% would allow own data to be shared with university scientists
- 82% would allow own data to be shared with for-profit companies
- No variation in willingness according to purpose (except litigation)
- Main concerns:
  - Sharing might discourage people from joining trials (37%)
  - Data may be used in marketing (34%)
  - Data may be stolen (30%)
  - Misuse of data, e.g. discrimination (22%), exploited for profit (20%)

Mello et al 2018, NEJM 2018 Jun 7; 378(23):2202-2211

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MRC's data sharing policy

Data arising from research we fund should be managed and shared as widely as possible to maximise patient and public benefit.

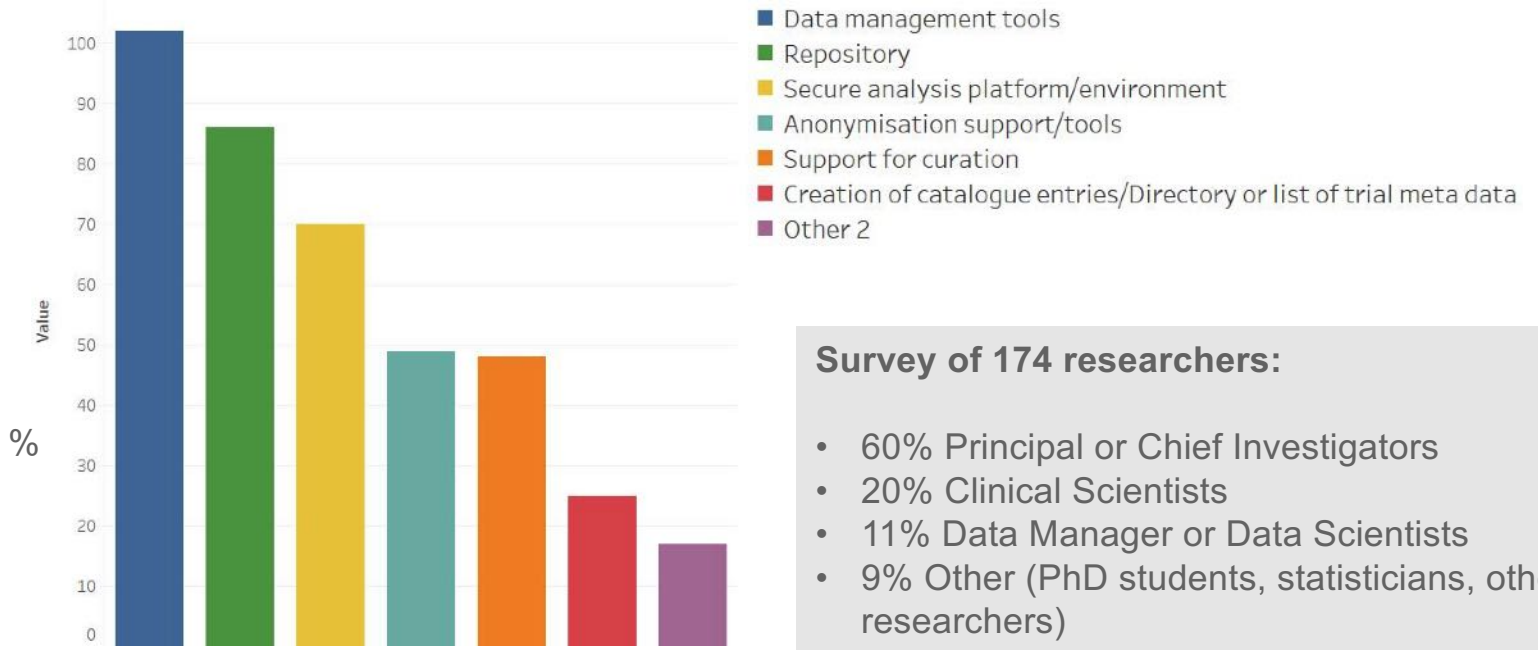
Appropriately justified costs for preparing and/or anonymising data can be included in grant proposals.

Sharing should be controlled/managed to safeguard against risks to participant privacy

MRC Data Sharing Policy https://mrc.ukri.org/documents/pdf/mrc-data-sharing-policy/

Medical Research Council

What services do researchers have access to?

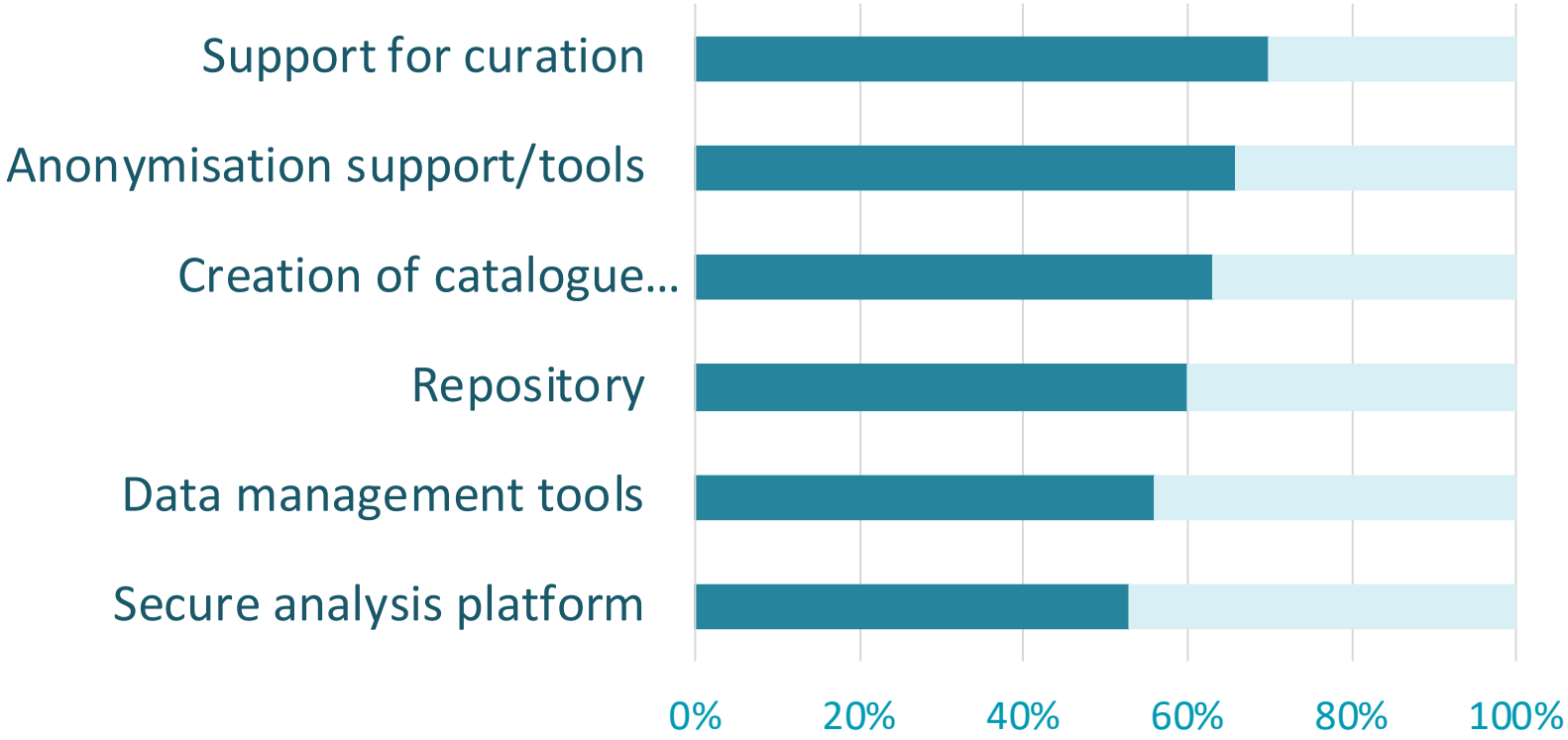


Survey of 174 researchers:

- 60% Principal or Chief Investigators
- 20% Clinical Scientists
- 11% Data Manager or Data Scientists
- 9% Other (PhD students, statisticians, other researchers)

Medical Research Council

What services do researchers need?



Medical Research Council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Data Sharing
Anonymisation and Access

Managing privacy risks

Working within the law

- Data Protection – Corporate responsibility
- Common law of confidentiality – Pts reasonable expectations – relationships with individuals

No surprises

Personal Data Vs Confidential information

Personal Data

- Structured information
- About or relating to a living individual
- **Identifiable**:

from the data alone, or from it in combination with other information you have access to

Corporate responsibility

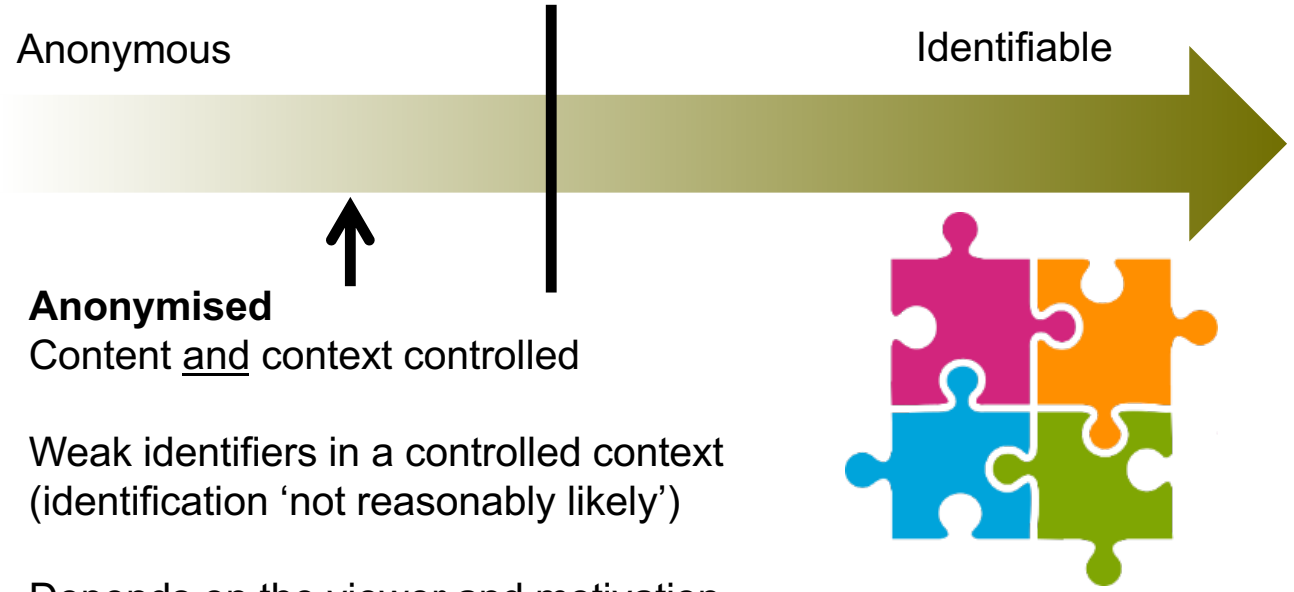
Confidential Information

- **Identifiable**
- Not already in public domain
- Given with expectation it will be kept confidential

Applies after death

Information is broader than data

Identifiability is a continuum, the law is binary

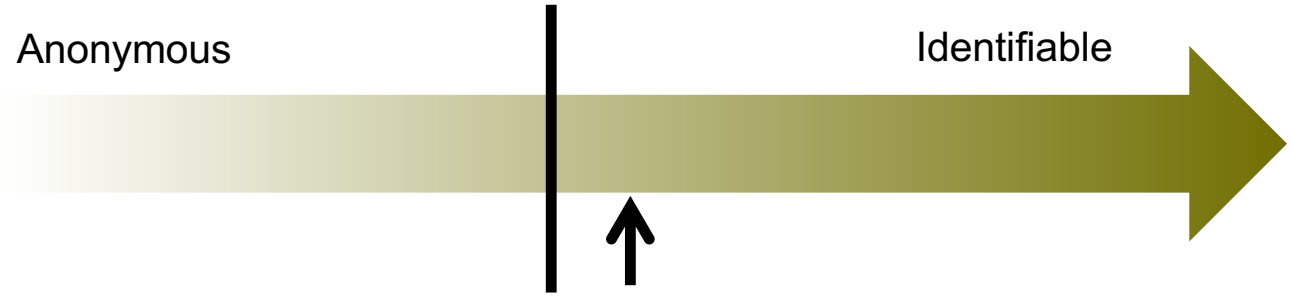


Anonymised
Content and context controlled

Weak identifiers in a controlled context
(identification ‘not reasonably likely’)

Depends on the viewer and motivation

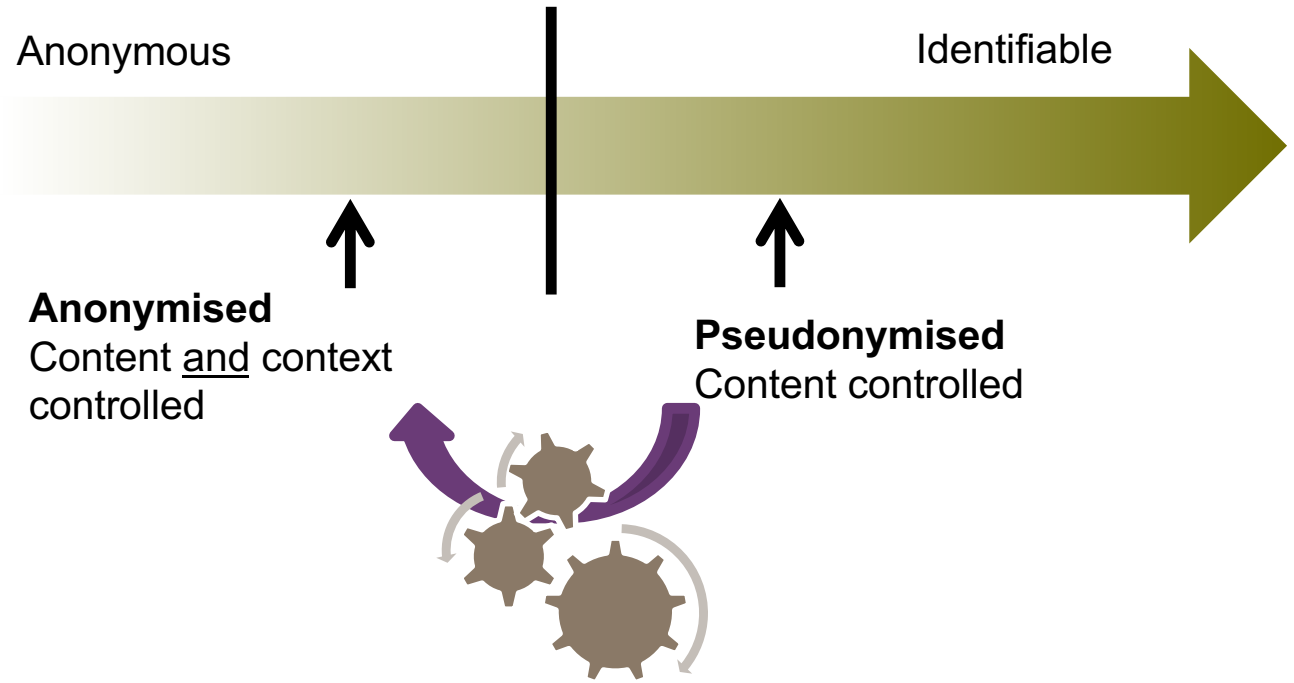
Identifiability is a continuum, the law is binary



Pseudonymised
Content controlled

Weak identifiers not in a controlled context (identification could be likely)

Identifiability is a continuum, the law is binary



Context controls relevant for data sharing

Sharing with other organisations

- **Legal data sharing agreements**
- + some things on the right

Identification is not reasonably likely by available means

Sharing within an organisation

- No access to identifiers
- ?Safe haven / TRE?
- Employment contracts (sanctions)
- Local policies
- Professional standards
- Training
- ???? Are these adequate to render anonymous

Sharing Patient Information – Who decides?

- **NHS IG department**
- **Caldicott Guardian**
- **R&D Office**
- **HRA and HCRW Approval** (REC and assessors)
- **Central and regional health data providers** in UK
- **Confidentiality Advisory Group** (s251 support England & Wales, CPI without consent) – National Data Opt-out
- **Public Benefit and Privacy Panel** (Scotland, ISD or +1 Health Board, with and without consent)…
- What do patients understand?

Sharing Patient Information – How do you decide?

Is it identifiable/confidential, is it research, consent status, security arrangements…?

Five safes

- Safe projects - appropriate use?
- Safe people - trusted?
- Safe settings - facilities, authorisations?
- Safe data - disclosure risk?
- Safe outputs - results non-disclosive?

Scales not limits, **risk proportionate**

Might not need controls for all

Data sharing principles

FAIR Principles

- Findable
- Accessible
- Interoperable
- Reusable

Medical Research Council

Regulatory Support Centre

www.mrc.ukri.org/regulatorysupportcentre

Medical Research Council

Case Study: a contested trial

Case Study: a contested trial (1)

The background

- Clinical trial results contested by a patient group
- Freedom of Information (FOI) requests to access data for a ‘re-analysis’
- FOI tribunal required release of partial dataset - as already shared with collaborators for sub-studies
- Data released by FOI is public → increased risk of re-identification of participants if other data released and matched up

UKRI Medical Research Council

Case Study: a contested trial (2)

The problem

How to share data and limit risk?

The solution

- Listing the data in a clinical trials metad
- Anonymising the data
- Managing access via an independent data access committee
- Providing access to data only within a secure data environment
- Using a data sharing agreement

UKRI Medical Research Council

ClinicalStudyDataRequest.com (CSDR)

MRC , Wellcome Trust, CRUK and Gates Foundation joined CSDR in 2017

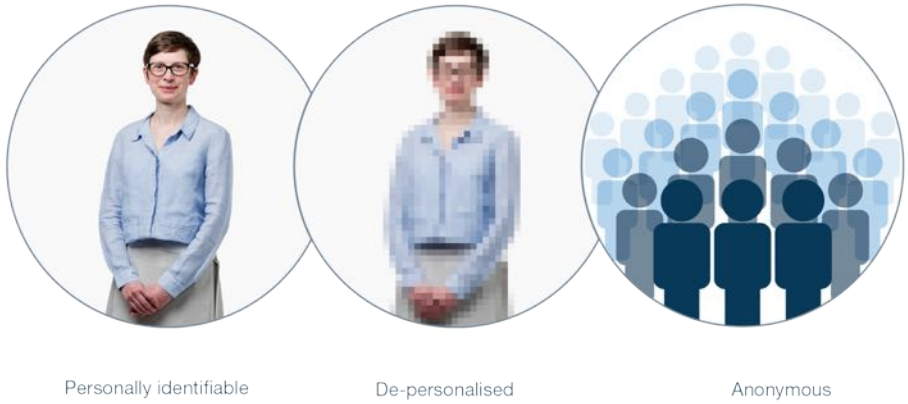
- Study **metadata catalogue** (not a repository)
- Increases **findability** of clinical trials
- Facilitates data sharing by providing a **controlled-access** mechanism
- 3300+ trials sponsored by pharmaceutical companies
- 18 trials supported by Academic Funders

UKRI Medical Research Council
CANCER RESEARCH UK
wellcome
BILL & MELINDA GATES foundation
astellas
BAYER
NOVARTIS
Roche
SANOFI
Sumitomo Dainippon Pharma
sunovion
Eisai
gsk
ucb
ViiV Healthcare
CHUGAI
A member of the Roche group

De-personalisation and anonymisation

Preparing the data

- Removing identifiers – names, addresses, dates of birth, financial data
- Degrading identifiable data – changing dates to ages (age-bands)
- Checking data, e.g.
  - Quality assessment tools (e.g. QAMyData)
  - Statistical Disclosure Control (e.g. SDCMicro)
  - K-anonymity



UKRI Medical Research Council

CSDR Independent Access Review Panel

Members

- Study proposals (purpose)
- Research applicant (user)
- Academic institution (signatory to data sharing agreement)

UKRI Medical Research Council

UK SeRP – secure access environment

UK Secure e-Research Platform (Swansea University)

- Virtual remote access
- Provision of analysis tools within secure platform
- Monitored use of data when required
- Controlled export of results

Medical Research Council

Case study: a contested trial (3)

Applying the Five Safes

- Safe people – Independent Review Panel assesses trustworthiness of users; Data Sharing Agreement (DSA)
- Safe projects – Independent Review Panel assesses project protocol and purpose
- Safe settings – SeRP platform access controls to limit unauthorised use; DSA
- Safe data – reduced disclosure risk in dataset (anonymisation)
- Safe output – controls on data release (SeRP)

UKRI Medical Research Council

A Question for you…

In order to facilitate data sharing

- What one thing would you prioritise in your organisation?

If ideas spring to mind please raise your hand

Otherwise please write on Post-it

UKRI Medical Research Council

Symposium

From the NHS Research & Development Forum

NHS

Research and Development Forum

Non-Commercial Research Sponsors Symposium for Health & Care

19th November 2019

HRA Operational Update

Health Research Authority

Dr Janet Messer,
Director of Approvals Service,
HRA

10 November 2019

NHS
Health Research Authority

Radiation Assurance

- Open to all oncology, rheumatology, neurology & cardiology studies in NHS/HSC secondary care
- Still recruiting reviewers

Current HRA-managed timeline: 31 days
Current self-managed timeline: 34 days

97 HRA-managed studies/4 self-managed studies

NHS
Health Research Authority

Feedback from applicants

“The reviews have been well accepted by all UK sites participating in our studies.”

“Streamlining the process though a central contact and inbox, has also taken a lot of the burden away from the research teams. Reviewers are quickly identified, and we are always kept up date on progress. Overall it has been a very positive experience for our centre.”

Take home messages - Radiation

- Speak to your CREs to register as HRA reviewers now. Let us know any local resistance
- Speak to your radiation department and discuss the Research Exposure Form
- Submit all eligible studies to Radiation Assurance studies
- Get payments process sorted
- Test the process – don’t wait for it to become part of HRA Approval

NHS
Health Research Authority

Pharmacy Assurance

- Open to all oncology and phase III non-oncology studies in NHS/HSC secondary care in England and Wales
- Early submission before e-submission
- Don’t need IRAS form

Current HRA-managed timeline: 27 days
Current self-managed consistency review timeline: 4 days

15 HRA-managed studies/2 self-managed studies

Health Research Authority

Feedback from applicants

“…impressed with the timelines in which the study was reviewed”

“allows the information to be efficiently shared with the sites … making the setup process quicker”

NHS
Health Research Authority

Take home messages - Pharmacy

- Speak to your pharmacy department – discuss the Pharmacy Technical Review Form
- Submit all eligible studies to Pharmacy Assurance as early as possible
- Get payments process sorted
- Test the process – don’t wait for it to become part of HRA Approval

NHS
Health Research Authority

Combined Ways of Working

NHS
Health Research Authority

Combined Ways of Working

- Piloting a co-ordinated and more streamlined CTIMP review process in the UK
- MHRA & HRA in partnership with the Devolved Administrations
- Aligns with EU Clinical Trial Regulation 536/2014

Health Research Authority

CWoW performance

88 completed applications

Mean average 49 days (range 17 – 74 days)

70 completed substantial amendments

Mean average 33 days (range 2-84)

(as of 5.11.19)

Health Research Authority

CWoW – general feedback

- Overall the end to end timelines are good
- The guidance is clear and helpful
- Response to requests for further information within 14 days can be challenging
- Some internal organisational changes required
- Increased communication between different regulatory teams
- Generic e-mails preferable rather than personal e-mails

Health Research Authority

CWoW – Feedback

“It’s great to have a more joined up approach from the regulators. The interaction and co-ordination between the REC and the MHRA works really well.”

Health Research Authority

CWoW – Feedback

“Overall we have seen a significant decrease in MHRA and REC approval timelines which has been welcomed by our clients; the pilot process was straightforward and fitted well into our established processes.”

Health Research Authority

Thank you for listening

Contact information:

- **Dr Janet Messer**
- Hra.approvalprogramme@nhs.net

Follow us on Twitter **@HRA_Latest**
Sign up for our monthly newsletter at **www.hra.nhs.uk**

Symposium

From the NHS Research & Development Forum

NHS

Research and Development Forum

Non-Commercial Research Sponsors Symposium for Health & Care

19th November 2019

What you need to know about the new EU Regulations for medical devices (MDR)

Dr Tracy Assari

Research Governance Lead

Cambridge University Hospitals NHS Foundation Trust

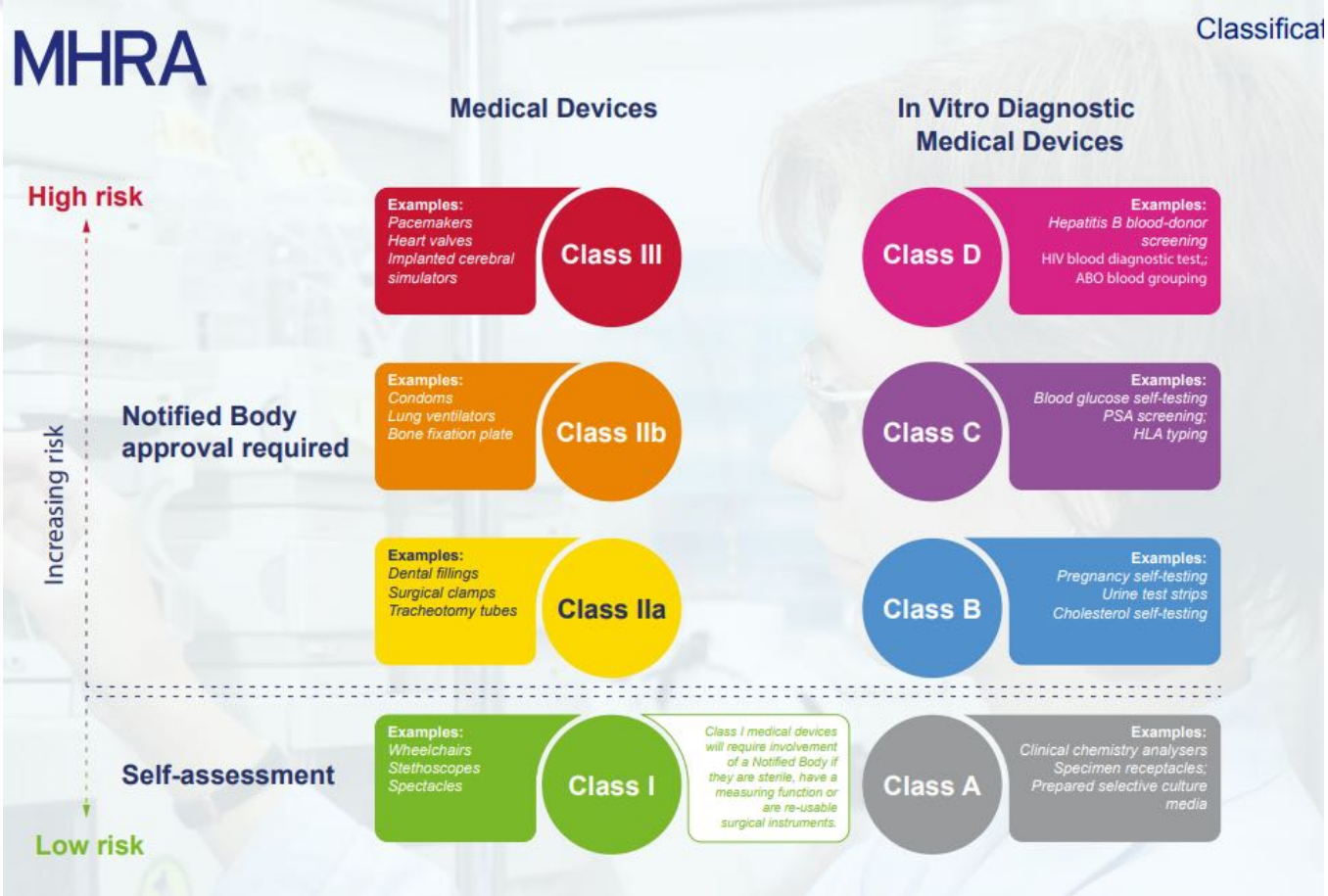
What is a Medical Device

Definition*: 'Medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings

Eg.

dental/ surgical instruments, hospital bed, bandages and splints, artificial hips, incubators, insulin injectors scanners, scalpels

A medical device cannot be marketed in Europe without carrying a **CE marking**. All but the very lowest risk devices (eg. unmedicated bandages) must be verified by an independent certification body, called a Notified Body, before the CE marking can be affixed

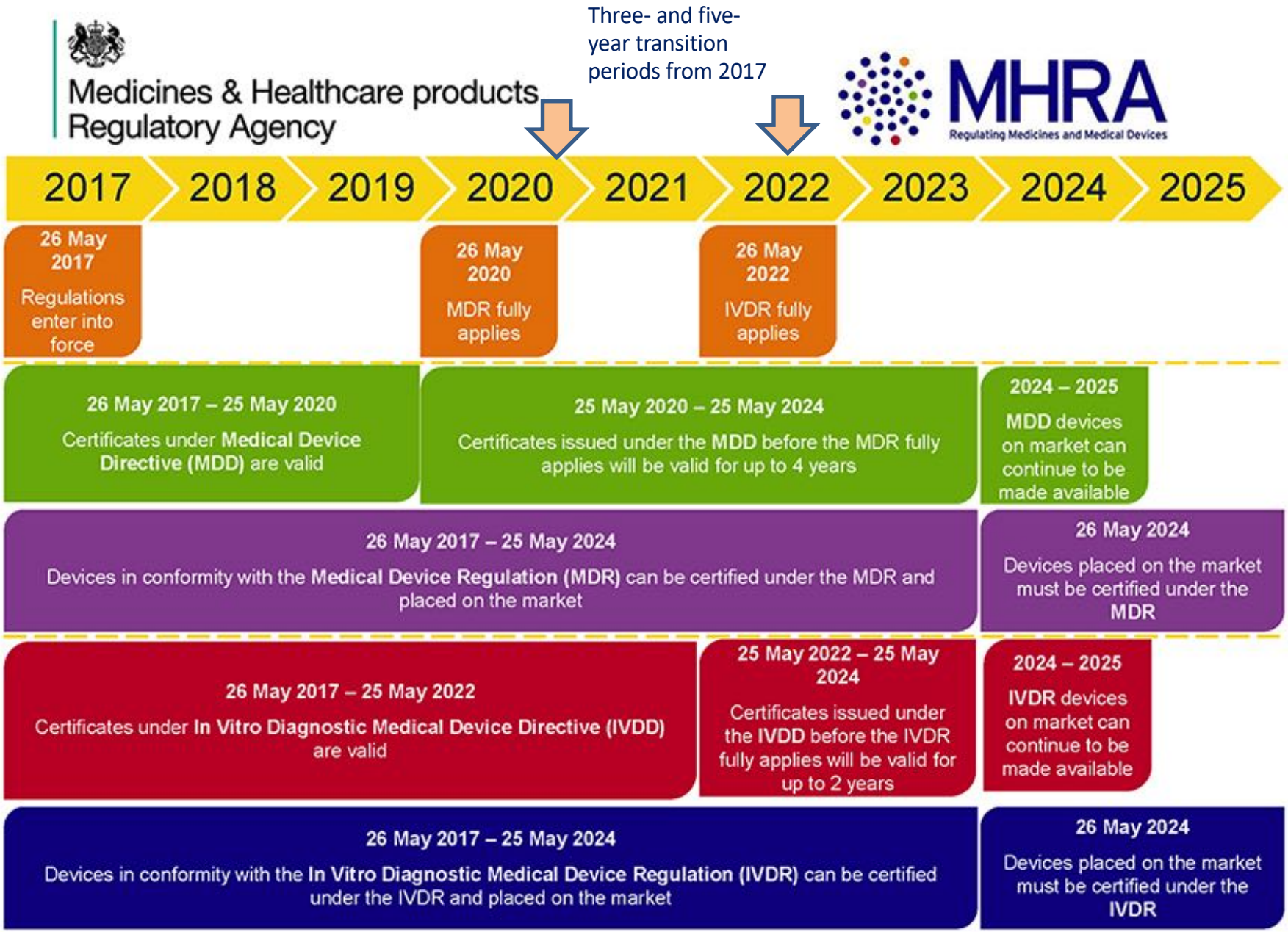


History of Medical Device Regulation:

- **Late 1960s** - Scientific and Technical Branch (STB) established to improve the quality and safety of medical equipment.
- **1980s** - the STB became part of the NHS Procurement Directorate, which was later split into the NHS Supplies Authority and the Medical Devices Directorate (MDD).
- **1994** - The MDD in effect became the Medical Devices Agency
- **2003** – Medical Devices Agency which then merged with its medicines counterpart to become the MHRA.

The Regulations

- The Medical Devices Regulations 2002 ("the Regulations"), as amended, transpose various EC Directives into UK law, included the Active Implantable Medical Devices Directive (AIMDD) and the Medical Devices Directive (MDD)
- The new **Medical Device Regulation (MDR)** and the **In Vitro Diagnostic Medical Device Regulation (IVDR)** entered into force on 25 May 2017


Medicines & Healthcare products Regulatory Agency
Three- and five-year transition periods from 2017
MHRA
Regulating Medicines and Medical Devices
2017
2018
2019
2020
2021
2022
2023
2024
2025
26 May 2017
Regulations enter into force
26 May 2020
MDR fully applies
26 May 2022
IVDR fully applies
26 May 2017 – 25 May 2020
Certificates under Medical Device Directive (MDD) are valid
25 May 2020 – 25 May 2024
Certificates issued under the MDD before the MDR fully applies will be valid for up to 4 years
2024 – 2025
MDD devices on market can continue to be made available
26 May 2017 – 25 May 2024
Devices in conformity with the Medical Device Regulation (MDR) can be certified under the MDR and placed on the market
26 May 2024
Devices placed on the market must be certified under the MDR
26 May 2017 – 25 May 2022
Certificates under In Vitro Diagnostic Medical Device Directive (IVDD) are valid
25 May 2022 – 25 May 2024
Certificates issued under the IVDD before the IVDR fully applies will be valid for up to 2 years
2024 – 2025
IVDR devices on market can continue to be made available
26 May 2017 – 25 May 2024
Devices in conformity with the In Vitro Diagnostic Medical Device Regulation (IVDR) can be certified under the IVDR and placed on the market
26 May 2024
Devices placed on the market must be certified under the IVDR

Key elements of the new legislation include:

***Expansion of the definition of medical devices**:* includes certain products which previously did not fall under the definition of a medical device.eg. eye contact lens solution, liposuction equipment and laser equipment used for hair and tattoo removal (Borderline products eg. Medicated surgical dressings are determined by the MHRA.

***EUDAMED database*:** The Commission will establish a centralised significantly expanded EU database for the storage of information on medical devices (EUDAMED) that will become a public tool

***Introduction of a risk based classification system*:** A new system for risk classification, in line with international guidelines, will apply to in-vitro diagnostic medical devices. Manufacturers will need to demonstrate that their medical device meets the requirements in the MDR and IVDR by carrying out a conformity assessment. Each medical device must receive a unique identification number (UDI) in the future.

***Financial compensation measures must be in place*:** The regulations require manufacturers to have measures in place to provide sufficient financial coverage in respect of their potential liability. Such financial coverage must be proportionate to the risk class, type of device and the size of the enterprise

***Enhanced vigilance and market surveillance*:** Once devices are available for use on the market, manufacturers will be obliged to collect data about their performance, and EU countries will coordinate more closely in the field of market surveillance.

***Tighter regulatory controls*:** impose tighter pre-market controls on high-risk devices. MDR will require device manufacturers to conduct clinical performance studies and provide evidence of safety and performance**,** EU cross-border clinical trials will be subject to a single coordinated assessment, device manufacturers will be required to collect and retain post-market clinical data.

Post Market Surveillance System (PMSS): manufacturers must also establish a PMSS, which should be proportionate to the risk class and the type of device in question.

Responsible Person (RP): Medical device manufacturers and authorised representatives will be required to designate at least one person with responsibility for regulatory compliance; that person(s) must hold the prerequisite academic expertise and work experience in the field of medical devices.

In Summary if you are manufacturing a medical device, you must meet new obligations set out in the Regulations. You will need to ensure:

- the device has been correctly classified against the new risk classification criteria (Annex VIII of the MDR and IVDR)
- general safety and performance requirements are met, including for labelling and technical documentation and quality management systems (Annex I of the MDR and IVDR)
- increased requirements for clinical evidence are met (Annex XIV of the MDR and IVDR)
- manufacturers have a person responsible for regulatory compliance in place (Article 15 of the MDR and IVDR)
- economic operators in the supply chain are compliant
- sufficient financial coverage is in place, in respect of a manufacturer's potential liability (Article 10 of the MDR and IVDR)
- the new vigilance reporting timescales are met and that an annual periodic safety update report is created (Chapter VII, Section 1 and 2 of the MDR and IVDR)

PIP SCANDAL - 2010


Breast implant crisis puts watchdog in spotlight

36 NEWS

PIP implant fear amid payout plea

- The implants were manufactured by the French company Poly Implant Prothese (PIP) and in 2010 it emerged they had been made with substandard, industrial-grade silicone.
- The scandal affected about 300,000 women in as many as 65 countries, including France, the UK, Germany, Venezuela and Brazil.
- Compensation for damage caused by defective medical devices is still on-going.
- A structural weakness in the system along with inconsistent interpretation of the directives in different countries was recognised.

With the new MDR

- Users can claim compensation for damage caused by defective devices.
- In the case of non-European manufacturers, the Authorized Representative will be held responsible together with the manufacturer.
- The new regulations will ensure vital information is easy to find through more stringent traceability measures.
- All patients will receive an implant card with all the essential information, and a unique device identifier will be mandatory for every product

DEVICE TYPES

3D printed devices – a case by case assessment will be required to determine a product's status and classification

Software/Apps – classification rules will change with more software requirements

Devices with no medical purpose (products falling under Annex XVI – clinical investigations of these product types will now be regulated by MHRA.

Drug-device combination products - Must now include: CE certificate issued by a Notified Body for the medical device component or Notified Body Opinion (NBO) on the conformity of the device (Article 117). This does not apply in the case of combined advanced therapy medicinal products as defined under Article 2(1)(d) of Regulation (EC) No 1394/2007.

Implantable devices (Article 18 of MDR)

Health institutions will need to provide patients with implantable devices with an implant card, which shall bear the patient's identity, as well as rapid access to certain information, including:

- The identification of the device, including the device name, serial number, lot number, the UDI, the device model, and the name, address and website of the manufacturer;
- Warnings, precautions or measures to be taken by the patient or a healthcare professional;
- The expected lifetime of the device and any necessary follow-up.

In Vitro Diagnostic Medical Devices

The MHRA provides an abridged definition of an in vitro diagnostic medical device as:

"any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body." (full definition can be found in Article 2(2) of the IVDR)*

The new regulations are likely to cover entities such as biomarkers, regenerative medicine, software modifications to equipment, new implantable materials such as those for dental use and diagnostic kits.

Performance evaluation studies - There will be a few study categories that will require MHRA approval, however this will not come into effect until May 2022.

Medical device research in the NHS

As the subject of a 'clinical investigation', in a research study/trial

Under the new regulations:

- Many medical devices will be reclassified as higher risk and a new classification for reusable surgical devices has been created. This means that many more research studies using medical devices or involving in vitro diagnostics will fall under the scope of regulation.

Article 15 "Clinical investigation" is replaced by twenty articles in new EU MDR, Articles 62 through 82. New process for submitting clinical investigation applications

Studies will need to be conducted to specific standards to comply with the requirements for the manufacture of the investigational entity which include the General Safety and Performance Regulations (GSPR) - Annex 1 of EU 2017/745. EU MDR now clearly establishes the requirements for GCP and risk management.

The new EU MDR Articles 62 through 82 address all the familiar topics related to clinical investigations:

- Informed consent - Protection of vulnerable participants. Articles 63-66 cover informed consent in specific grounds
- Studies will need to collect particular types of data and clinical evaluation must be updated throughout device life cycle with clinical data
- Articles 62 through 82 describe “what” is required, and should be read in conjunction with the more detailed “how” to do of the new Annex on “Clinical investigations”, Annex XV

Developing an in-house medical device

Used in a health care institution to meet the needs of a specific group

Devices that are manufactured or modified and used within health institutions shall be considered as having been put into service (Article 5 of MDR).

Under the new regulations, health institutions will have to apply for exemption for these activities or else commit to the legal status of manufacturer and comply with the requirements of the MDR.
In order to apply for an exemption, health institutions will need to

- ensure products meet the relevant General Safety and Performance Requirements (Annex 1 of EU 2017/746)
- have technical documentation and appropriate quality management system in place;
- devices must not be transferred to another legal entity
- ensure certain information is publicly available
- justify applying for the exemption – where the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market

Custom-made for a specific individual

Compliance with General Safety and Performance Regulations (GSPR)

· Written prescriptions for individual patients from an authorised prescriber
· For class III devices a notified body may be required to authorise the device
· Vigilance reporting
· Periodic safety updates
· Specific documentation Unique Device Identification does not apply.

The role of Sponsor

For the first time, the MDR has established the formal role of a sponsor as subject of medical device regulation (Article 73 of MDR / Article 69 of IVDR). The sponsor is defined as any individual, company, institution or organization which assumes responsibility for the initiation, including management and arrangement of financing the clinical investigation

Sponsor of study to be conducted in more than one Member State (MS) can submit a single application electronically to all MSs

- Sponsor must propose a coordinating MS
- Sponsor must appoint monitor who is independent from investigational site
- Furthermore, sponsors from outside of the EU will have to have a legal representative who is based in the EU

Conclusions:

- Comparing the MDD and the MDR the requirements how to conduct a clinical investigation do hardly change (or do not change at all).
- Provided that your current Quality System is compliant to the MDD/AIMDD, ISO 14155:2011 and Declaration of Helsinki, there is not much to change.
- Mainly due to centralised electronic system, the MDR might even make everything easier for conducting clinical investigations!
- MHRA will be updating the guidance on their website to bring it in line with the MDR, the application process and information requirements will not significantly change.

BREXIT

- The EC has made it clear that in a "no deal" scenario, the EU-27 will no longer recognize UK-based authorised representatives. This means they will not be recognised as able to carry out tasks on the manufacturer's behalf for the purposes of placing products on the EU market.

What this means:

- A new role – the **UK Responsible Person** –to act on the manufacturer's behalf , has been created under the UK MDR 2002 (as amended by the UK MDR 2019), applicable in a no-deal Brexit.
- The UK Responsible Person must be established in the UK and acts on behalf of a manufacturer established outside the UK, to carry out specified tasks in relation to the manufacturer's obligations. This includes registering with the MHRA before the device is placed on the UK market.
- Only a manufacturer /designated UK Responsible Person can legally place a device on the UK market.
- If you are a designated UK Responsible Person of a non-UK manufacturer, MHRA require documentary evidence supporting this position. eg. letter of designation, signed contract, confirming they are acting with the consent of the overseas manufacturer and adheres to legislation applying for the devices being placed on the UK market.
- The registering entity must have a "*registered place of business*" in the UK. In case of the the Responsible Person, they will then assume the registration obligation and will also assume the manufacturer's reporting obligations on device vigilance.
- In order to place devices on the EU market, manufacturers with an Authorised Representative based in the UK will need to establish a new Authorised Representative in an EU country.

USEFUL READING:

- https://www.ema.europa.eu/en/news/first-guidance-new-rules-certain-medical-devices
- https://www.gov.uk/guidance/medical-devices-eu-regulations-for-mdr-and-ivdr
- http://eumdr.com/
- https://www.meddeviceonline.com/doc/key-changes-to-understand-in-the-new-european-mdr-and-ivdr-0001

THANK YOU

Symposium

From the NHS Research & Development Forum

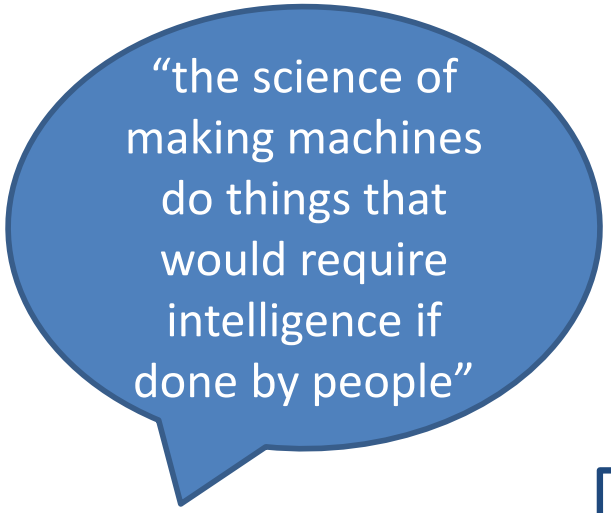
NHS

Research and Development Forum

Non-Commercial Research Sponsors Symposium for Health & Care

19th November 2019

How we sponsor AI studies



AI definitions discussed on page 14
Artificial Intelligence: How to get it right. NHS X, September 2019

Helen Street
Research Governance Clinical Informatics Lead
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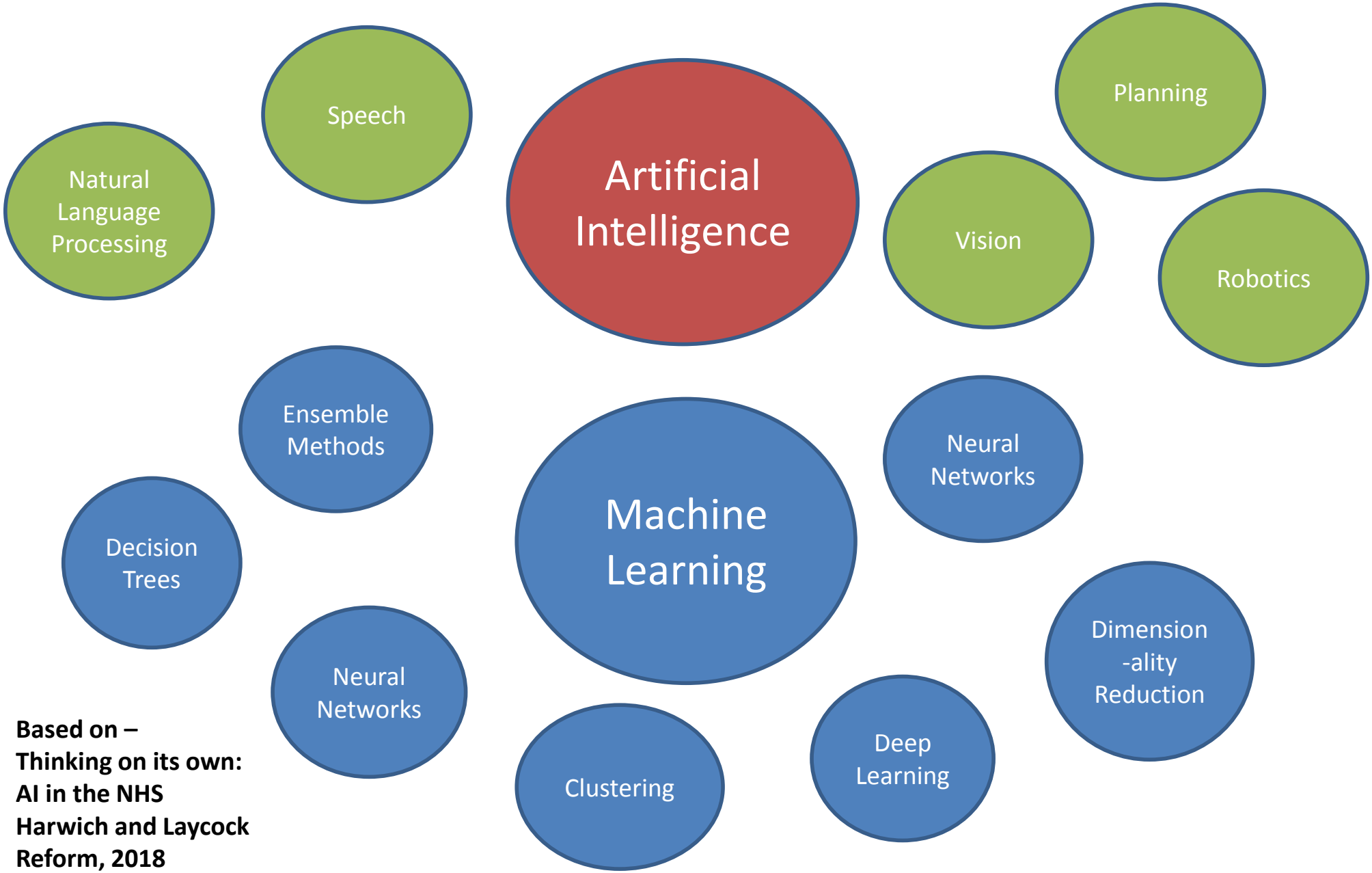


Based on –
Thinking on its own:
AI in the NHS
Harwich and Laycock
Reform, 2018

House

Cat

Dog

Dog

Dog

Dog

AI in the NHS

Diagnostics	Knowledge Generation	Public Health	System Efficiency	P4 Medicine
• Image Recognition e.g. • Symptoms Checkers and Decision Support • Risk Stratification	• Drug Discovery • Pattern Recognition • Greater knowledge of rare diseases • Greater understanding of casuality	• Digital epidemiology • National screening programmes	• Optimisation of care pathways • Prediction of Do Not Attends • Identification of staffing requirements	• Prediction of deterioration • Personalised treatments • Preventative advice

Figure 1 [5–12]

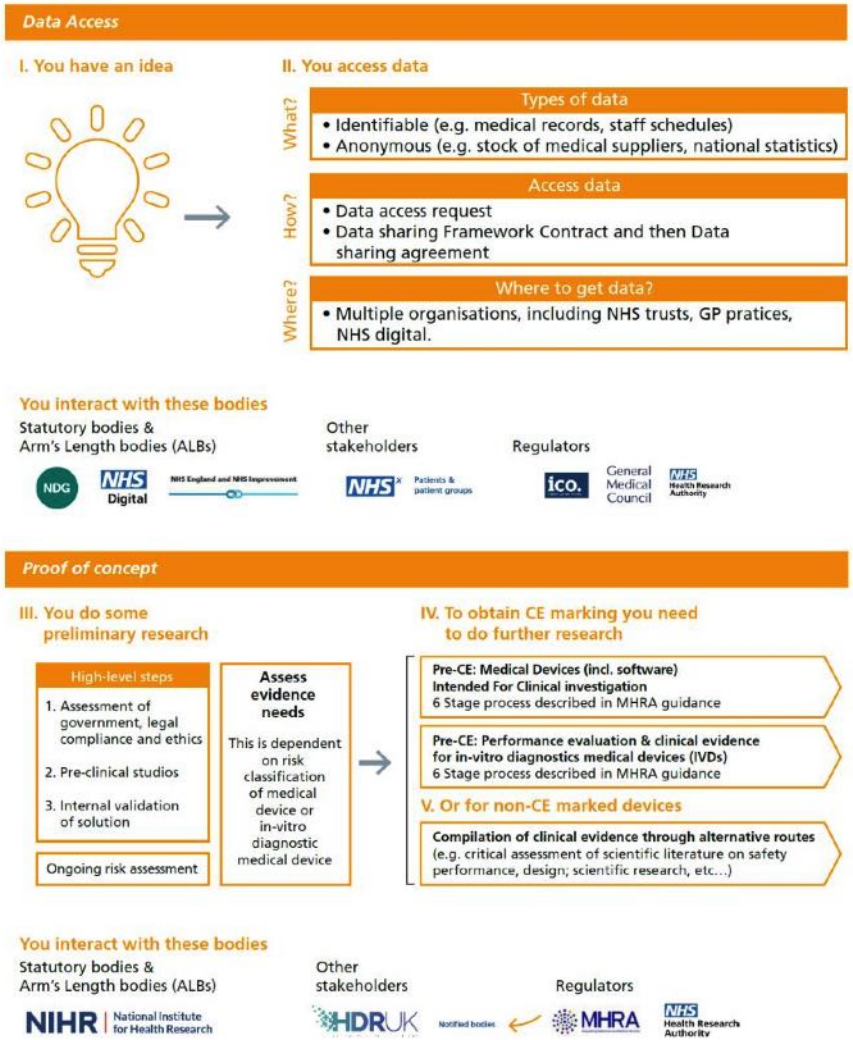
Dr Indra Joshi and Jessica Morley – Introduction
Artificial Intelligence: How to get it right. NHS X, September 2019

Guidance

Code of conduct for data-driven health and care technology

Updated 18 July 2019

- Principle 1: Understand users, their needs and the context
- Principle 2: Define the outcome and how the technology will contribute to it
- Principle 3: Use data that is in line with appropriate guidelines for the purpose for which it is being used
- Principle 4: Be fair, transparent and accountable about what data is being used
- Principle 5: Make use of open standards
- Principle 6: Be transparent about the limitations of the data used
- Principle 7: Show what type of algorithm is being developed or deployed, the ethical examination of how the data is used, how its performance will be validated and how it will be integrated into health and care provision
- Principle 8: Generate evidence of effectiveness for the intended use and value for money
- Principle 9: Make security integral to the design
- Principle 10: Define the commercial strategy



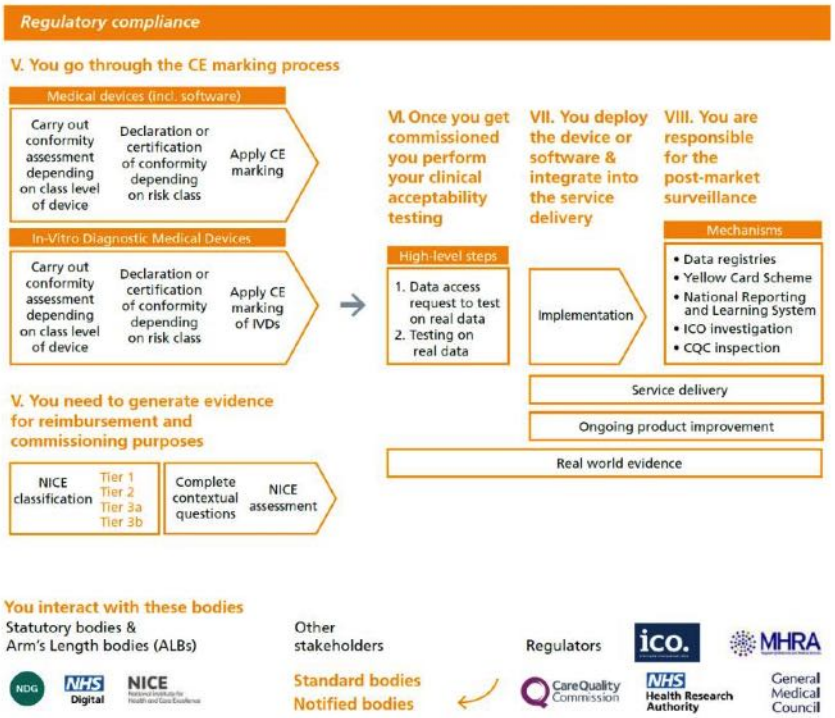


Figure 6: current regulator journey map for data driven technologies in health and care

Eleonara Harwich and Claudia Martinez – Mapping the regulatory journey
Artificial Intelligence: How to get it right.
NHS X, September 2019

Data access

- Identifiable or anonymous data
- From multiple organisations including NHS Digital, NHS trusts and GP practices

Proof of concept

- Preliminary research and internal validation
- Pre-CE marking – possible clinical investigation/evaluation

Regulatory compliance

- Go through CE marking process
- Perform clinical acceptability testing
- Implementation and post-market surveillance
- Generate evidence for reimbursement and commissioning

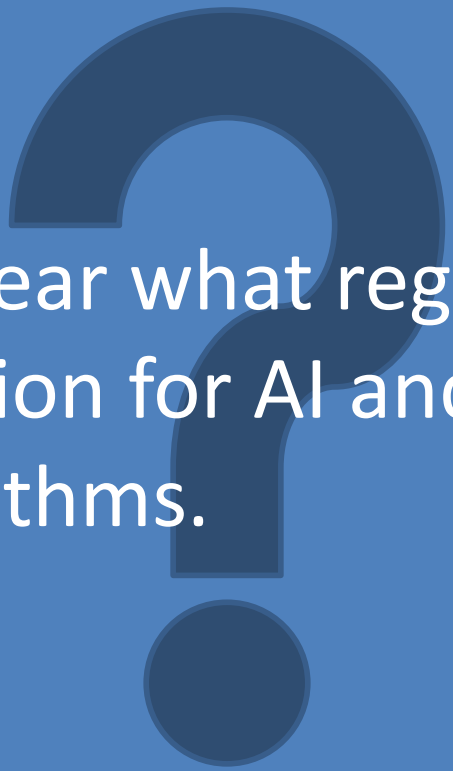
Annex VIII of the Medical Device Regulation: Section 6.3. Rule 11

Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:

- death or an irreversible deterioration of a person's state of health, in which case it is in class III; or
- a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.

Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb.

All other software is classified as class I



It is currently unclear what regulation will look like for the validation for AI and how it will work for adaptive algorithms.

NHSX

MHRA

Data access

- Identifiable or anonymous data
- From multiple organisations including NHS Digital, NHS trusts and GP practicies

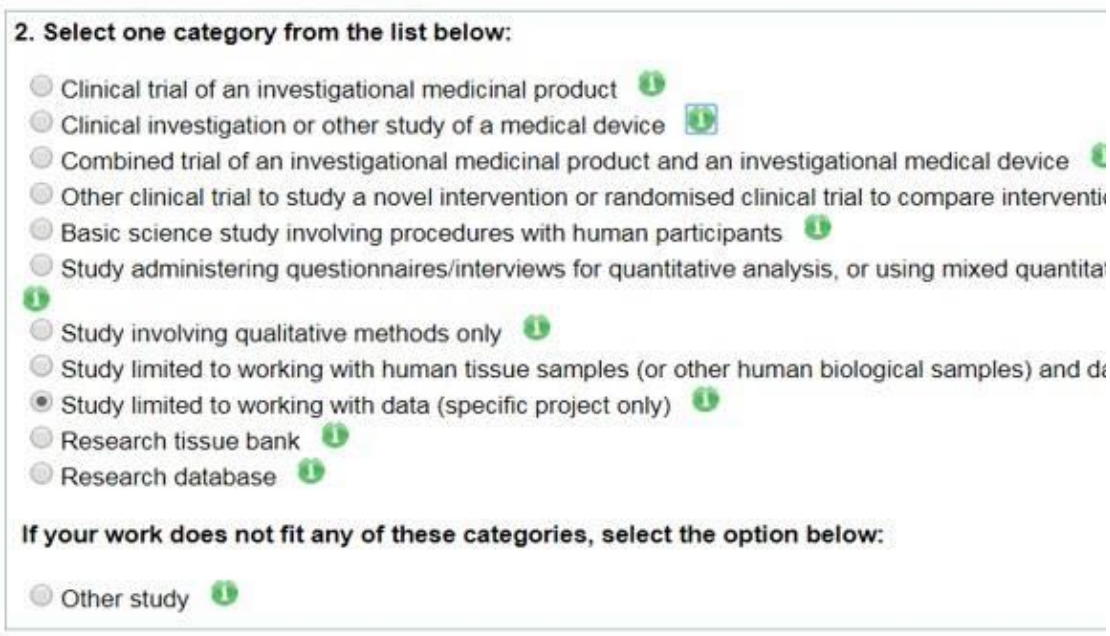
Proof of concept

- Preliminary research and internal validation

=

Study limited to working with data

NHS
Health Research Authority




eHospital

Routinely collected data - Legal basis

- Consent is not the legal basis for processing under GDPR. Requirement for transparency.
- Common law on confidentiality – only the care team should have access to identifiable information unless section 251 consent waiver is approved by CAG.
- National-opt out does not apply to anonymous data.

MRC Medical Research Council

Regulatory Support Centre

General Data Protection Regulation (GDPR): Consent in Research and Confidentiality

Robust anonymisation of data

- Remove all direct identifiers
- Minimise data collected
- Consider anonymity of the combined data
- Pay attention to rare diseases and outliers in cohort
- Genetic data may not always be automatically identifiable

MRC Medical Research Council

Regulatory Support Centre

Identifiability, anonymisation and pseudonymisation

Guidance note 5

This guidance was developed with the participation of the Information Commissioner's Office.

Data user/sharing agreements

- **Appropriate safeguard to protect anonymous data**
- **Limit use of data to protocol**
- Forbid attempts to identify patients or combine data from other projects/sources
- Limit onward sharing and outline how data should be dealt with at end of study.
- **Outline security arrangements for storage and processing**
- **Intellectual property**

Commercial strategy and IP

- Principle 10: Define the commercial strategy
- Consider provision for IP whenever sharing data to ensure use of NHS data returns benefit to NHS
- NHSX and Office of Life Science working on data sharing principles for NHS and commercial models
- Proposed National Centre of Expertise to facilitate

Routinely collected data – Ethics

Anonymised data studies are often exempt from NHS ethics…

- We are sending some studies for proportionate review
- We review all other data studies by committee

Consent is not required as data is anonymous, but patient wishes should be considered from an ethical perspective, as well as to meet the GDPR requirement for transparency

- We are reviewing the Trust generic consent forms
- We are reviewing our Trust transparency statement
- We are considering our PPI strategy and working with HDRUK.

Public Opinion and Trust

Building and maintaining public and patient trust is vital to the development of AI in the NHS.

Effective communication and transparency is key.

Understanding Patient Data
https://understandingpatientdata.org.uk/
Look out for forthcoming work around public attitudes to commercial uses of patient data


ODI
Data Ethics Canvas
Data sources
Name/describe key your project's data sources, whether you're collecting data yourself or accessing via third parties.
Is any personal data involved, or data that is overwise sensitive?
Limitations in data sources
Are there limitations that could influence your project's outcomes?
Consider:
> bias in data collection, inclusion/exclusion, analysis, algorithms
> gaps or omissions in data
> provenance and data quality
> other issues affecting decisions, such as team composition
Sharing data with others
Are you going to be sharing data with other organisations? If so, who?
Are you planning to publish any of the data? Under what conditions?
Ethical and legislative context
What existing ethical codes apply to your sector or project? What legislation, policies, or other regulation shape how you use data? What requirements do they introduce?
Consider: the rule of law; human rights; data protection; IP and database rights; anti-discrimination laws; and data sharing, policies, regulation and ethics codes/frameworks specific to sectors (eg health, employment, taxation).
Rights around data sources
Where did you get the data from? Is it produced by an organisation or collected directly from individuals?
Was the data collected for this project or for another purpose? Do you have permission to use this data, or another basis on which you're allowed? What ongoing rights will the data source have?
Your reason for using data
What is your primary purpose for collecting and using data in this project?
What are your main use cases and business model?
Are you making things better for society? How and for whom?
Are you replacing another product or service as a result of this project?
Communicating your purpose
Do people understand your purpose – especially people who the data is about or who are impacted by its use?
How have you been communicating your purpose? Has this communication been clear?
How are you ensuring more vulnerable individuals or groups understand?
Positive effects on people
Which individuals, groups, demographics or organisations will be positively affected by this project? How?
How are you measuring and communicating positive impact? How could you increase it?
Negative effects on people
Who could be negatively affected by this project?
Could the way that data is collected, used or shared cause harm or expose individuals to risk of being re-identified? Could it be used to target, profile or prejudice people, or unfairly restrict access (eg exclusive arrangements)?
How are limitations and risks communicated to people? Consider: people who the data is about, people impacted by its use and organisations using the data.
Minimising negative impact
What steps can you take to minimise harm?
What measures could reduce limitations in your data sources? How are you keeping personal and other sensitive information secure?
How are you measuring, reporting and acting on potential negative impacts of your project?
What benefits will these actions bring to your project?
Engaging with people
How can people engage with you about the project?
How can people affected correct information, appeal or request changes to the product/service? To what extent?
Are appeal mechanisms reasonable and well understood?
Openness and transparency
How open can you be about this project? Could you publish your methodology, metadata, datasets, code or impact measurements?
Can you ask peers for feedback on the project? How will you communicate it internally?
Will you publish your actions and answers to this canvas openly?
Ongoing implementation
Are you routinely building in thoughts, ideas and considerations of people affected in your project? How?
What information or training might be needed to help people understand data issues?
Are systems, processes and resources available for responding to data issues that arise in the long-term?
Reviews and iterations
How will ongoing data ethics issues be measured, monitored, discussed and actioned?
How often will your responses to this canvas be reviewed or updated? When?
Your actions
What actions will you take before moving forward with this project? Which should take priority?
Who will be responsible for these actions, and who must be involved?
Will you openly publish your actions and answers to this canvas?
Open Data Institute #DataEthicsCanvas
theodi.org/tools-resources
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References and reading

AI

Artificial Intelligence: How to get it right -Putting policy into practice for safe data-driven innovation in health and care. October 2019. NHSX. https://www.nhsx.nhs.uk/assets/NHSX_AI_report.pdf

Thinking on its own: AI in the NHS. Eleonora Harwich and Kate Laycock. January 2018, Reform Health https://reform.uk/research/thinking-its-own-ai-nhs

Department of Health and Social Care. Code of conduct for data-driven health and care technology.GOV.UK 2019 https://www.gov.uk/government/publications/code-ofconduct-for-data-driven-health-and-care-technology/initial-code-of-conduct-for-datadriven-health-and-care-technology

Medical Devices – Software

Guidance: Medical device stand-alone software including apps (including IVDMDs) v1.05

MHRA. June 2018. https://www.gov.uk/government/publications/medical-devices-software-applications-apps

Data regulation and ethics.

GDPR Guidance MRC Regulatory Support https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/gdpr-resources/

Anonymisation: managing data protection risk code of practice. ICO 2012. https://ico.org.uk/media/1061/anonymisation-code.pdf

ODI. Data Ethics Canvas User Guide. https://docs.google.com/document/d/1MkvoAP86CwimbBD0dxySVCO0zeVOput_bu1A6kHV73M/edit.

Symposium

From the NHS Research & Development Forum

NHS

Research and Development Forum

Non-Commercial Research Sponsors Symposium for Health & Care

19th November 2019

Newcastle Joint Research Office

International Research Sponsorship in the NHS

Newcastle University

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Background

Newcastle Joint Research Office

"Lead the way in delivering world class, cutting-edge diagnostics, treatment, care and research"

"To realise our capability internationally"

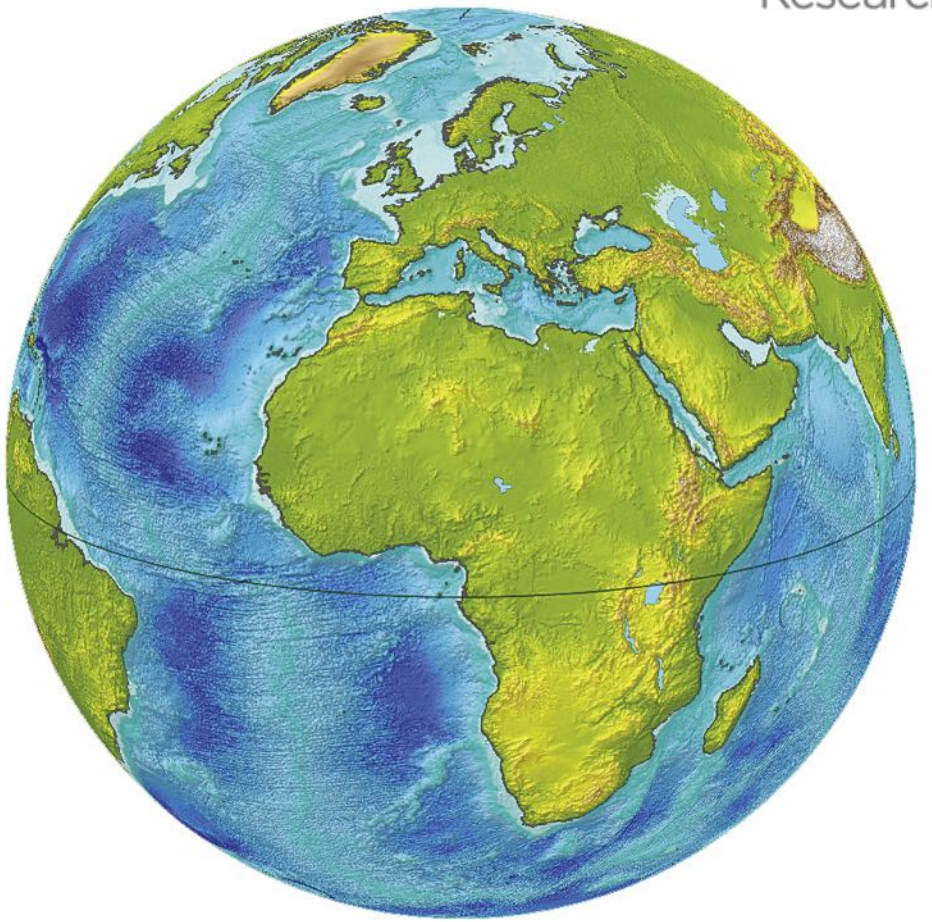
Newcastle University

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Why Bother?

Newcastle Joint Research Office

- Sponsorship
- University Links/NJRO
- Trust Strategy
- Rare Diseases



Newcastle University

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Challenges

Newcastle Joint Research Office

- Knowledge
- Process
- Third parties, third party
- Insurance
- Contracting
- The Board

Newcastle University

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The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Risk Mitigation

Newcastle Joint Research Office

Reduce → Solo Sponsorship
CTU/CRO
Project Management

Avoid → Territories
Central Distribution (If possible)

Accept → There is RISK – Some Degree of Fire Fighting

Newcastle University

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Future Planning

Newcastle Joint Research Office

- Funding
- QMS Updates
- Capacity
- Inspection Planning
- BREXIT Planning
- Vendors
- Cross-Processes
- Relationships

Newcastle University

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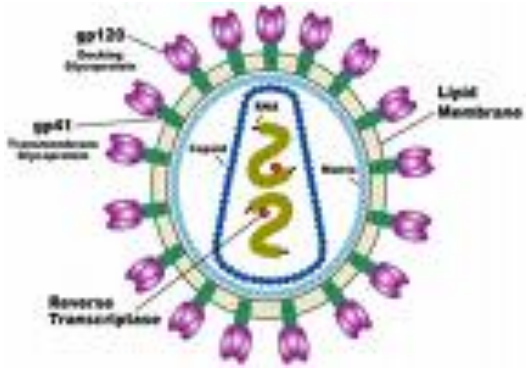
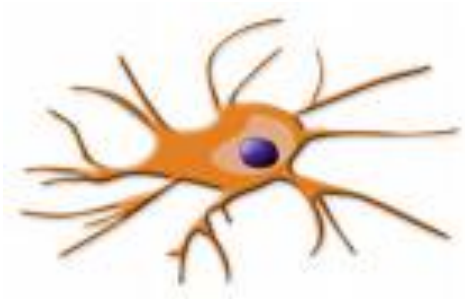
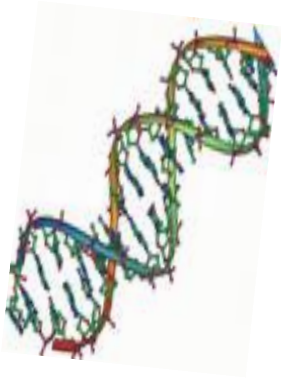
How we Sponsor…..
Advanced Therapy Investigational Medicinal Products (ATIMP) Trials







NHS Research and Development Forum

Michelle Quaye
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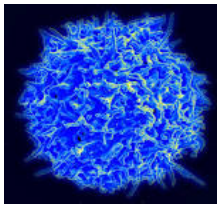
NHS R&D Forum Non-Commercial Research Sponsors Symposium for Health & Care
19th November 2019

What are ATMPs?

Biological medicinal products based on genes and/or cells classified as either:

Gene Therapy Medicinal Product	Cell Therapy Medicinal Product	Tissue Engineered Medicinal Product



Combined ATMP: Medical Device + cells/tissue

Definitions – Annex I, Part IV, 2.1 to Directive 2001/83/EC amended by 2009/120/EC & EC Regulation No 1934/2007

Product Classification

MHRA
Regulating Medicines and Medical Devices

Advanced therapy medicinal products advice form

Contact deta

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific Recommendation on classification of Advanced Therapy Medicinal Products Request Form and Briefing Information Article 17 - Regulation (EC) No 1394/2007

The request for scientific recommendation should be sent to AdvancedTherapies@ema.europa.eu (no fee required).

Submission of scientific recommendation should follow the submission dates listing here.

Please send this form in Word format as it is. Do not convert it to PDF.

Note that all the fields followed by a red asterisk (*) are mandatory. If any of the mandatory fields is missing, the request will not be processed.

Information on the Request*

Company developing the product (applicant)	
Person authorised to communicate on behalf of the applicant	
Proposed product invented name or identifier[1]	
Short descriptor (or name when available) of	

- Trial classification
- Regulatory requirements
- Manufacture requirements
- * Costs *

Regulatory Requirements

‘Clinical Trials’

SI 2004 No.1031
for Human Use
Regulations 2004

No.1928
an Use (Clinical Trials)
egulations 2006

No.1882
se (ATMP and Miscellaneous

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Gene therapy medicinal products

Web pag Cell-therapy and tissue engineering

Gene ther

Web page	Relevant guidelines
Cell-therapy and tissue engineering	• The **overarching guideline** for human cell- based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) • Reflection paper on **stem cell-based medicinal products** (EMA/CAT/571134/2009) • Reflection paper on in-vitro cultured **chondrocyte** containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009) • Guideline on **xenogeneic cell-based medicinal products** (EMEA/CHMP/CPWP/83508/2009) • Guideline on potency testing of **cell based immunotherapy medicinal** products for the treatment of cancer (CHMP/BWP/271475/06) • Reflection paper **on clinical aspects related to tissue engineered products** (EMA/CAT/573420/2009) • Guideline on **safety and efficacy follow-up and risk management** of advanced therapy medicinal products (EMEA/149995/2008)

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Speak to the Regulators

MHRA regulatory advice meetings

- Pre-grant application/Pre-CTA submission

MHRA innovation office

- a single point of access to free and expert regulatory information, advice and guidance
- Access HRA, MHRA, HFEA, HTA, NICE
- innovationoffice@mhra.gov.uk

HTA

- Advice on tissues and cells donation, procurement, testing
- enquiries@hta.gov.uk

Challenges

Regulatory - GCP for ATMP

- Comply with the required regulations
- Safety Reporting
  - Consider ATIMP, Tissues and cells, Devices, administration procedures, Conmeds
  - Alert cards
- Long-term follow-up
- Product traceability – 30+ year archiving
- Risk assessment and mitigation

Commercialisation

- Conflict of interest
- Commercial collaborations
  - Data, IP

Challenges Continued….

Funding

- High cost trials
- Long-term follow-up
- Monitoring and auditing

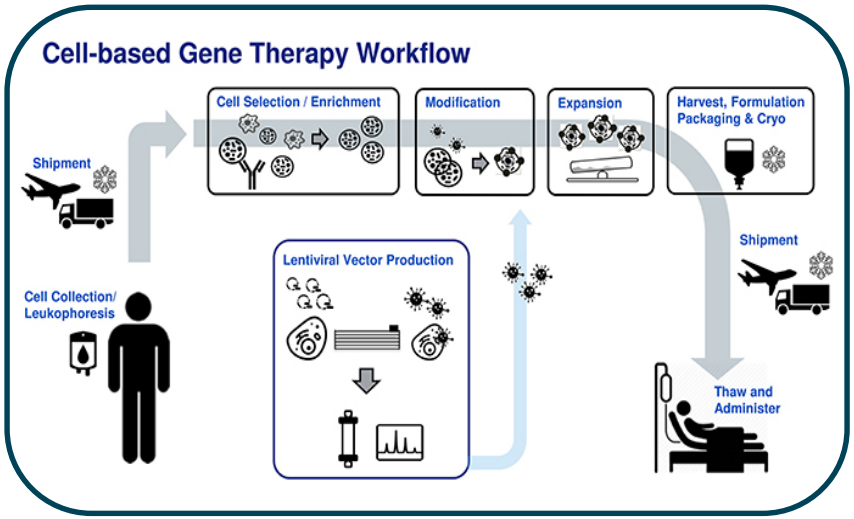
Manufacturing

- Outsource manufacturing
- Selection and oversight
- Shortage of manufacturers/QPs/slots
- Manufacture preclinical/clinical batch - comparability
- Specifications/requirements – out of spec
- Contracting/Liability

Challenges Continued…

Product Logistics

- Frozen product (<-80°C, liquid nitrogen)
- Multiple Cold chain Shipments
- Segregated storage - minimise cross contamination
- Short Shelf life
- Real-time QP release
- Traceability
- **ATIMP Management Plans**



https://doi.org/10.3389/fmed.2018.00150

Trial Site Feasibility

- GMO Risk assessments / notifications
- HTA human application licences
- Emergency facilities/ITU access
- Pharmacy
- Training

Where to find out more……

MHRA Regulating Medicines and Medical Devices

innovationoffice@mhra.gsi.gov.uk

Good Clinical Practice Guide
'Grey guide'

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products

EUROPEAN COMMISSION

Brussels, 10.10.2019
C(2019) 7140 final

GUIDELINES

on Good Clinical Practice specific to Advanced Therapy Medicinal Products

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf

HSE

http://www.hse.gov.uk/biosafety/gmo/

HTA Human Tissue Authority

enquiries@hta.gov.uk

https://www.hta.gov.uk/policies/regenerative-medicine-and-regulation-advanced-therapies-medicinal-products-atmps

Thank you!

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