Symposium

From the NHS Research & Development Forum

NHS
Research and Development Forum

Research but not as we know it: Managing novel methods in research Symposium

2nd March 2020

Welcome

About The NHS R&D Forum

- A Professional Network & Community
- Individuals working in Research Management, Research Support & Research Leadership roles
- Working in with and for Providers or Commissioners of health and care

Research management teams are enablers of high value, quality research & innovation for improved health & care.

As a Forum

We act together to

Influence partners & policy makers. A professional voice. Consultations & "around the table".

SHAPE

Support in daily roles. Knowledge exchange, working out loud. Training courses & resources.

LEAD

HELP

Drive solutions to problems & set standards.

THRIVE

Meet together UK-wide. Peer groups to learn and share. Events, conference, forums, meetings

CONNECT

Sustainable as a network & community of practice. Build on our capabilities. Grow to do more.

The Forum aims to improve practice and shape the landscape

1.

For the NHS, patients, health & care

2.

For quality research

3.

For our community

4.

For evidence & improvement

Purpose of today

- Life Science Strategy/ Industry Sector Deal 2
- Help us to run novel studies so that we can do more
- Learn from each other
- Work through the challenge together
- Build relationships
- Enjoyment!

House keeping

#novelmethods

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Department of Health & Social Care

The Life Sciences Industrial strategy & the NHS: A Policy Perspective on Novel & Innovative Trials

Emma Lowe
Research Policy Senior Manager – Industry Relations and Growth

2 March 2020

@emma_k_lowe

UK Life Sciences Industry

The life sciences industry is one of the most important pillars of the UK economy, contributing over **£70 billion a year and 240,000 jobs across the country.**

Life Sciences Industrial Strategy and Sector Deals

The Life Sciences Industrial Strategy (2017) proposed a strategic goal to grow the proportion of clinical trials with novel methodology over the next 5 years.

Innovation in Trial Methodology

Standard

Randomised Controlled Trials

Innovative
(where an RCT isn't the right approach)

Complex Innovative Design Trials

Targeted, Stratified

Real world evidence

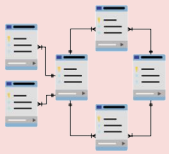
Innovation in Trial Delivery

Standard
(still common)

Paper based, manual, on-site monitoring, 100% source data verification (SDV)

Innovative

Digital (eg. digital trial management systems (including but not limited to eCRFs), e-consent, virtual/ siteless studies, ePROMs)



Streamlining processes across sites (eg. data sets used for central feasibility and eligibility assessment)

Risk adapted and proportionate approaches (eg. Risk adapted monitoring, cluster randomisation)

Leading innovation in innovative trials

Building the evidence base

- NIHR MRC Trial Methodology Hubs
- Experimental Cancer Medicine Centres led publication on design and delivery of complex innovative design trials

  https://www.nature.com/articles/s41416-019-0653-9

MHRA Innovation Office

- Informal, exploratory discussions at any point in the trial design process

Making innovative trials 'business as usual' across the system

- Learning and skills development
- Identifying and sharing expertise
- Publishing guidance and examples


today
yesterday
tomorrow

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Clinical Research of the Future: An Industry Perspective

Dr Sheuli Porkess – Executive Director, Research, Medical & Innovation, ABPI

NHS R&D Forum Symposium, 2 March 2020

abpi
Bringing medicines to *life*

Outline

- **About the ABPI**
- **Overview of commercial clinical research in the UK**
- **What's on the horizon?**
- **Focus on Complex Innovative Design (CID) trials**
- **Recommendations for UK clinical research**

Our mission

Medicines are transforming our lives like never before. We want the UK to be the best place in the world to research, develop and use the medicines of the future.

Our objectives

Building a thriving environment for medicine discovery so the UK can be the best place in the world to research and develop new medicines and vaccines.

Improving access to new medicines and vaccines so everyone in the UK can get the latest treatments.

Enhancing reputation by demonstrating the high ethical standards we set ourselves and that society expects from us.

Representing our members, using their insight and experience to tell the story of how they change the lives of millions of people every day.

How we work


Members
Research Funders
Patient Organisations
International (EFPIA & IFPMA)
Regulators (MHRA, HRA)
abpi
Bringing medicines to life
UK Trade Associations
PHE / NHS
Government DHSC / BEIS / OLS / DEFRA
Professional Organisations


Thought Leadership
Evidence & Data
Partnerships with Stakeholders

Clinical Research Working Group (CRWG)

The ABPI works with Government on ensuring delivery of commitments in the Life Sciences Industrial Strategy & Sector Deals

- Key commitment from Sector Deal 2: strengthening the UK environment for clinical research
- ABPI is the co-secretariat and sits on the Life Science Council's CRWG
- CRWG workstreams including:
  - Complex Innovative Design (CID) trials - 2018 report
  - Five centres for late phase commercial research
  - Clinical research workforce
  - UK offer on data & digital for clinical research
  - UK as a competitive environment for clinical research

The UK's clinical research environment

ABPI Clinical Trials Report – October 2019

- Data collected annually & retrospectively
- Number of commercial clinical trials initiated, by country, phase and disease area.
- Global comparators:
  - Selection of EU countries
  - Selection of non-EU countries e.g. USA
- 2019 report also includes China, Brazil, South Africa and Switzerland (from 2016)
- This data acts as a benchmark for the UK's position globally, for the period immediately after the referendum
- 7 policy recommendations

https://www.abpi.org.uk/media/7607/rmi-0128-0919-clinical-trials-report.pdf

The landscape today

At £4.3 billion a year the industry invests far in excess of any other sector.

Over the last decade, an average of **28% of EU** clinical trial applications have come from the UK.

870,250 participants took part in clinical research across England. This is the equivalent of **2,383** per day!

In 2017, there were **24,000 jobs** in the UK across research and development.

MHRA received 955 requests for clinical trial authorisations (CTA) in 2018.

Sources: https://www.abpi.org.uk/media/7607/rmi-0128-0919-clinical-trials-report.pdf
https://www.nihr.ac.uk/about-us/our-contribution-to-research/research-performance/annual-statistics.htm

UK ranks highly for early trials

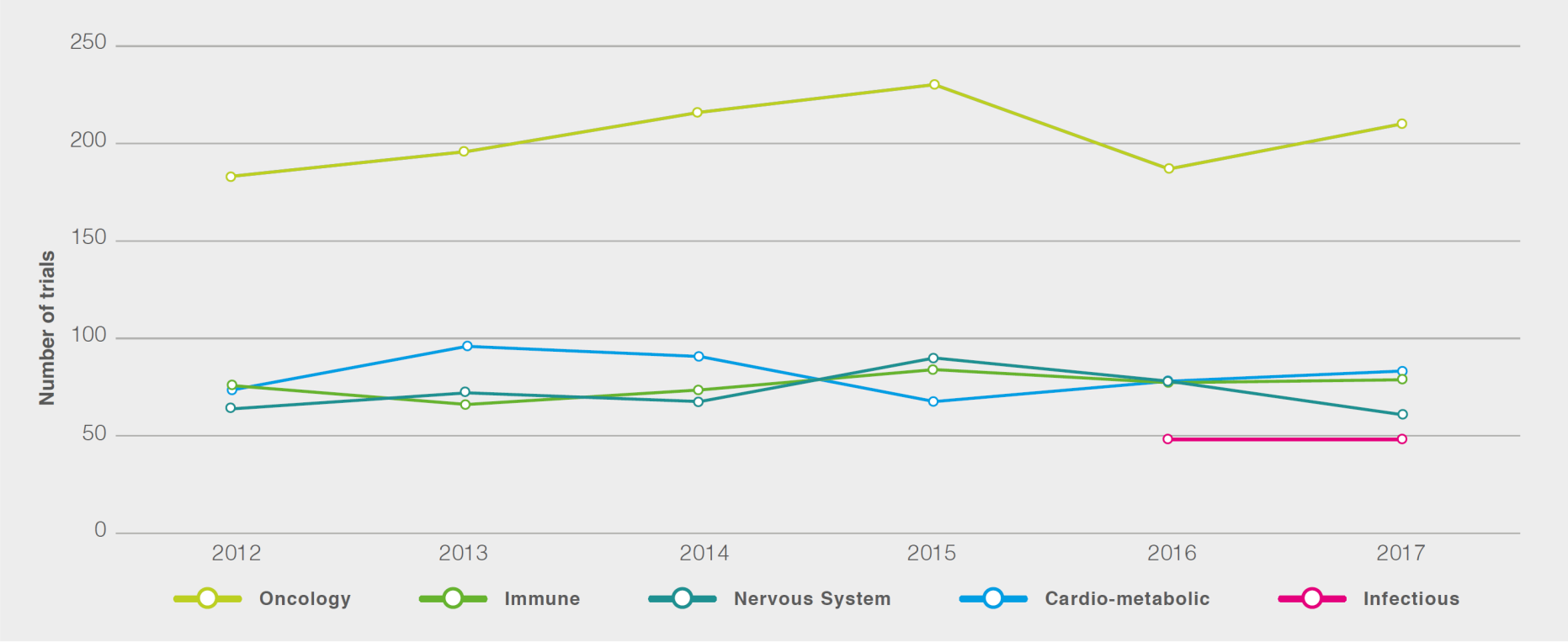
Table 1. Number of commercial clinical trials started in 2017, by phase and country

Rank	Country	Phase I	Country	Phase II	Country	Phase III
1	USA	614	USA	970	USA	528
2	China	194	**UK**	**253**	Germany	276
3	**UK**	**147**	Germany	232	Canada	259
4	Germany	136	Japan	227	Spain	258
5	Japan	111	Spain	204	**UK**	**243**
6	Australia	82	France	176	Poland	243
7	Canada	72	Canada	176	Italy	235
8	France	52	Italy	141	Japan	235
9	Spain	49	China	122	France	210
10	Italy	19	Australia	112	Australia	180
11	Poland	15	Poland	98	China	146
12	Switzerland	14	Switzerland	30	Brazil	116
13	Brazil	10	Brazil	23	South Africa	72
14	South Africa	5	South Africa	17	Switzerland	65

Source: https://www.abpi.org.uk/media/7607/rmi-0128-0919-clinical-trials-report.pdf

Oncology remains the UK's strongest area

Figure 5. Number of commercial clinical trials started in the UK, by disease area

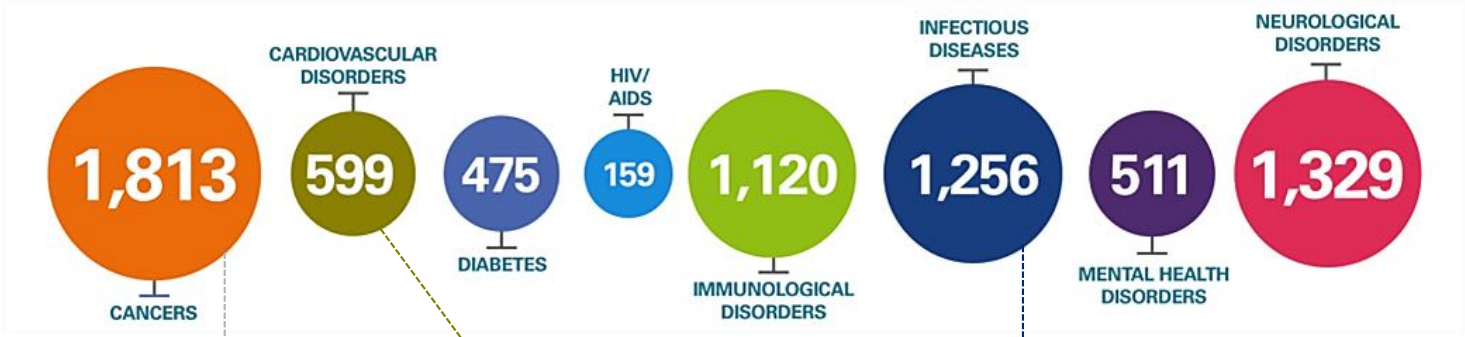


Source: https://www.abpi.org.uk/media/7607/rmi-0128-0919-clinical-trials-report.pdf

What’s on the horizon?

The drug discovery & development pipeline

Over 7,500 new medicines in development globally



2 out of 3
European patients diagnosed with cancer survive at least 5 years*

*in 2012 compared with 2002

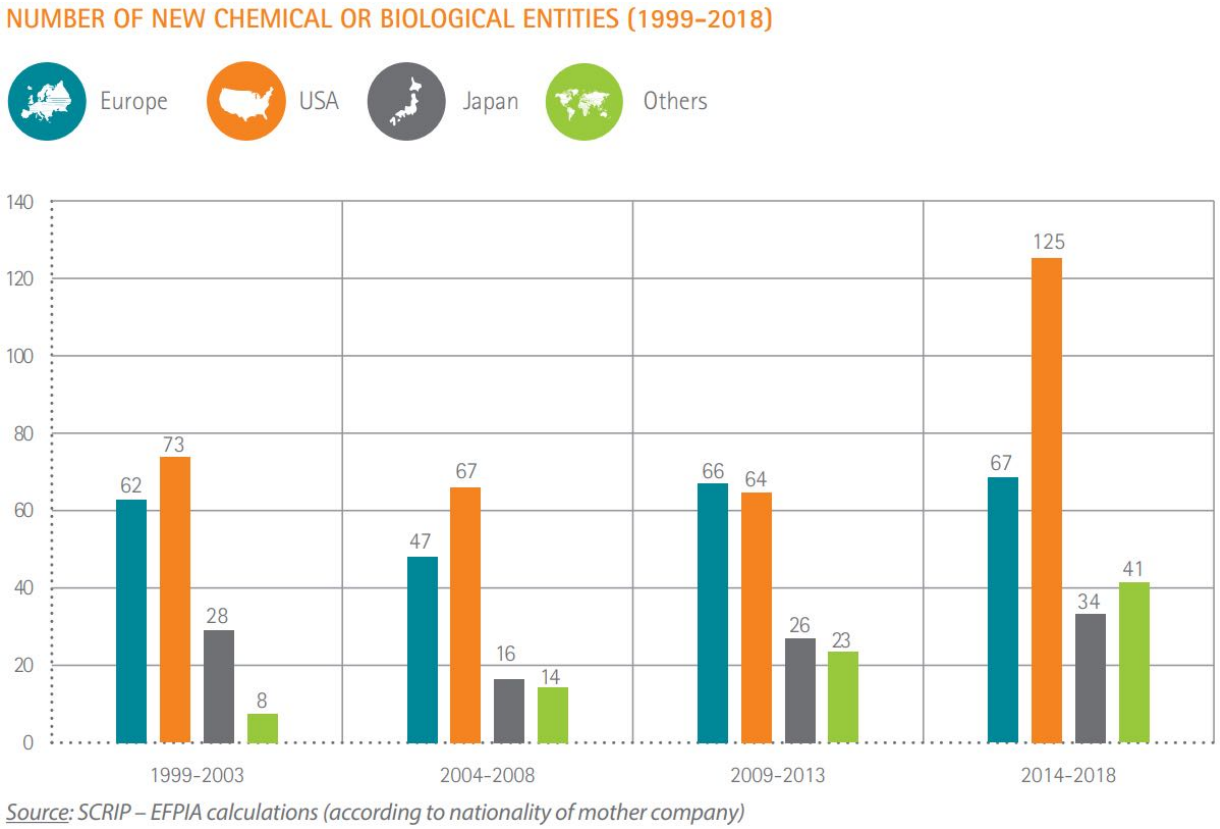
37%
Decrease in the death rate from Cardiovascular Disease between 2010 - 2012, in the EU5*

*France, Germany, Italy, Spain, UK

+133%
cure rate increase for patients with Hepatitis C between 1999 - 2015

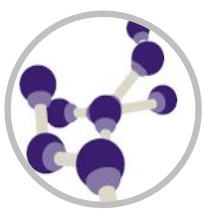
Source: EFPIA 2018 Annual Report: https://www.efpia.eu/media/412957/efpia-2018-annual-report.pdf

Global development of new modalities



Source: https://www.efpia.eu/media/413006/the-pharmaceutical-industry-in-figures.pdf

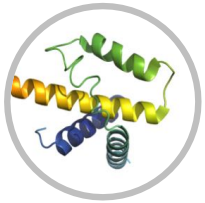
New chemical and biological modalities



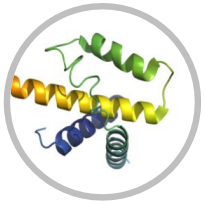
Small-molecule chemistry

Monoclonal antibodies

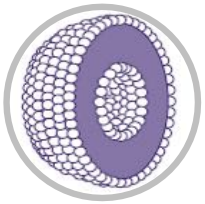
Antibody drug conjugate



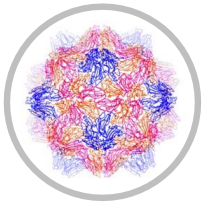
Peptide-based therapeutics



Next-generation peptides

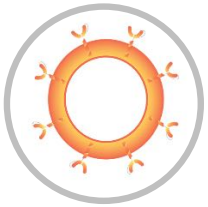


Nano-technology platforms



Oncolytic viruses

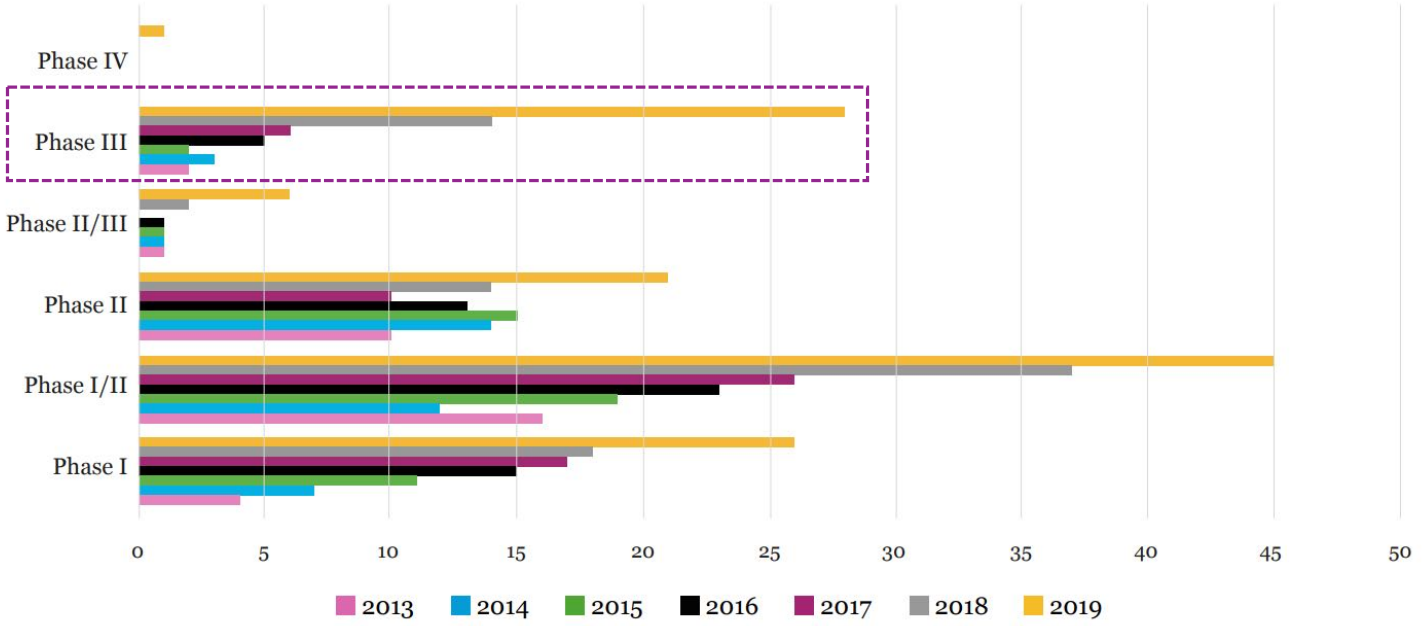
Gene therapy



CAR-T cells

Advanced therapy medicinal products (ATMPs)

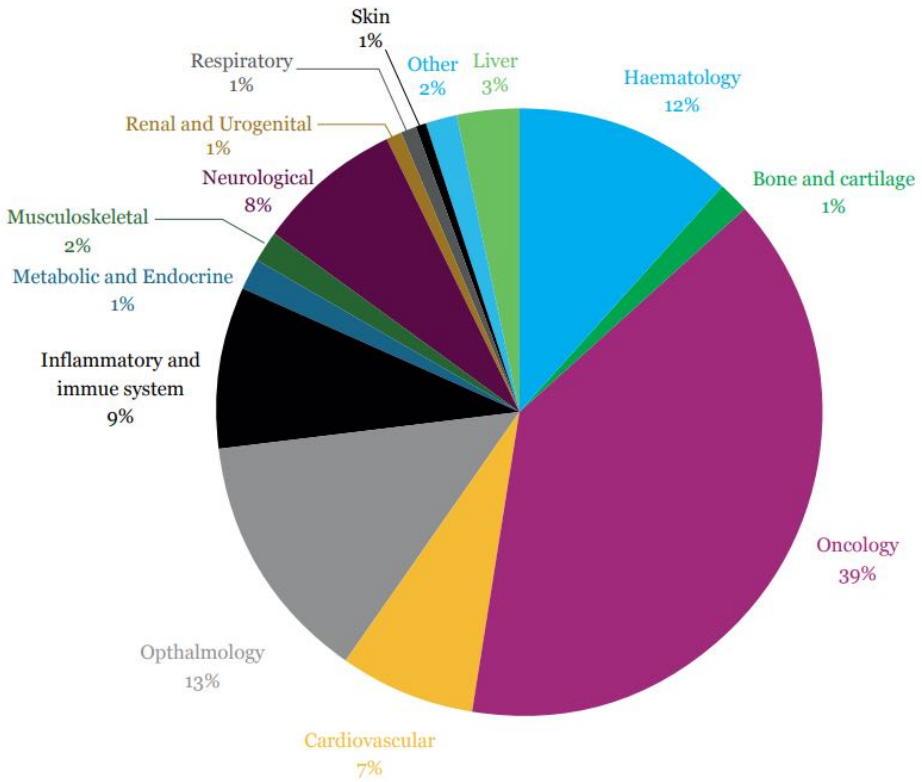
Figure 6. ATMP clinical trials in the UK by clinical phase from 2013-2019



Source: https://ct.catapult.org.uk/sites/default/files/publication/Clinical%20Trials%20Commentary_for%20publication_150120.pdf

Advanced therapy medicinal products (ATMPs)

Figure 3. Distribution of UK ATMP clinical trials according to therapeutic area in 2019

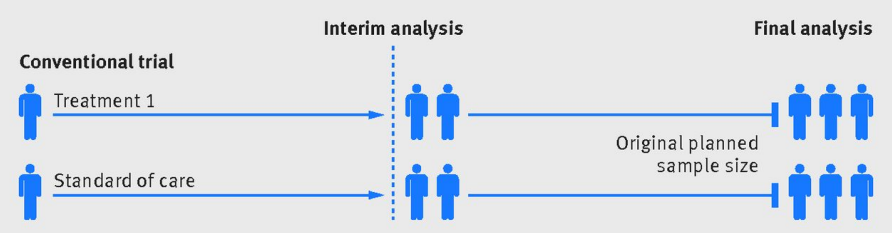


Source: https://ct.catapult.org.uk/sites/default/files/publication/Clinical%20Trials%20Commentary_for%20publication_150120.pdf

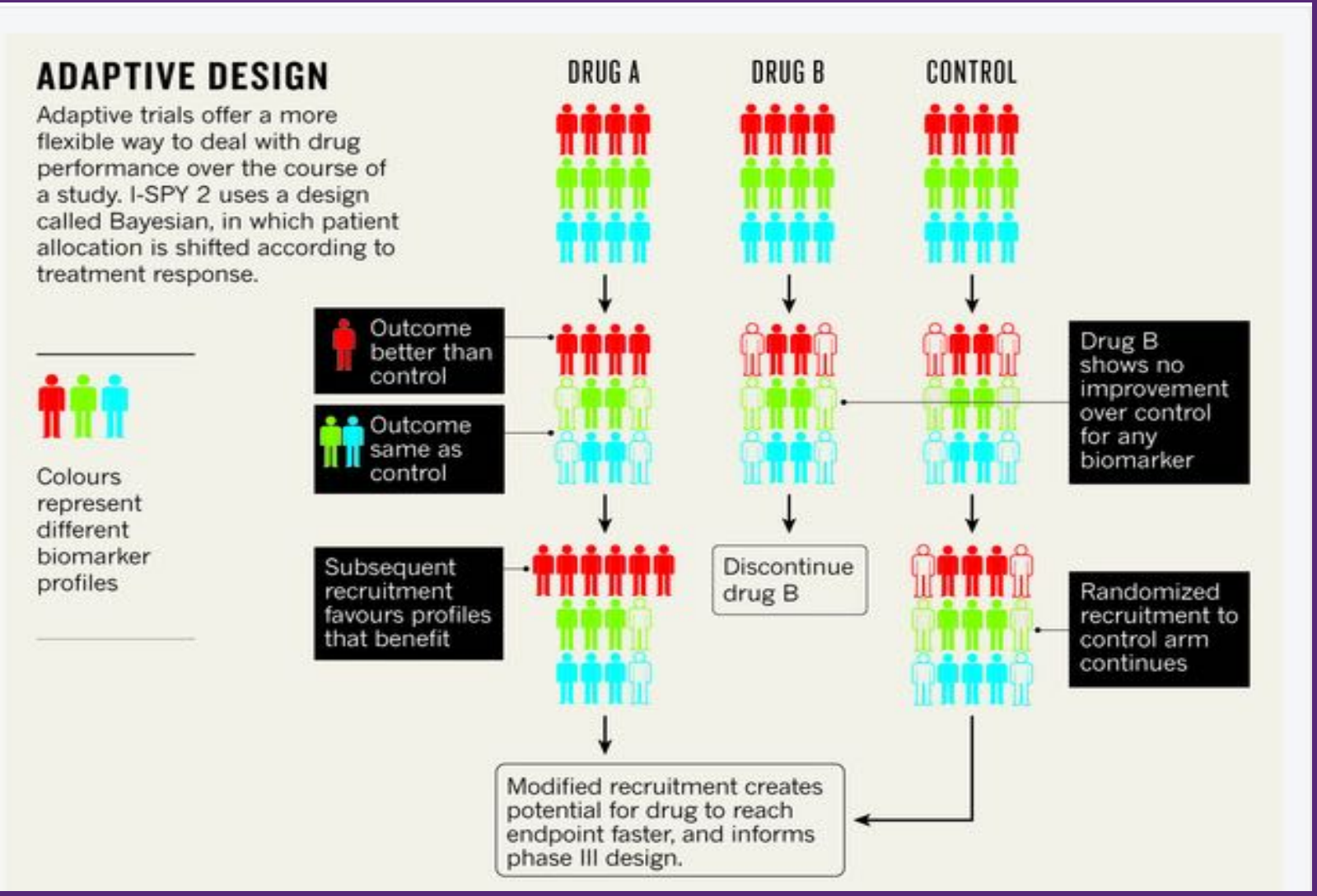
Complex Innovative Design (CID) trials

Advances in clinical trial methodology

Randomised control trials



Complex Innovative Design (CID) Clinical Trials


ADAPTIVE DESIGN
Adaptive trials offer a more flexible way to deal with drug performance over the course of a study. I-SPY 2 uses a design called Bayesian, in which patient allocation is shifted according to treatment response.
DRUG A
DRUG B
CONTROL
Outcome better than control
Outcome same as control
Drug B shows no improvement over control for any biomarker
Colours represent different biomarker profiles
Subsequent recruitment favours profiles that benefit
Discontinue drug B
Randomized recruitment to control arm continues
Modified recruitment creates potential for drug to reach endpoint faster, and informs phase III design.

Benefits of adaptive design trials

Patients randomised to treatments which are more likely to be effective = reduced sample size

Better understanding of treatment doses = improve probability treatment is successful in phase 3

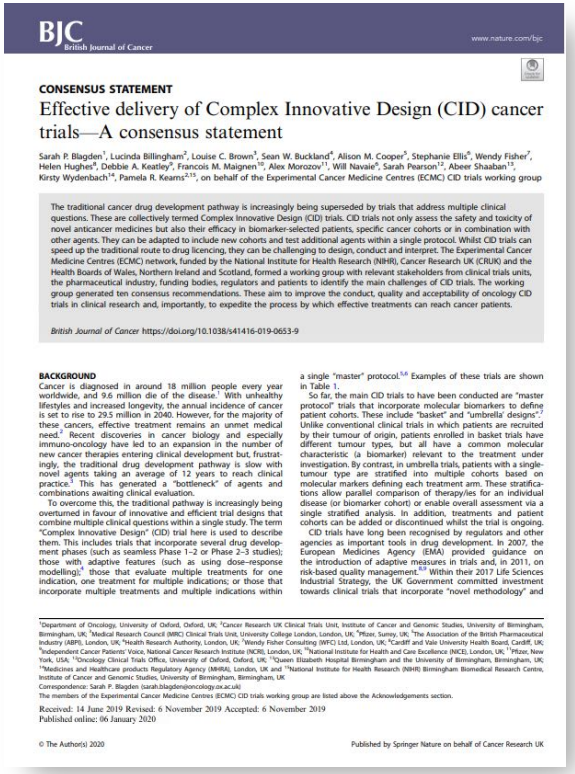
Stopping trials early for futility or efficacy = patients don't continue to receive an ineffective treatment

Checking assumptions still hold = trial retains sufficient power to assess trial objectives

Targeting patients most likely to benefit from the treatment = reduces variability to treatment

Faster decision making = promising treatments make it to patients quicker

CID trials – A consensus statement



BJC
British Journal of Cancer
www.nature.com/bjc

CONSENSUS STATEMENT

Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement

Sarah P. Blagden[1], Lucinda Billingham[2], Louise C. Brown[3], Sean W. Buckland[4], Alison M. Cooper[5], Stephanie Ellis[6], Wendy Fisher[7], Helen Hughes[8], Debbie A. Keatley[9], Francois M. Maignen[10], Alex Morozov[11], Will Navaie[5], Sarah Pearson[12], Abeer Shaaban[13], Kirsty Wydenbach[14], Pamela R. Kearns[2,15], on behalf of the Experimental Cancer Medicine Centres (ECMC) CID trials working group

The traditional cancer drug development pathway is increasingly being superseded by trials that address multiple clinical questions. These are collectively termed Complex Innovative Design (CID) trials. CID trials not only assess the safety and toxicity of novel anticancer medicines but also their efficacy in biomarker-selected patients, specific cancer cohorts or in combination with other agents. They can be adapted to include new cohorts and test additional agents within a single protocol. Whilst CID trials can speed up the traditional route to drug licencing, they can be challenging to design, conduct and interpret. The Experimental Cancer Medicine Centres (ECMC) network, funded by the National Institute for Health Research (NIHR), Cancer Research UK (CRUK) and the Health Boards of Wales, Northern Ireland and Scotland, formed a working group with relevant stakeholders from clinical trials units, the pharmaceutical industry, funding bodies, regulators and patients to identify the main challenges of CID trials. The working group generated ten consensus recommendations. These aim to improve the conduct, quality and acceptability of oncology CID trials in clinical research and, importantly, to expedite the process by which effective treatments can reach cancer patients.

British Journal of Cancer https://doi.org/10.1038/s41416-019-0653-9

BACKGROUND

Cancer is diagnosed in around 18 million people every year worldwide, and 9.6 million die of the disease.[1] With unhealthy lifestyles and increased longevity, the annual incidence of cancer is set to rise to 29.5 million in 2040. However, for the majority of these cancers, effective treatment remains an unmet medical need.[2] Recent discoveries in cancer biology and especially immuno-oncology have led to an expansion in the number of new cancer therapies entering clinical development but, frustratingly, the traditional drug development pathway is slow with novel agents taking an average of 12 years to reach clinical practice.[3] This has generated a "bottleneck" of agents and combinations awaiting clinical evaluation.

To overcome this, the traditional pathway is increasingly being overturned in favour of innovative and efficient trial designs that combine multiple clinical questions within a single study. The term "Complex Innovative Design" (CID) trial here is used to describe them. This includes trials that incorporate several drug development phases (such as seamless Phase 1–2 or Phase 2–3 studies); those with adaptive features (such as using dose–response modelling);[4] those that evaluate multiple treatments for one indication, one treatment for multiple indications; or those that incorporate multiple treatments and multiple indications within a single "master" protocol.[5,6] Examples of these trials are shown in Table 1.

So far, the main CID trials to have been conducted are "master protocol" trials that incorporate molecular biomarkers to define patient cohorts. These include "basket" and "umbrella" designs".[7] Unlike conventional clinical trials in which patients are recruited by their tumour of origin, patients enrolled in basket trials have different tumour types, but all have a common molecular characteristic (a biomarker) relevant to the treatment under investigation. By contrast, in umbrella trials, patients with a single-tumour type are stratified into multiple cohorts based on molecular markers defining each treatment arm. These stratifications allow parallel comparison of therapy/ies for an individual disease (or biomarker cohort) or enable overall assessment via a single stratified analysis. In addition, treatments and patient cohorts can be added or discontinued whilst the trial is ongoing.

CID trials have long been recognised by regulators and other agencies as important tools in drug development. In 2007, the European Medicines Agency (EMA) provided guidance on the introduction of adaptive measures in trials and, in 2011, on risk-based quality management.[8,9] Within their 2017 Life Sciences Industrial Strategy, the UK Government committed investment towards clinical trials that incorporate "novel methodology" and

[1]Department of Oncology, University of Oxford, Oxford, UK; [2]Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Studies, University of Birmingham, Birmingham, UK; [3]Medical Research Council (MRC) Clinical Trials Unit, University College London, London, UK; [4]Pfizer, Surrey, UK; [5]The Association of the British Pharmaceutical Industry (ABPI), London, UK; [6]Health Research Authority, London, UK; [7]Wendy Fisher Consulting (WFC) Ltd, London, UK; [8]Cardiff and Vale University Health Board, Cardiff, UK; [9]Independent Cancer Patients' Voice, National Cancer Research Institute (NCRI), London, UK; [10]National Institute for Health and Care Excellence (NICE), London, UK; [11]Pfizer, New York, USA; [12]Oncology Clinical Trials Office, University of Oxford, Oxford, UK; [13]Queen Elizabeth Hospital Birmingham and the University of Birmingham, Birmingham, UK; [14]Medicines and Healthcare products Regulatory Agency (MHRA), London, UK and [15]National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, Institute of Cancer and Genomic Studies, University of Birmingham, Birmingham, UK
Correspondence: Sarah P. Blagden (sarah.blagden@oncology.ox.ac.uk)
The members of the Experimental Cancer Medicine Centres (ECMC) CID trials working group are listed above the Acknowledgements section.

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Published by Springer Nature on behalf of Cancer Research UK

How improving CID trials could get innovative treatments to patients faster

06 Jan 2020 Posted in Opinion By Ali Hansford

Blog

Recommendations have been published in the British Journal of Cancer on how best to conduct Complex Innovative Design (CID) trials. Dr Ali Hansford, Head of Regulatory Strategy Policy, looks into these recommendations in more detail.

https://www.abpi.org.uk/media-centre/blog/2020/january/how-improving-complex-innovative-design-trials-could-get-innovative-treatments-to-patients-faster/

Blagden, S.P., Billingham, L., Brown, L.C. et al. Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement. Br J Cancer (2020). https://www.nature.com/articles/s41416-019-0653-9

Consensus recommendations (1)

- **Trial Planning and Design**: Engage with regulators and health technology assessment bodies as early as possible. This early mutual understanding will maximise the chance of a successful clinical trial application and future marketing authorisation and reimbursement decisions.
- **Protocol Development**: Clearly describe any possible future changes to the study from an early stage. This will reduce the cost and time to make these changes, if and when required.
- **Patients and public involvement (PPI):** May require specific training, support, and perhaps also accreditation. This applies to patients and the public who are involved in reviewing patient information sheets, which can be more complicated for CID trials.
- **Patient Facing Documentation**: Provide three-part patient information comprising of an invitation document, a study arm-specific document and a handbook. A single patient information sheet is likely to be too long and complicated for a CID trial. Also consider formats other than the written word, such as videos.
- **Statistical Considerations**: Ensure the study is designed to provide the flexibility to incorporate individual variations for different treatments, diseases and molecular characteristics as the study progresses. The heavier statistical workload to deliver CID trials should not be underestimated when considering the resources required.

Source: https://www.nature.com/articles/s41416-019-0653-9

Consensus recommendations (2)

- **Defining Leadership and Oversight**: Convene an experienced Trial Management Group to oversee the study. As CID trials may ask multiple questions, it might be necessary for the trial lead to be shared or transferred between specialists over time.
- **Dissemination of Results**: Timely reporting of data when a research question is answered, or a study arm is completed. Promptly sharing findings with the scientific community reduces the risk of a different research group duplicating effort.
- **Staff Training**: Include training specifically for CID trials in the curricula of relevant health care professionals to ensure appropriate resources are in place to deliver CID trials.
- **Approval and Reimbursement Decisions**: Utilise existing accelerated access initiatives to ensure effective medicines discovered through CID trials are rapidly approved and made available to patients.
- **Evaluating the impact on public health**: Conduct impact analyses on CID trials to ensure they deliver on their promise to provide safe and timely access to medicines. No formal comparisons of CID trials with traditional studies have yet been performed to confirm that they provide a faster route to patients.

Source: https://www.nature.com/articles/s41416-019-0653-9

Building a UK fit for the future of clinical research - Recommendations

Building a UK fit for the future of clinical research

1. Increasing investment in clinical research
2. Simplifying the processes for setting-up and running clinical trials
3. Building a workforce fit for the future
4. Harnessing the UK's data infrastructure for medicines R&D
5. Embedding patient involvement in clinical research
6. Ensuring continuing high standards for transparency
7. Securing a future UK-EU relationship on medicines and research

Source: https://www.abpi.org.uk/media/7607/rmi-0128-0919-clinical-trials-report.pdf

Symposium

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Research but not as we know it: Managing novel methods in research Symposium

2nd March 2020

Managing Real World study designs: experience from Birmingham Research Office

Joanne Plumb,
Deputy Director of Research Development,
University Hospitals Birmingham NHS Foundation Trust
Jo Gray
Clinical Manager NIHR / WT CRF
University Hospitals Birmingham NHS Foundation Trust

Research & Innovation at UHB

The Research Development & Innovation Strategy

- Improved Patient Outcomes & Experience
- Maximise benefits for patients
- Drive Innovation
- Extending the Evidence base for best practice
- Efficiency/Productivity Gains
- Impact for Patient, Organisation, wider health economy

Research & Innovation Activity

Clinical Research Trials

6000 studies registered

3000+ actively recruiting studies

350+ new trials a year

16000+ new patients recruited to NIHR portfolio trials annually

Innovation Infrastructure

Medical Devices Testing and Evaluation Centre (ERDF MD-TEC)

WM Genomic Medicine Centre

Regional Screening service for Familial Hypercholestrolaemia

WM Academic Health Sciences Network

HDRUK , DIH hubs , Global Digital Exemplar

Research Infrastructure

NIHR Clinical Research Facility

NIHR Birmingham Biomedical Research Centre

Midlands and Wales Advanced Therapy Treatment Centre (ATTC)

NIHR CLAHRC Applied Research Centre

NIHR Surgical Reconstruction & Microbiology Research Centre

Scar Free Foundation Burns Research Centre

Cancer Research UK Birmingham Centre

NIHR Experimental Cancer Medicine Centre

NIHR Global Surgical Research Centre

Implications for RD&I

- Innovative trial design – adaptive / basket/ pragmatic trial rather than traditional RCT's
- Long running trials – Sponsor / CI site
- Governance process / HRA approvals
- Information Governance
- Costing model for complex novel trial design
- Research delivery teams
- Trials Acceleration Platform

Delivering the undeliverable ?

Developing the teams to deliver

- Development of senior staff
- Operational management skills
- Workforce modelling skills
- Need element of influencing a change of culture in NHS
- enable the patient pathways to co-exist at touch points with service delivery

Priorities

- Sharing successful models
- Underpinning of knowledge for delivery staff as well as managers
- Influencing investigators to ensure costs are adaptable in line with protocol adaptations
- Opportunities to showcase successful and unsuccessful methods
- Transparency agenda

MW-ATTC Clinical S

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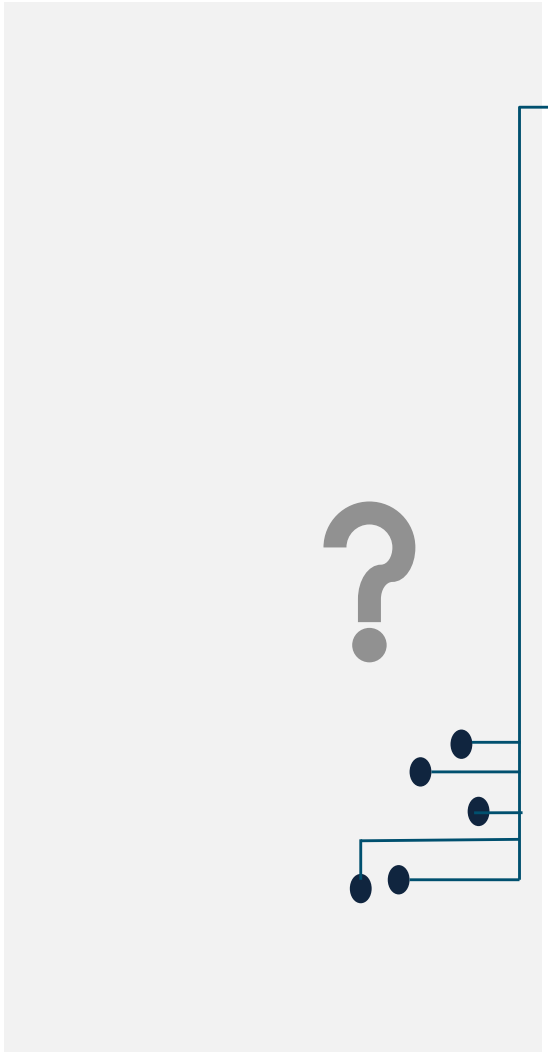


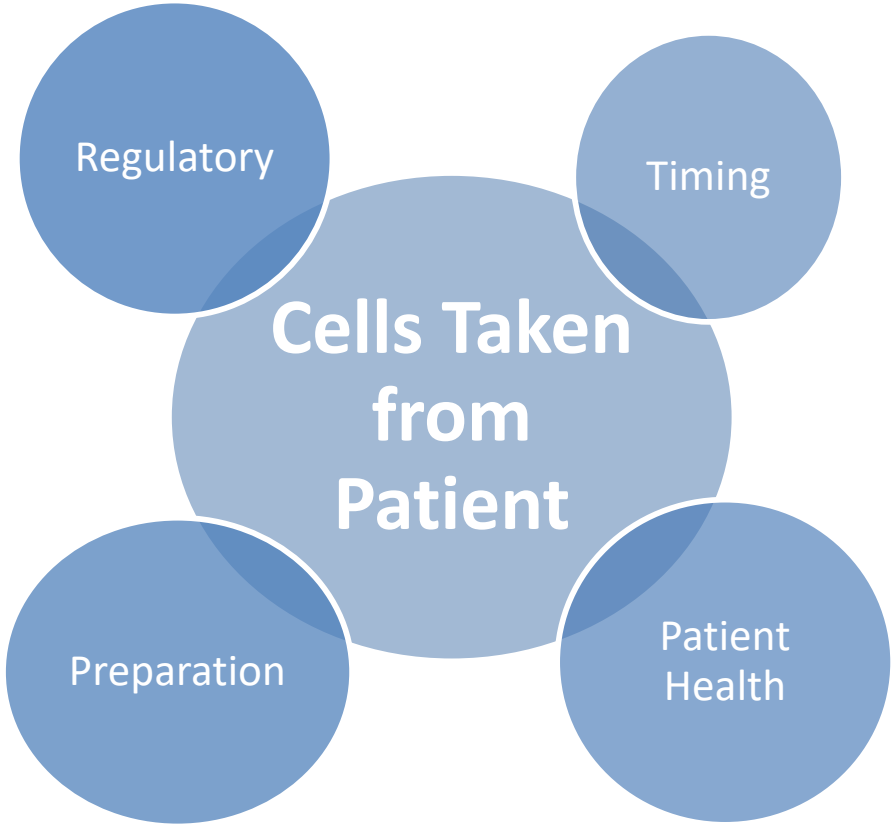
MW-ATTC
Midlands & Wales
Advanced Therapy Treatment Centre

- **4 Hospitals**
- Birmingham,
- Cardiff and Vale,
- Nottingham,
- Swansea

- **+1 Hospital**
- Leicester

- **+2 Hospitals…**

Procurement / Receipting and Pharmacy



- Paper exercise
- Practical exercise
- Ready to roll

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Midlands-Wales Advanced Therapy Treatment Centre

- Blagden, S.P., Billingham, L., Brown, L.C. *et al.* Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement. *Br J Cancer* (2020).
- https://doi.org/10.1038/s41416-019-0653-9

- Jackson A.; Armstrong C.; Lowe F.; Yap C. Research nurse and patients perspective on innovative early phase trial designs
  Trials; vol. 20 Oct 2019

Symposium

From the NHS Research & Development Forum

NHS
Research and Development Forum

Research but not as we know it: Managing novel methods in research Symposium

2nd March 2020

MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

UCL

This is a platform alteration

Experience from the MRC Clinical Trials Unit at UCL

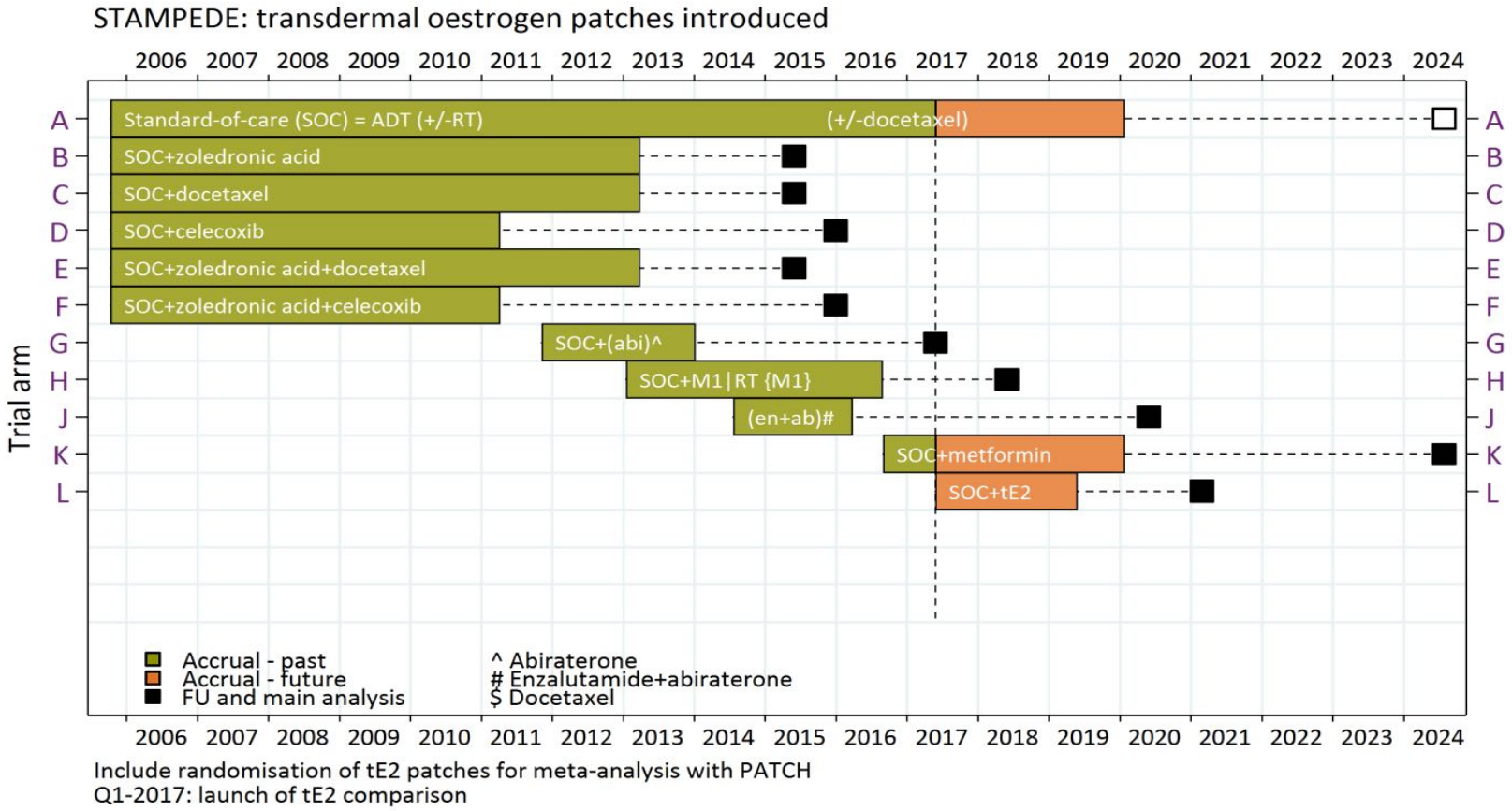
Sharon Love
Associate Professor Trial Conduct Methodology
Monday 2nd March 2020

Platform trial - definition

- Master protocols
- Living protocols
- Complex Innovative Design trials (CID)

a trial
with more than one primary hypothesis
and an adaptive element

Platform trial - STAMPEDE



Platform trial – challenges

- Protocol structure
- New comparison
- CRF and database structure
- Simultaneous tasks

Platform trial – protocol structure

Two main approaches

- Single protocol with sections for comparisons
- Master protocol with separate comparison-specific protocols each individually version controlled

Platform trial – new comparison

Operational Components	Project Timeline
Criteria for inclusion of new comparison	
Grant application/Scientific peer review	
Funding & Biomarker development	
Protocol development	
Regulatory application	
Contracts and drug supply	
CRFs and DB development	
Site Implementation	

Platform trial – new comparisons

New comparisons are a substantial amendment

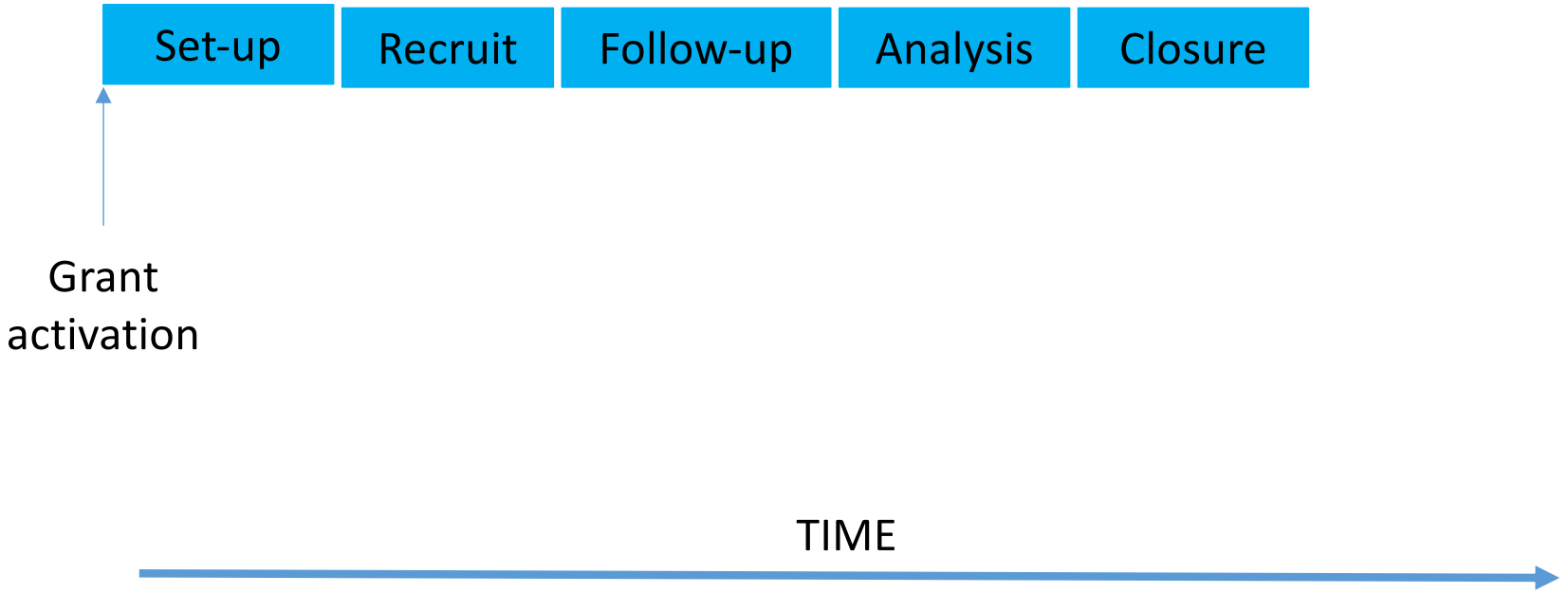
- Similar to a new trial so all parties need a system to deal with these
- Scientific rationale
- Drug procurement
- Change in risk to the trial
- Potentially a different PI for each comparison
- Keeping all trial committees relevant
- May need new QA In labs

Platform trial – Case Report Forms

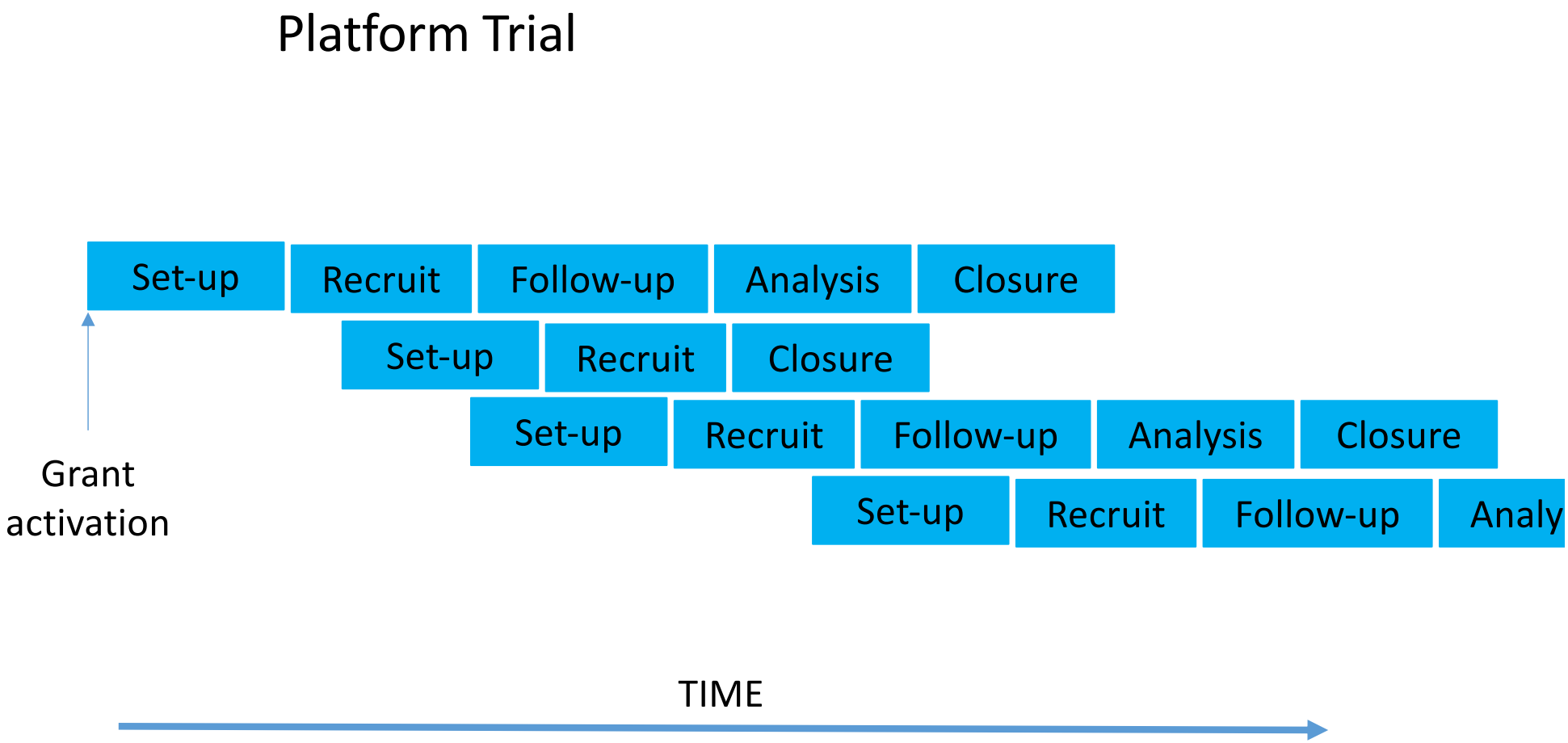
- Generic CRF across all comparisons supplemented by comparison specific sections
- Comparison specific CRF only

Platform trial- simultaneous tasks

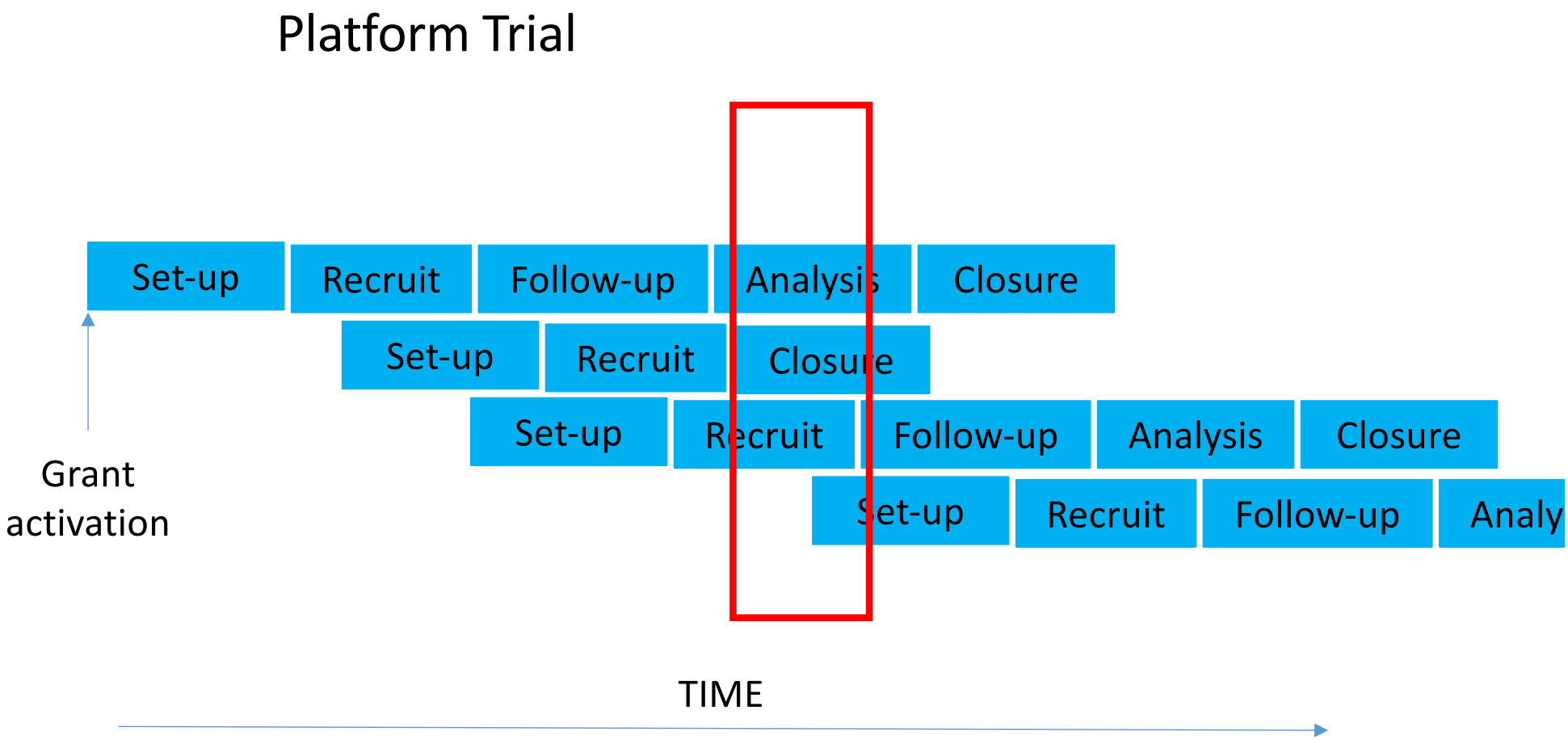
2 arm randomised controlled trial



Platform trial- simultaneous tasks

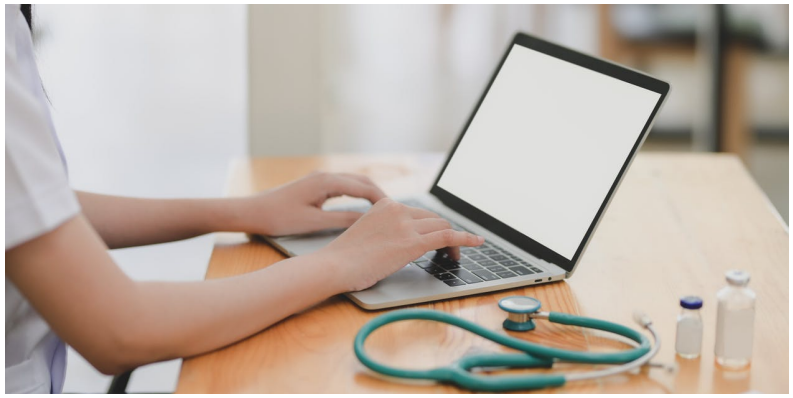


Platform trial- simultaneous tasks



Platform trial - sites

- Also performing simultaneous tasks



Schiavone et al. Trials (2019) 20:264
https://doi.org/10.1186/s13063-019-3216-8

Trials

METHODOLOGY Open Access

This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols

Francesca Schiavone[1,2*†], Riya Bathia[1,2†], Krishna Letchemanan[1,2†], Lindsey Masters[1,2], Claire Amos[1,2], Anna Bara[1,2], Louise Brown[1,2], Clare Gilson[1,2], Cheryl Pugh[1,2], Nafisah Atako[1,2], Fleur Hudson[1,2], Mahesh Parmar[1,2], Ruth Langley[1,2], Richard S. Kaplan[1,2], Chris Parker[3,4], Gert Attard[5], Noel W. Clarke[6], Silke Gillessen[7,8], Nicholas D. James[9], Tim Maughan[10], Matthew R. Sydes[1,2] and On behalf of past and present members of the STAMPEDE and FOCUS4 Trial Management Group

Abstract

Background: There are limited research and literature on the trial management challenges encountered in running adaptive platform trials. This trial design allows both (1) the seamless addition of new research comparisons when compelling clinical and scientific research questions emerge, and (2) early stopping of accrual to individual comparisons that do not show sufficient activity without affecting other active comparisons. Adaptive platform design trials also offer many potential benefits over traditional trials, from faster time to accrual to contemporaneously recruiting

Platform trial practical references

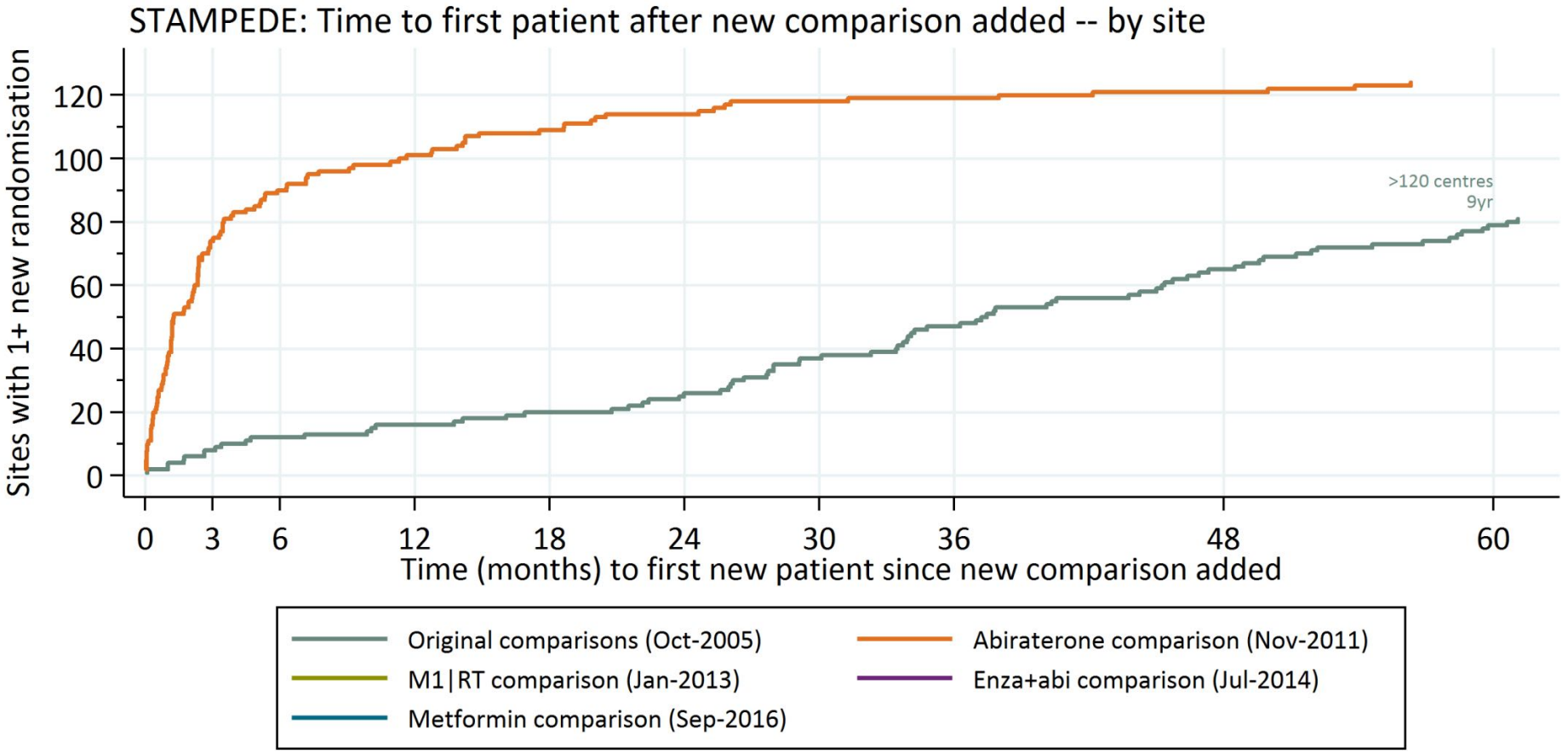
Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons

Hague et al. Trials (2019) 20:294

https://doi.org/10.1186/s13063-019-3322-7

Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement

British Journal of Cancer https://doi.org/10.1038/s41416-019-0653-9



The trial started with one 6-arm randomisation
The has been amended 4 times to introduce new arms
centres activated in total
Original comparison capped on graph at 5yr
--- Graph drawn 28-Apr-2017

MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

UCL

This is a platfo on

Experi ials Unit at UCL

Thank You

Sharo

Associ essor Trial Conduct Methodology

Monday 2nd March 2020

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NHS

Research and Development Forum

Research but not as we know it: Managing novel methods in research Symposium

2nd March 2020

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Innovative Trial Design – MHRA perspective

Dr Kirsty Wydenbach
Senior Clinical Assessor / Deputy Unit Manager CTU

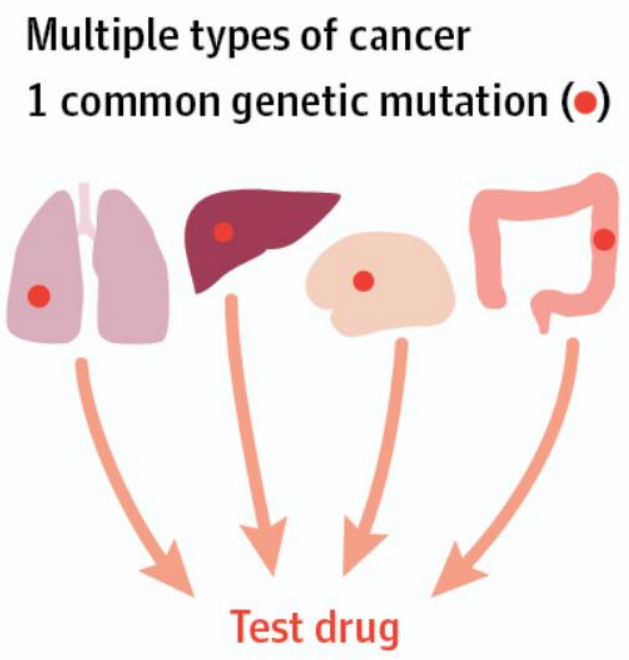
March 2nd 2020
Research but not as we know it: Managing novel methods in Research Symposium

Agenda

- Common GNA document
- CT Regulation Update
- MHRA-HRA pilot - CWoW
- Innovative trial designs
- Seeking advice

What do we mean by novel design?

- **Basket**
- Umbrella
- Matrix
- Platform
- Seamless phase



JAMA Oncol. 2017;3(3):423.
doi:10.1001/jamaoncol.2016.5299

What do we mean by novel design?

- Basket
- **Umbrella**
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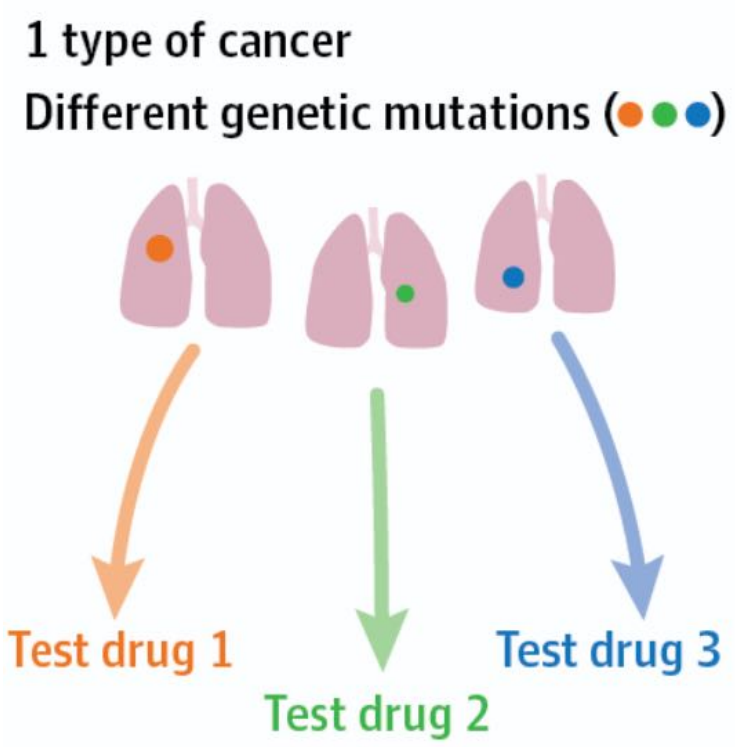
- Seamless phase



JAMA Oncol. 2017;3(3):423.
doi:10.1001/jamaoncol.2016.5299

What do we mean by novel design?

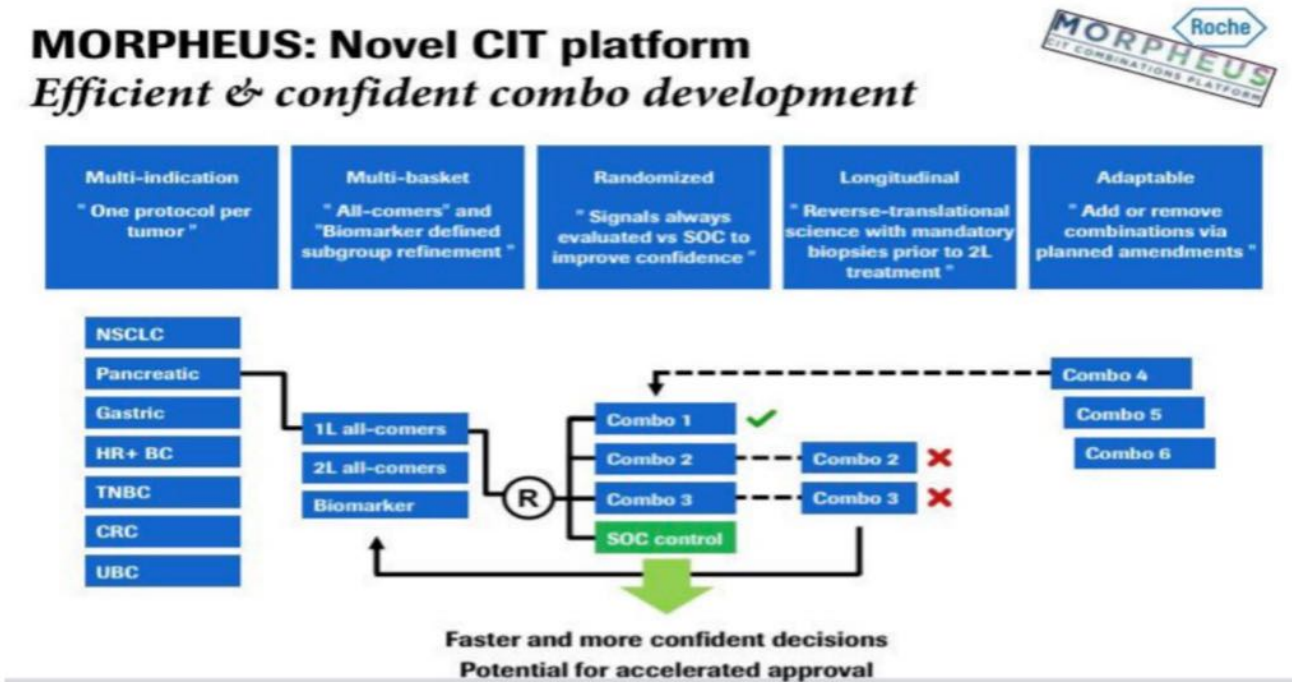
- Basket
- Umbrella
- **Matrix**
- Platform
- Seamless phase

NCI-MATCH Objective

- To determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of the cancer type
- This is a signal-finding trial; treatments that show promise can advance to larger, more definitive trials

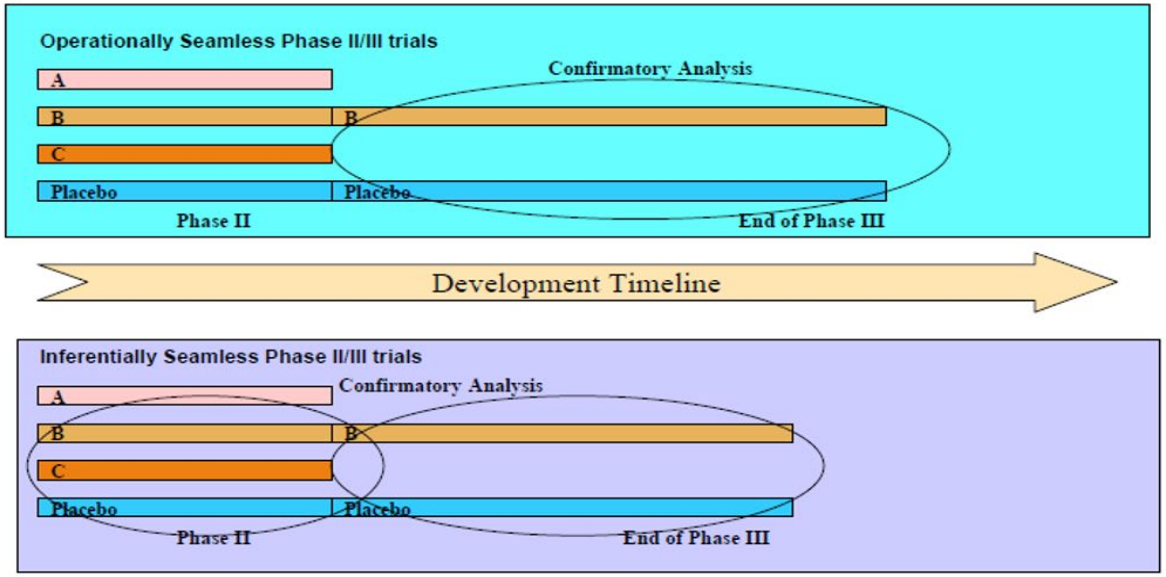
What do we mean by novel design?

- Basket
- Umbrella
- Matrix
- **Platform**
- Seamless phase



What do we mean by novel design?

- Basket
- Umbrella
- Matrix
- Platform
- **Seamless phase**



What do we mean by novel design?

- Basket
- Umbrella
- Matrix
- Platform
- Seamless phase

- Plus others yet to come….

The MHRA supports innovation

- Many trials with innovative designs are already ongoing in the UK: the MHRA welcomes and supports safe innovative approaches to clinical trials.

- Not just oncology
  - These designs are suited to non-oncology indications, including rare diseases, or for personalised medicine applications
  - Can also include design space

- No one size fits all: each trial is assessed at an individual level.

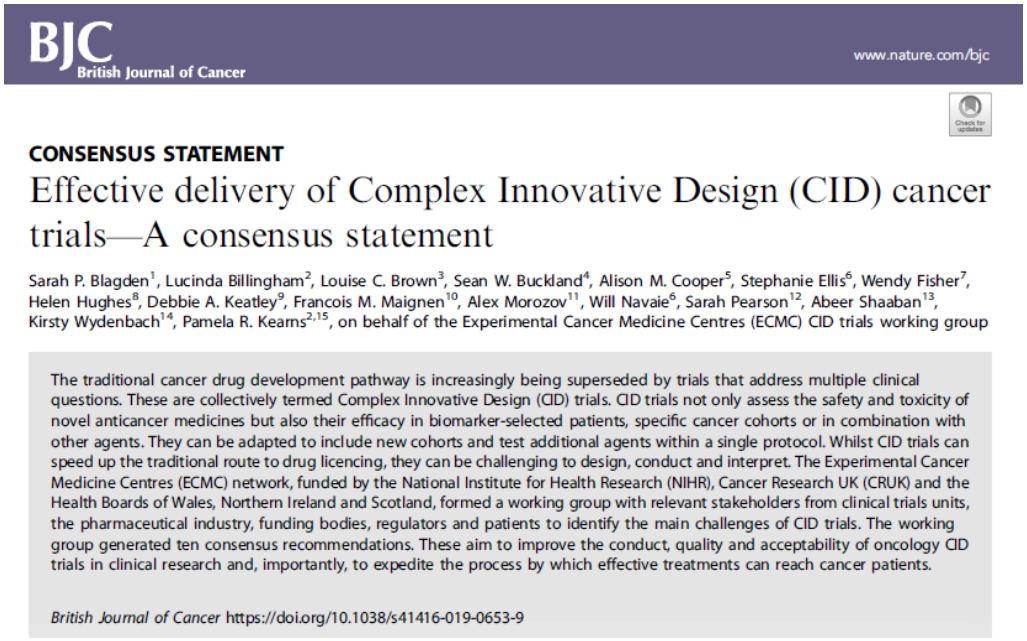
Current approach

- We continue to see all types of design and increase our experience about what is acceptable and where the current limits may lie.
  - Majority approved
  - Active tracking of all novel designs
    - Not to be published just yet but will consider this in the future

- Application process and review is as for any clinical trial

Guidance

- MHRA contributed to a consensus paper – other contribution from ABPI, BIA, CRUK, DHSC, HRC Wales, HRA, ECMC, CTUs, RECs, academic institutions, NICE, NIHR, Patients ICPV, Researchers and R&D Managers from across the UK
  - https://www.nature.com/articles/s41416-019-0653-9



BJC British Journal of Cancer www.nature.com/bjc

CONSENSUS STATEMENT

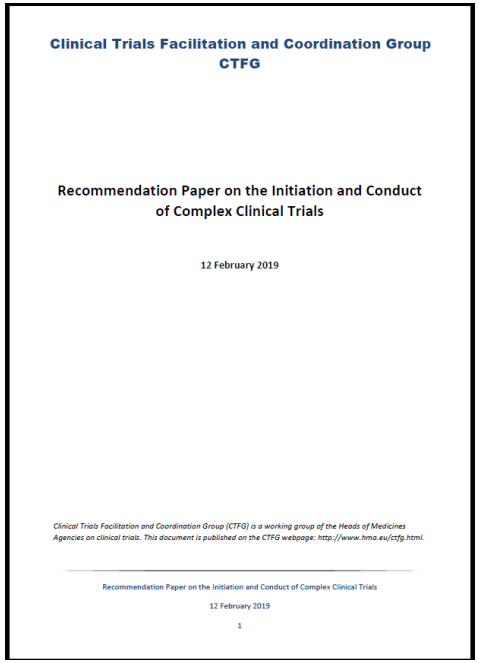
Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement

Sarah P. Blagden[1], Lucinda Billingham[2], Louise C. Brown[3], Sean W. Buckland[4], Alison M. Cooper[5], Stephanie Ellis[6], Wendy Fisher[7], Helen Hughes[8], Debbie A. Keatley[9], Francois M. Maignen[10], Alex Morozov[11], Will Navaie[6], Sarah Pearson[12], Abeer Shaaban[13], Kirsty Wydenbach[14], Pamela R. Kearns[2,15], on behalf of the Experimental Cancer Medicine Centres (ECMC) CID trials working group

The traditional cancer drug development pathway is increasingly being superseded by trials that address multiple clinical questions. These are collectively termed Complex Innovative Design (CID) trials. CID trials not only assess the safety and toxicity of novel anticancer medicines but also their efficacy in biomarker-selected patients, specific cancer cohorts or in combination with other agents. They can be adapted to include new cohorts and test additional agents within a single protocol. Whilst CID trials can speed up the traditional route to drug licencing, they can be challenging to design, conduct and interpret. The Experimental Cancer Medicine Centres (ECMC) network, funded by the National Institute for Health Research (NIHR), Cancer Research UK (CRUK) and the Health Boards of Wales, Northern Ireland and Scotland, formed a working group with relevant stakeholders from clinical trials units, the pharmaceutical industry, funding bodies, regulators and patients to identify the main challenges of CID trials. The working group generated ten consensus recommendations. These aim to improve the conduct, quality and acceptability of oncology CID trials in clinical research and, importantly, to expedite the process by which effective treatments can reach cancer patients.

British Journal of Cancer https://doi.org/10.1038/s41416-019-0653-9

- CTFG Stakeholder workshop on ‘complex trial designs’ held March 2018.
- “Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials” published February 2019
  - http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf



Clinical Trials Facilitation and Coordination Group
CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

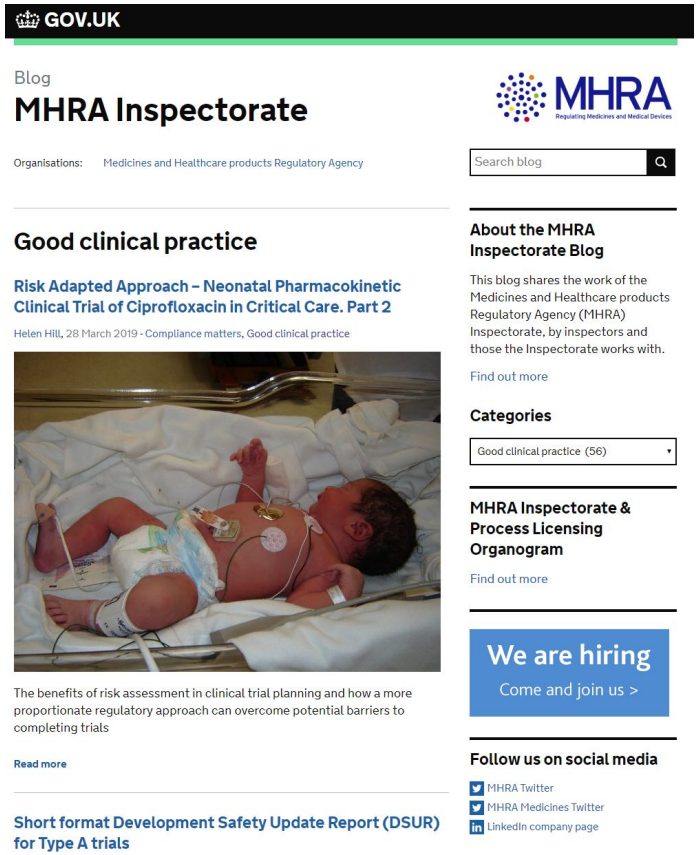
Clinical Trials Facilitation and Coordination Group (CTFG) is a working group of the Heads of Medicines Agencies on clinical trials. This document is published on the CTFG webpage: http://www.hma.eu/ctfg.html.

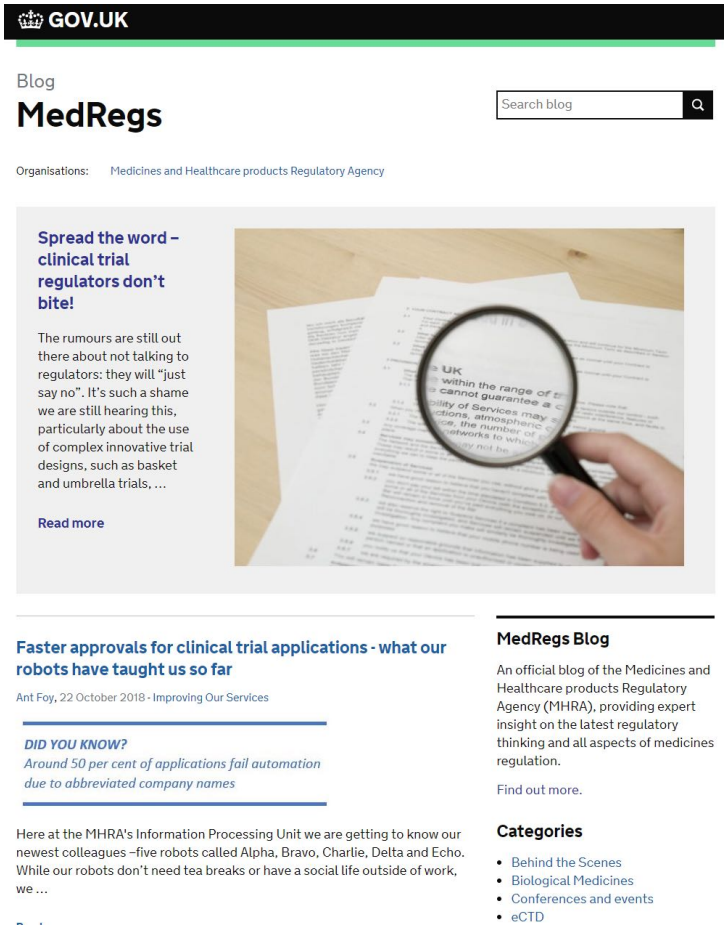
Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
12 February 2019
1

Blogs

https://mhrainspectorate.blog.gov.uk/category/good-clinical-practice/

https://medregs.blog.gov.uk/





Common pitfalls:

- Never-ending trial
- Converting a previous trial into a novel design
- Changing a primary objective so not aligned with original hypothesis
- Amendments not justified

Top tips – initial applications

- Justify the choice of trial design: why adaptive design rather than traditional? Organisational reasons are not an acceptable rationale!
- List the planned adaptations: pre-planned, not ad-hoc
- Additions of new IMPs and/or new trial populations: independent arms? Why as part of the initial trial?
- List criteria for closing or expanding an arm. When progression to separate Phase 3?
- Shared control arm. What happens if standard of care changes?

Top tips – amendments

- If the changes are major: Why it is still the same trial and not a new trial?
- Re-assess the benefit-risk: for each arm and for the entire trial.
- Discuss safety oversight of the entire trial.
- Consider using tables.
- General reminders:
  - Provide the original wording, the new wording and a rationale to support the change.
  - Regulatory constraints: there is no request for information round!

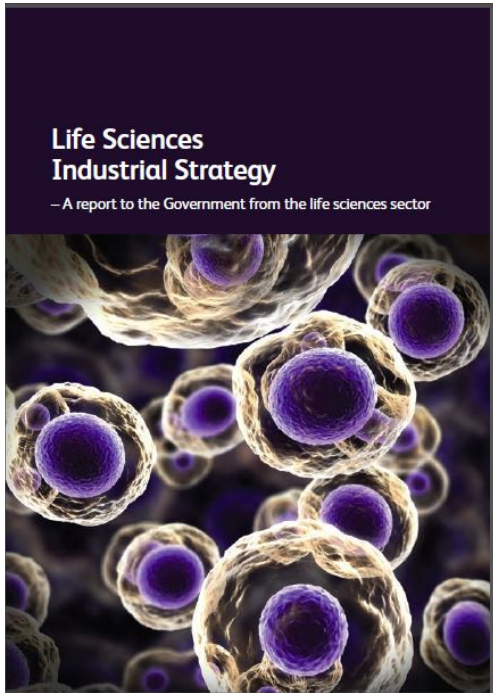
What’s next

Life Sciences Industrial Strategy 2017 report to the UK Government:

Our goal

"As the UK seeks to do more **complex and innovative trials**, MHRA needs to continue engaging with sponsors to **assist with innovative protocol designs** and should facilitate efficient approval of complex trials and amendments to such trials, for example, to add new arms.

The **UK should attempt to lead the innovation** in clinical trial methodology, such as basket trials, and should also attempt to embed routine genomic analysis to make trials more targeted, smaller and more likely to deliver high efficacy."



MHRA implementation plan for novel trials

- Key outcome: Strengthened UK environment for clinical research that provides support for innovative trial design
- Includes
  - Engagement with stakeholders on novel trials and our advice services
  - Workshop(s)
  - Internal training
  - Possible guidance for industry
- Already engaging with NIHR and NICE
  - NIHR workshop December 2019 and March 2020

MHRA survey

Survey went live 23rd December.

Being disseminated by multiple trade bodies (ABPI, BIA…) plus researchers (ECMC, CGTC…)

Or go directly to the blog!

After the survey

- Results of survey will shape the agenda for a 2 day workshop – 1 day on novel trials, 1 day on innovation office and advice services
  - Possible input from NICE
  - Planned for June 2020

- Publication
  - Either a report of the workshop, as a form of informal guidance, or more formal recommendations
  - Aiming for September 2020

Finally…..

The biggest barrier to innovation and research from our perspective is not coming to ask our advice early enough (or at all !)

The clinical trials unit can offer

- Scientific advice
- Broader scope meetings
- Regulatory advice
- Innovation office meetings
- SCOPE advice – is a study a CTIMP or not
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456

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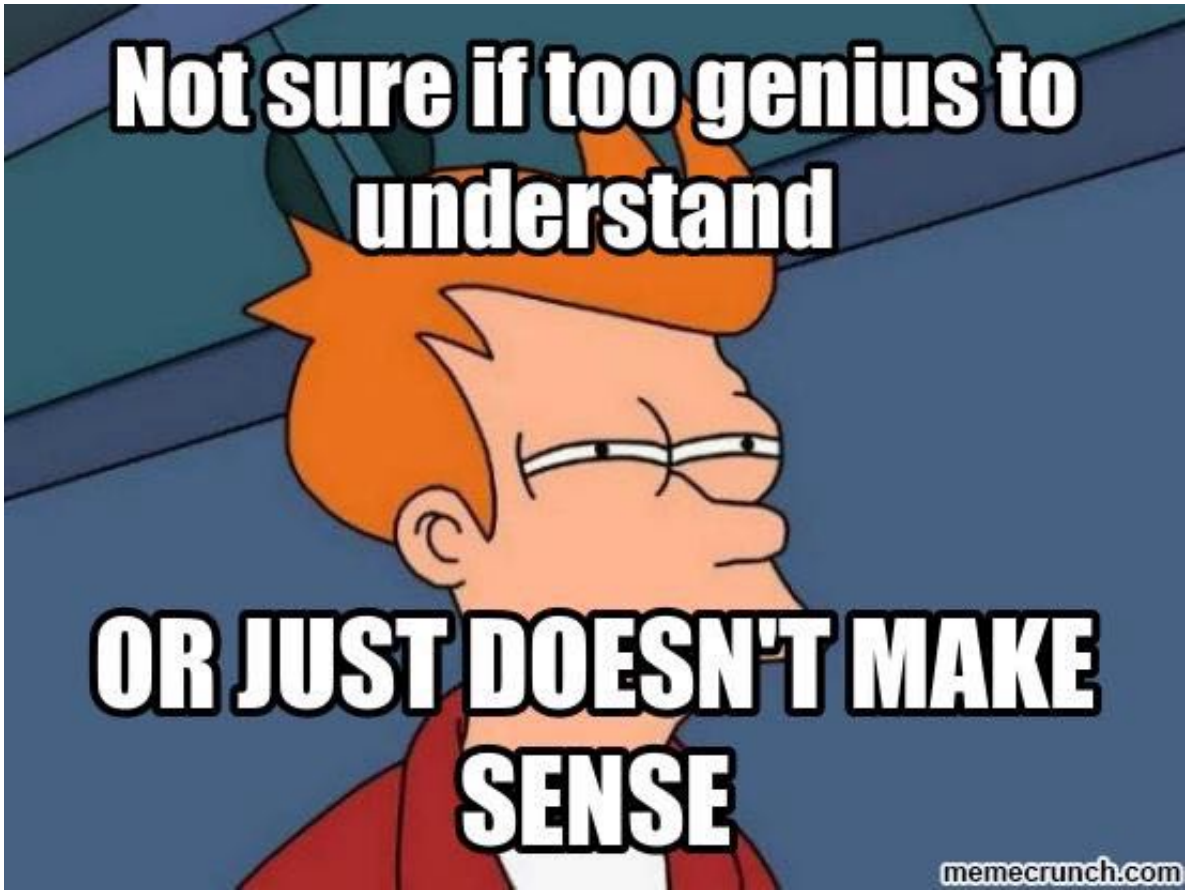
Scientific advice (fee paid)	Request for Scientific Advice scientific_advice@mhra.gov.uk (web form)	To request a scientific advice meeting
Innovative products & cross regulatory agency advice, including ATMPs	Innovation Office Form (email or web form) Innovationoffice@mhra.gov.uk	Regulatory advice for developers of innovative products & processes

Questions?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Symposium

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2nd March 2020

Data Driven Technology

NHS
Health Research Authority

Will Navaie,
Engagement Manager, HRA
2nd March 2020

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What is data-driven technology?

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- Any technology that uses (patient) data
- Electronic Healthcare Platforms
- Apps
- Clinical decision aids
- Image recognition software

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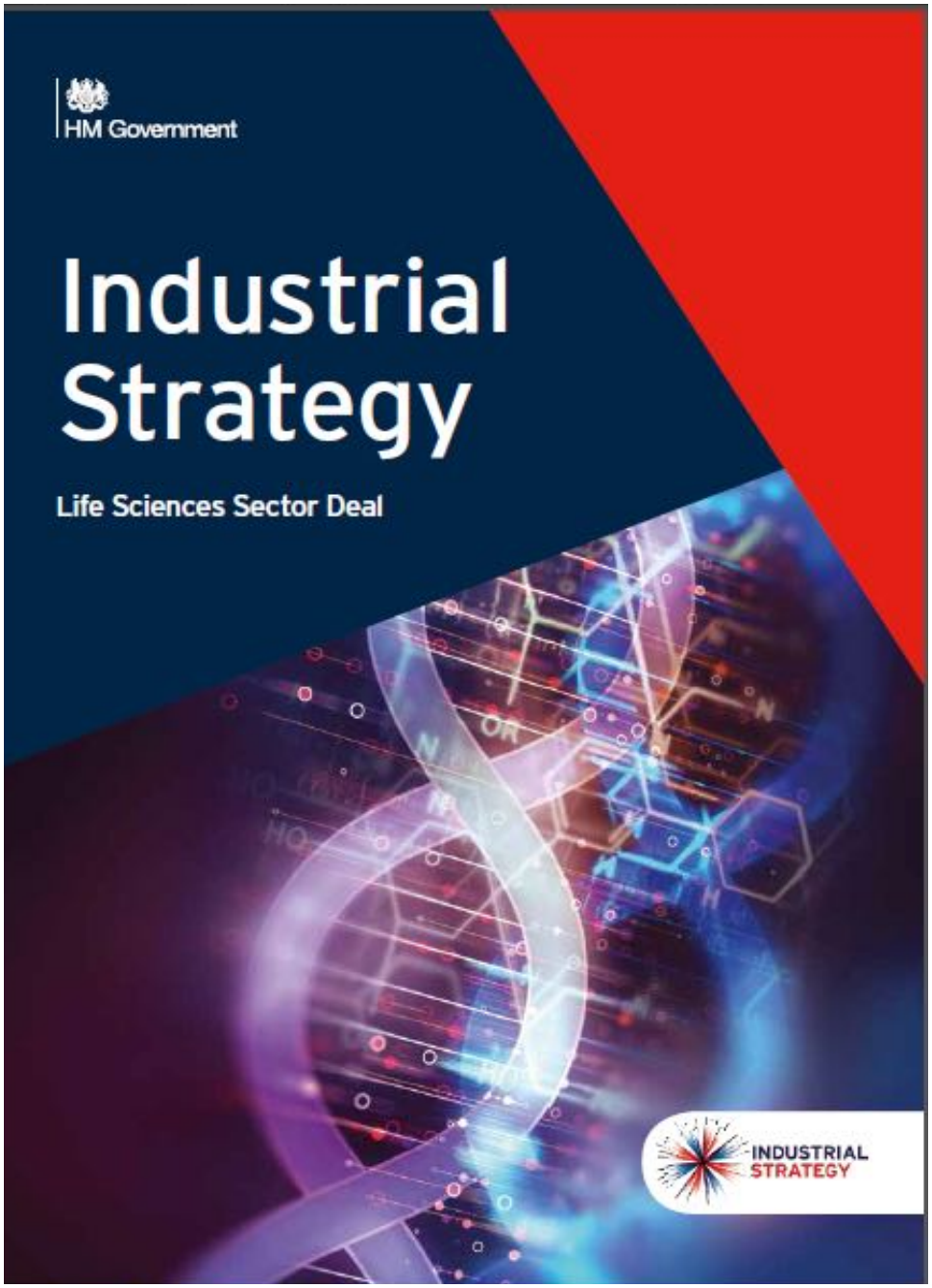
The Ambition



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"We will put the UK at the forefront of the artificial intelligence and data revolution"

"NHS data is a precious resource"

Mission: Use data, Artificial Intelligence and innovation to transform the prevention, early diagnosis and treatment of chronic diseases by 2030

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The Reality

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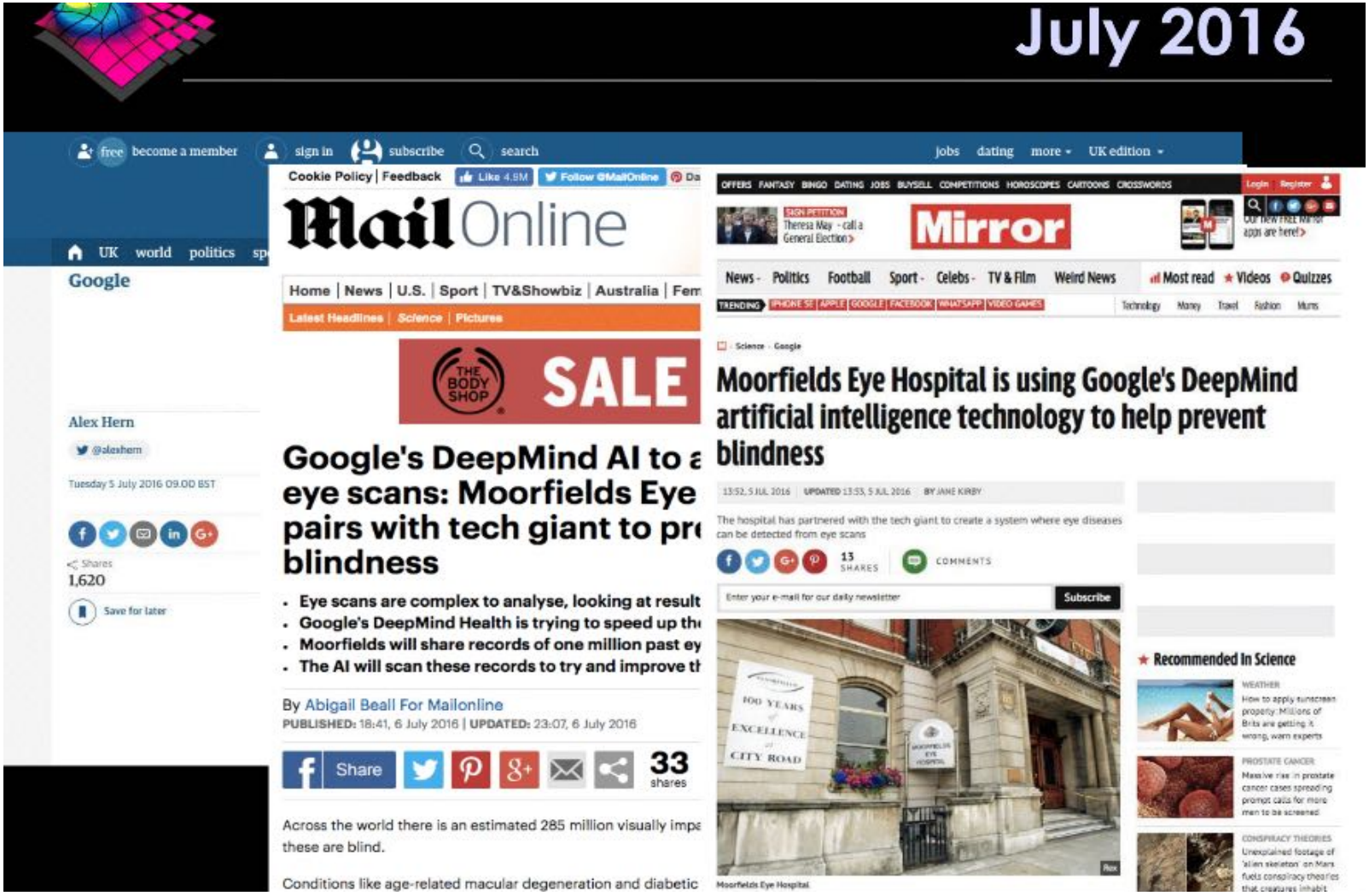
July 2016



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THE BODY SHOP SALE

Google's DeepMind AI to a eye scans: Moorfields Eye pairs with tech giant to pr blindness

- Eye scans are complex to analyse, looking at result
- Google's DeepMind Health is trying to speed up th
- Moorfields will share records of one million past ey
- The AI will scan these records to try and improve t

By Abigail Beall For Mailonline

PUBLISHED: 18:41, 6 July 2016 | UPDATED: 23:07, 6 July 2016

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Across the world there is an estimated 285 million visually impa these are blind.

Conditions like age-related macular degeneration and diabetic

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Moorfields Eye Hospital is using Google's DeepMind artificial intelligence technology to help prevent blindness

13:52, 5 JUL 2016 | UPDATED 13:53, 5 JUL 2016 | BY JANE KIRBY

The hospital has partnered with the tech giant to create a system where eye diseases can be detected from eye scans

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Moorfields Eye Hospital

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Massive rise in prostate cancer cases spreading prompt calls for more men to be screened

CONSPIRACY THEORIES
Unexplained footage of 'alien skeleton' on Mars fuels conspiracy theories that creatures inhabit

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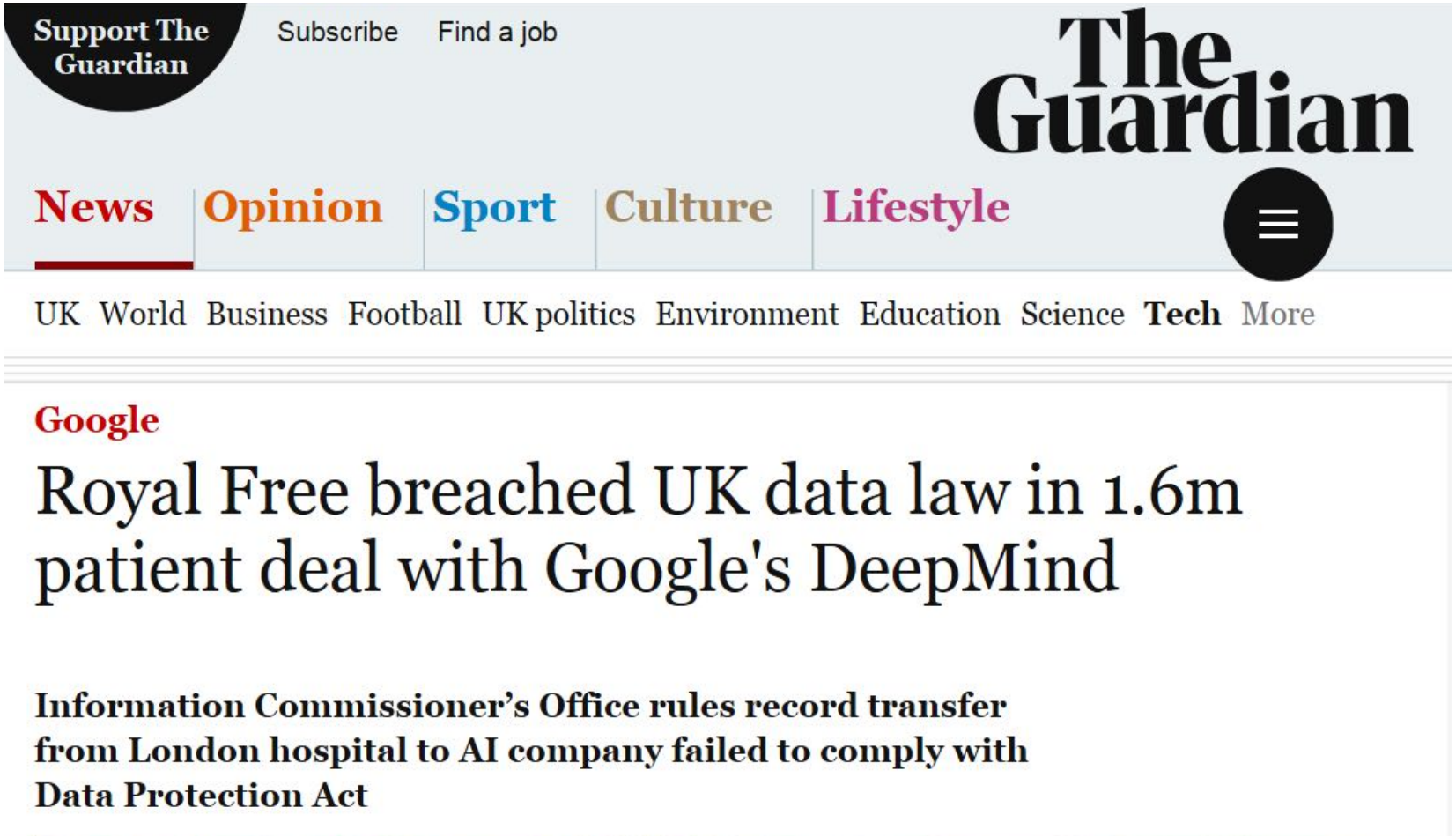

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The Issue

Health Research Authority

The Issue

The legal basis for the use of confidential patient information in data-driven technology pre and post-deployment is unclear.

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Legal Basis

You will be pleased to hear that I will not be talking about GDPR today.

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Legal Basis

That’s right, it’s common law….

WAY MORE COMPLICATED

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Legal Basis

In order to process identifiable patient data a sound legal basis will need to be sought:

- For direct care this can be implied consent.
- For indirect care this should be explicit consent or support under s251.

Individual or Direct Care

“A clinical, social or public health activity concerned with the prevention, investigation and treatment if illness and the alleviation of suffering of individuals. It includes supporting the individuals’ ability to function and improve their participation in life and society. It includes the assurance of safe and high-quality care and treatment through local audit , the management of untoward or adverse incidents, person satisfaction including measurement of outcomes undertaken by one or more registered and regulated health or social care professionals and their team with whom the individual has a legitimate relationship for their care.”

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NOT RESEARCH

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The use of patient data in the development of data-driven technology is **ALWAYS RESEACH**

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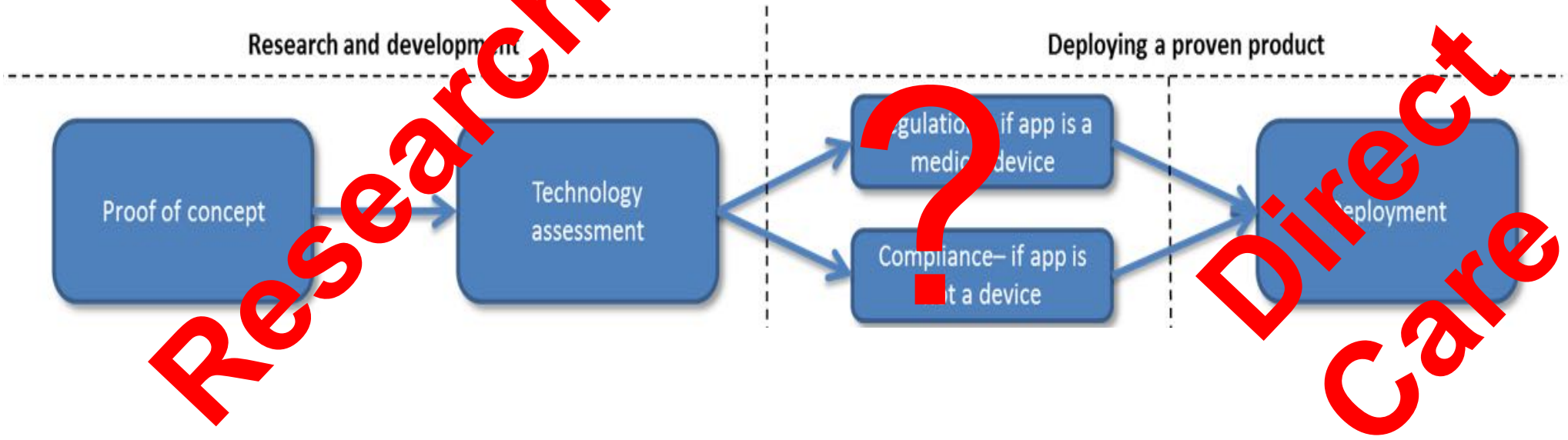

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In practical terms this means that some sort of approval from HRA will be required.

- With consent HRA Approval
- Without consent CAG (inc REC)

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What else do I need to think about?

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Software as a medical device

If the software has a medical purpose then it is a medical device.

Depending on it’s class it may need MHRA Approval.

Generally they require CE marking

Health Research Authority

Guidance

There is joint guidance from HRA, NHS Digital, MHRA and DHSC available.

This is being updated and will be available later in 2020.

NHS
Health Research Authority

Thank you for listening

will.navaie@hra.nhs.uk

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From the NHS Research & Development Forum

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Research and Development Forum

Research but not as we know it: Managing novel methods in research Symposium

2nd March 2020

World Cafe

Symposium
From the NHS Research & Development Forum

Ask

- What are the research management challenges?
- What are the solutions?
- Who owns it?
- What can we do?

Symposium

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