COMPLEX INNOVATIVE DESIGN (CID) TRIALS –

A REPORT FROM THE MINISTERIAL INDUSTRY STRATEGY GROUP CLINICAL RESEARCH WORKING GROUP

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Department of Health & Social Care

NHS National Institute for Health Research

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1 About the MISG CRWG

The Ministerial Industry Strategy Group (MISG) Clinical Research Working Group (CRWG) is a unique group which brings together government and industry with a shared goal of increasing the relative global proportion of Biotechnology and Pharmaceutical industry clinical research investment in the UK, through the creation of a strong strategic partnership with the NHS. The vision of the group is for the UK to be recognised by the Biotechnology and Pharmaceutical industry as a world class destination for clinical research. The MISG CRWG is committed to producing tangible differences which improve clinical research in the UK.

2 Summary

The developments in science and technology mean that innovative clinical trials are needed to assess new medicines, in different (often smaller, more specific) patient populations. We can and should look to be more efficient in how we assess new medicines. Being able to offer the UK as a place where innovative clinical trials are welcomed and supported by regulations and infrastructure will be a competitive advantage for the UK.

This is a key area of interest for many stakeholders and is referred to as “Complex Innovative Design” (CID) trials. It has been flagged as a goal in the UK Life Sciences Industrial Strategy, August 2017: “To support a 50% increase in the number of clinical trials over the next 5 years and a growing proportion of change of practice and trials with novel methodology over the next 5 years.” The European regulators group, the Clinical Trial Facilitation Group has active work in this area and the ECMC is writing a consensus paper on CID trials which is due in 2019.

Despite being a key area, there was a need to gather more evidence to support policy development. The MISG CRWG group conducted a survey in June 2018 to collate information about novel and innovative trial designs. This included responses gathered from industry, MHRA, NIHR, MRC and the NHS.

The survey showed that although innovative clinical trials are often described as umbrella / basket trials, adaptive trials and platform trials, this can be limiting. The survey showed that innovative clinical trial design extends more widely and can include: trial methodologies including design, delivery and analysis and innovative statistical analysis; use of patient records and registries; innovative solutions to trial delivery, including but not limited to use of digital tools and patient led trials.

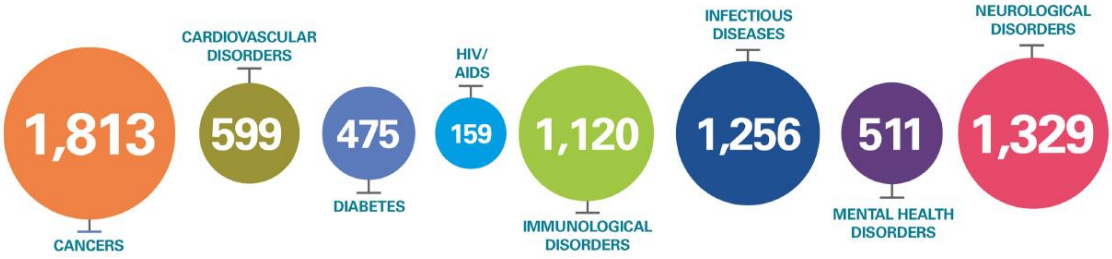
The wide-ranging scope reinforces that policy in this area needs to support innovation in clinical trial design, beyond the current issues with current designs. A flexible, agile approach is needed, encompassing the following principles:

- Education of all stakeholders
- Regulatory approaches and a regulatory advice service which are globally competitive
- Funding models which support innovation
- Evolving the UK NHS infrastructure to support innovative clinical trials
- Ensuring the robustness of NHS workforce to support clinical trials

3 The global development pipeline and R&D investment

Globally the industry is predicted to invest $181bn a year on R&D by 2022 (1) in a bid to realise the potential of more than 7,000 medicines and vaccines in development today (2).

Figure 1. The global development pipeline. *Reference: (2)*



In the UK in 2016, the gross expenditure on R&D (GERD) was £33.1 billion. This represented 1.67% of GDP, unchanged from 2015 (3). In 2016, pharmaceuticals continued to be the product group with the largest expenditure on R&D in the UK, spending £4.1 billion. This accounted for 19% of total expenditure on R&D performed in UK businesses (4).

4 Clinical research in the UK

4.1 Life Sciences Industrial Strategy & Sector Deal ambitions

In the Life Sciences Industrial Strategy (LSIS), under the section 'Reinforcing the UK science offer – Translational Science' and core recommendation to 'Further improve UK clinical trial capabilities', the strategic goal is to 'Support a 50% increase in the number of clinical trials over the next 5 years and a growing proportion of change of practice and trials with novel methodology over the next 5 years' (5). The suggested reinforcing actions for this are:

- Document the number of novel trial designs used as well as the quantity of 'change of practice' trials in the UK compared to elsewhere.
- The UK should work with industry and regulators to establish a working group to evaluate the use of digital health care data and health systems; to evaluate the safety and efficacy of new interventions; and to help ICH modernise its GCP regulations.
- Government should improve the UK's clinical trial capabilities so that the UK can best compete globally in our support for industry and academic studies at all phases.
- Design a translational fund to support the precommercial creation of clinically-useable molecules and devices to intervene and treat disease, which can then be explored in preclinical and early clinical studies.
- Use Government and charitable funding to attract up to 100 world-class scientists to the UK, with support for both their recruitment and their science over the next ten years.

And in the subsequent Sector Deal document (6), on 'novel and more efficient trial designs':

The LSIS also identified opportunities for undertaking novel and more efficient trial designs, including the use of digital real-world evidence, facilitated by innovative regulation. The UK and UK companies have already shown themselves to be world-leading in this field, e.g. GSK's ground-breaking Salford Lung Study. Further collaborations between companies and academia to develop innovative trials have recently been announced:

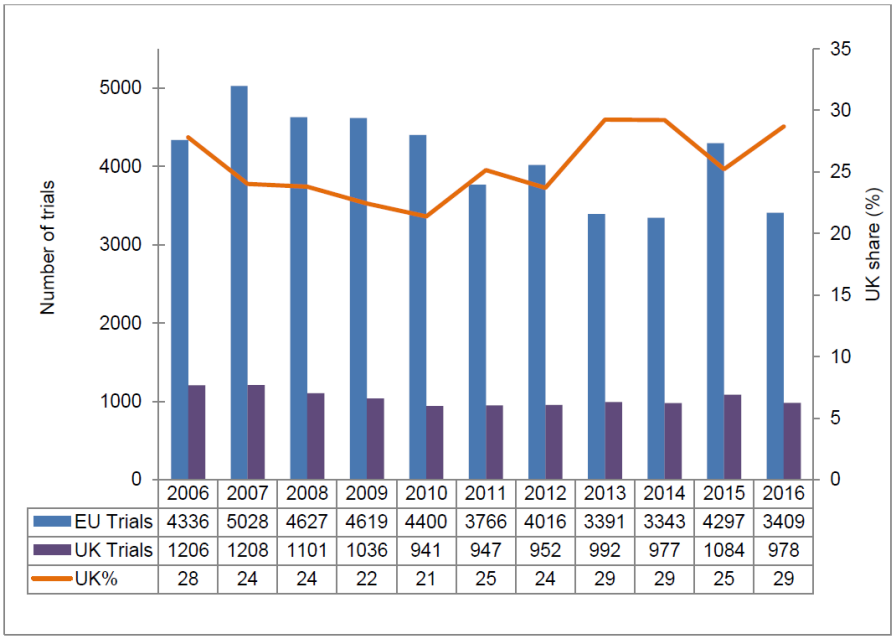
- The Medicines Company is looking at how late-stage trials can be run more cost-efficiently using streamlined processes and digital tools.
- Janssen & University of Oxford intend to collaborate on novel clinical trial methodologies (so-called platform trials) focusing on mental health disorders. The platform trial methodology is a new approach

that could allow multiple novel pharmaceutical agents and other therapies to be efficiently tested in parallel.

4.2 Clinical research performance in the UK

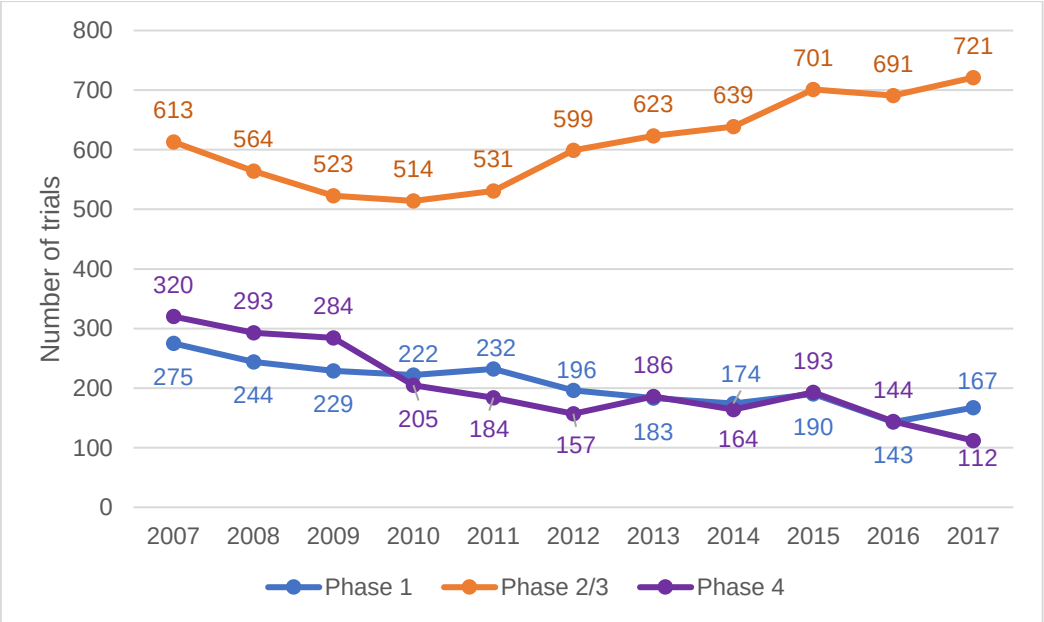
Over recent years, the UK has had a consistently strong performance in clinical research. Figure 2 compares UK Clinical Trial Authorisation (CTA) applications in the context of European applications. The data suggests that in 2016 the UK increased its share of European trials, with the UK taking 29% of total EU CTA applications. This comparative information is based on data from the EudraCT database (7).

Figure 2. UK CTA applications as a proportion of EU CTA applications 2006-2016. Reference: (8)



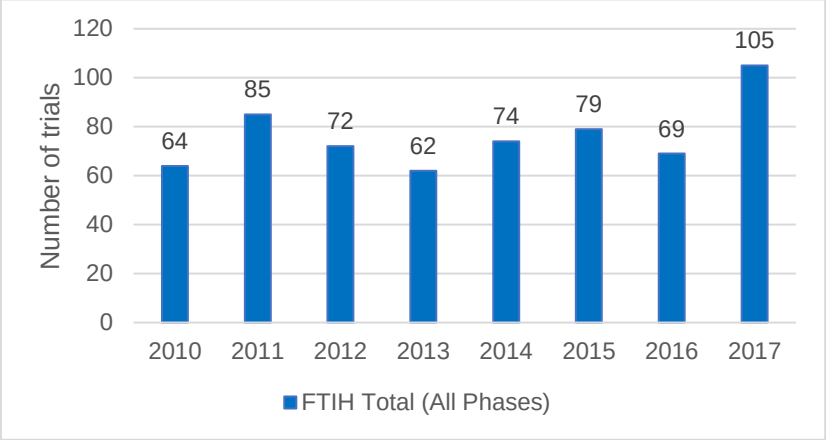
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
EU Trials	4336	5028	4627	4619	4400	3766	4016	3391	3343	4297	3409
UK Trials	1206	1208	1101	1036	941	947	952	992	977	1084	978
UK%	28	24	24	22	21	25	24	29	29	25	29

Figure 3. UK clinical trial applications received by Phase, 2007 – 2017. Reproduced from: (9)



	Phase 1	Phase 2/3	Phase 4	All Phases
2017 – Commercial	156	635	32	823
2017 – Non-commercial	11	86	80	177
2017 - Total	**167**	**721**	**112**	**1000**

Figure 4. UK First in Human (FTIH) totals by year. Reproduced from: (9)



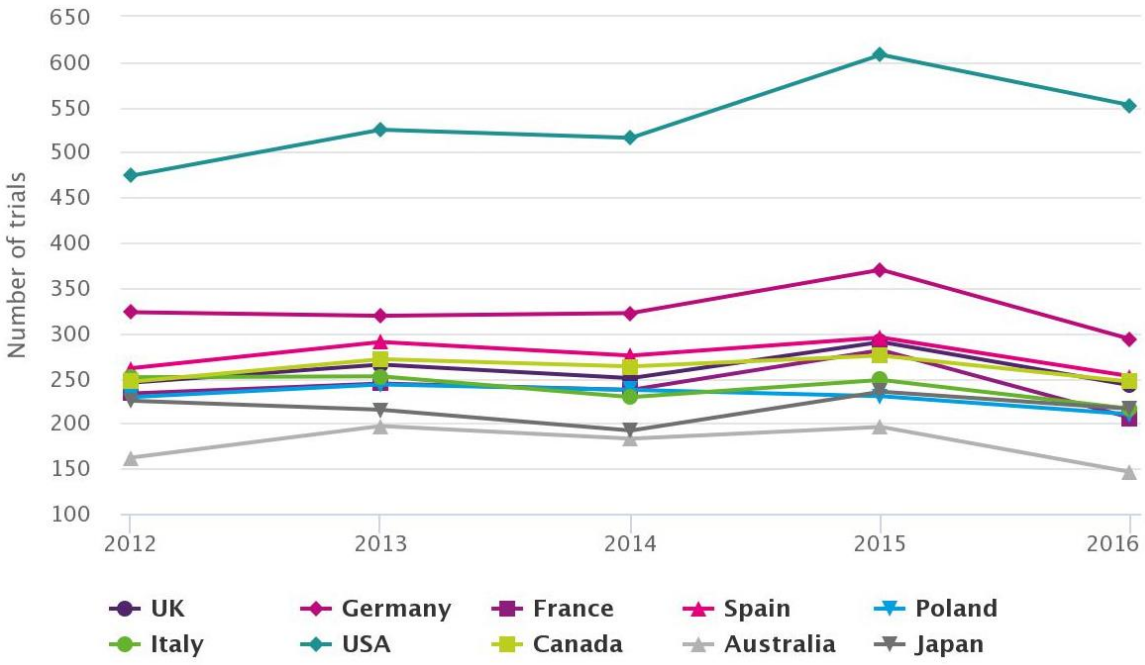
4.2.1 Commercial clinical trials: UK vs Global

Up to 2016, figures for the number of trials for Phase I clinical research clearly show a continuing and relatively strong performance by the UK (Figure 5). Although the US is way out ahead of all other countries, the UK performs strongly, leading the remainder of the peer group.

Looking at the long-term trend up to 2016, the UK is competitive for Phase II clinical trials amongst its peer group, generally only trailing the US and Germany (by a small margin). In 2016, Japan seems to benefit from a significant uptake in initiated Phase II trials, which could be linked to innovation programmes and investment in their regulatory agency, PMDA. Every other country reviewed saw a slight decline in Phase II trial initiations in 2016.

Up to 2016, the UK has continued to demonstrate competitive performance in its peer group for Phase III trials, although trailing behind the US which has just over double the number of Phase III trial starts in 2016 than its nearest competitor, Germany. The bigger trend in 2016 is the generalised decline in the number of trial initiations for Phase III trials. This may be temporary, or it may reflect a change in clinical development strategies to better fit the technologies explored and/or to support efficiencies in development overall. Such a conclusion requires a longer time series to average across.

Figure 5. Phase 3 clinical trials – UK vs global. Reference: (10)



4.3 Drivers of commercial clinical research in the UK

Despite the improving performance of clinical research in the UK, to fully embed the UK as an attractive place to do commercially funded research, the current environment would need further ongoing improvement in the key areas that drive research placement into the UK. The additional uncertainty of Brexit creates an additional challenge given the increasingly competitive global research environment.

The key drivers for commercial clinical research in the UK are:

- Reliability and Predictability
- Volume and Ambition
- Capacity and Capability
- BREXIT planning

For each driver, the MISG CRWG defined a set of problem statements, together with actions needed. Overarching action plans supporting all drivers have been defined as the following:

- Research delivery focusing on end-to-end accountability
- UK-wide working through systems and processes to deliver seamless study start up and delivery
- Use of Data for feasibility
- Use of Data for research
- Marketing messages to explain the offering of clinical research in the UK

Action plans on each of the issues identified above are being taken forward by the MISG CRWG and/or the ABPI Clinical Research Expert Network (CREN). However, a number of actions require influence beyond the MISG CRWG and ABPI and all actions would benefit from ongoing support from the LSIS Implementation Board in order to maintain and increase the attractiveness of the UK for clinical trials.

4.3.1 Making clinical research in the UK easier and faster

The ABPI Clinical Research Expert Network (CREN) is working with others on the actions below to ensure that the UK remains an attractive place for commercial clinical research in an international environment. These are also important to ensure that the UK is seen as a place in which investment in newer types of trials is feasible.

A) Work closely with the HRA to make clinical research in the UK easier

- Support the rollout of the revised Model Clinical Trials Agreement (mCTA) for commercially sponsored clinical research and input into ongoing developments of the mCTA
- Initiative for improving handling of amendments led by HRA
- UK-wide working (4 Nations initiative) – to ensure industry understands how the mCTA works and implements any changes / training
- Ensure sites follow HRA processes for study start up and amendments (including CREN input into HRA amendments review)

B) Working with NIHR to improve the delivery of studies in England

- Work with NIHR on maximising the offer to industry of the NIHR Study Support service and the Local Clinical Research Networks
- Maximise NIHR's involvement in study start-up and amendments, within HRA Approval
- Understand the use of health data for feasibility within NIHR-supported studies and support improvements to ensure robust feasibility
- UK-wide working – ensure industry understands how these changes and improvements work and how to implement them

C) Support NHS England proposal to simplify and strengthen arrangements for getting research projects up and running in the NHS

- Actively input into key initiatives, such as the single costing proposal for England (from 1st October 2018):

If the NHS England organisations chose to participate in any Commercial Contract Research Study which is submitted to the HRA for approval on or after 1 October 2018, the Provider must ensure that that participation will be in accordance with the National Directive on Commercial Contract Research Studies, at a price determined by NIHR for each Provider in accordance with the methodology prescribed in the Directive. The Standard Contract requires providers (and thereby commercial sponsors and Contract Research Organisations) to use a standard "methodology for setting prices payable by research sponsors to NHS providers for their participation". The standard methodology currently used is the NIHR CRN Industry costing template.

5 The challenges and barriers to conducting innovative clinical trials in the UK – a MISG CRWG survey

The developments in science and technology mean that innovative clinical trials are needed to assess new medicines, in different (often smaller, more specific) patient populations. Being able to offer the UK as a place where innovative clinical trials are welcomed and supported by regulations and infrastructure will be a competitive advantage for the UK. In order to inform policy, MISG CRWG undertook a survey to gather evidence.

5.1 Survey Methodology

In support of the LSIS, MISG CRWG collated information about novel and innovative trial designs and a summary of the findings is outlined below.

The questions asked were:

1. Please provide examples of novel or innovative designs you are using, developing, or receiving for approval

2. Have you experienced, or do you anticipate, any barriers to approval/implementation of these designs? (Please provide details)

3. Do you have any proposals as to how these barriers could be overcome?

4. Are you aware of any policy initiatives in this area? (If so, please provide details)

5.2 Survey Results

Around 70 responses were received in June 2018 with responses from industry, MHRA, NIHR, MRC and the NHS. These responses were then supplemented with information gathered from ABPI Expert Networks and from an OLS Industry Engagement meeting on the 12th July 2018.

5.2.1 Scope of innovative clinical trial design

Innovative clinical trials are often described as umbrella / basket trials, adaptive trials and platform trials. However, the survey showed that innovative clinical trial design extends more widely and can include:

- Trial methodologies
    - Design, delivery and analysis
    - Innovative statistical analysis
- Use of patient records and registries
- Innovative solutions to trial delivery
    - Document sharing portal
    - Monitoring drug compliance
    - Wearables to collect clinical endpoints
    - ePRO
    - Remote eConsent
- Patient-led trials

Of note, the novel and innovative therapies themselves were not included in the scope of this assessment.

5.2.2 Key challenges and barriers

A clear definition is needed for all stakeholders - regulators should have a discussion about an aligned definition based on the FDA definition.

Education

All stakeholders involved must have a greater understanding of the need to support innovative thinking and also of the practical implications of innovative clinical trial design.

Key groups identified include:

- Researchers & trial teams
- Statisticians
- Funders / grant application reviewers
- R&D (sponsor)
- R&D (site)
- REC committees
- Site teams

Regulatory

To be competitive, the UK needs to offer a fast scientific advice service for global protocols. This must then be supported by fast approval of the initial protocol and of the addition of subsequent arms of studies for the UK specific parts of studies. The MHRA's ongoing work in looking at innovative clinical trials must be supported to allow this to happen.

Funding

Due to the potential for increased initial costs to invest in innovative clinical trials, funding needs to reflect the need for greater up-front costs. The size and duration of protocols employing these designs cannot always be fixed. This makes costing difficult which is challenging for funders.

UK NHS infrastructure

This needs to be in place to enable innovative clinical trials to happen.

For example, pathology is key to defining different patient populations to enable innovative clinical trials to happen. This requires:

- A trained pathology workforce and the work of the NCRI CMPath to increase the numbers of molecular pathologists is welcomed and needs to be supported.
- Standardisation of pathology services and practices in order to enable research across sites and to ensure a better patient experience. Of note, Genomics England have work underway to transform pathology and diagnostic practice which could support this issue.

NHS Workforce

A robustness of the availability of key NHS workforce is needed in order to ensure clinical trials can happen. It is important to note that this includes all level of staff involved in research, particularly clinical research nurses and data managers. Better management of staff absences and gaps is needed in order that trials are not left without key personnel.

5.3 Suggested proposed solutions

Funding

- Core funding being made available for centres developing expertise in this area.
- Ensuring funders are made aware of the potential benefits in funding this type of trial.
- Routine presentations to funding bodies with the intention of making them feel confident in the designs and with the funding windows, including presenting case studies of experiences with implementing these designs.

- Specific funding calls aimed at innovative trial designs.
- Cover the costs of a light touch peer review and the study design phase prior to full submission, access to funds should be made available in advance of the full application or allow retrospective inclusion.
- Academia and funding bodies to work together in order to co-create funding solutions.

Education/training

- Education for staff in R&D departments on the potential efficiencies of these designs and why clinical research seems to be heading in this direction may help. Currently these departments appear to be understaffed and struggling to process the complexities of these designs.
- Greater support is needed for the provision of further research staff at NHS sites and development of streamlined trials that are easier to run.
- Central support to co-ordinate non-UK site opening would greatly facilitate rare disease trials, which are much more reliant on participation from a greater number of countries than other diseases.
- A better understanding of biomarker-guided trial designs by regulators, funders and other stakeholders. To this end, the MRC Stratified Medicine Working Group has developed an online tool (www.BiGTeD.org) to provide guidance on the various biomarker-guided trials that have been proposed.
- Knowledge sharing/education of stakeholders by those with hands-on experience of running biomarker-guided trials.

Regulators

- It may be useful for policies related to adaptive designs to encourage new drug application sponsors to engage closely with regulatory scientists before and during trial conduct, to reduce the likelihood of repeating past scenarios in which regulators found results from adaptive trials insufficient (11).

Others

- Provide motivation to investigators to accept the increased chance of early termination in return for a higher chance of successful funding compared to a traditional design.
- Production of dedicated tools or software to allow the more wide-spread use of novel designs.
- Greater recognition of the multi-disciplinary collaboration required for these types to trials.
- Improved communication with patients as well as with funders/regulators about what personalised treatment means and how the trials work.

6 MISG CRWG Recommendations

The MISG CRWG recommends the following, in order to support innovative clinical trials in the UK:

1. A core educational resource to be developed and made available for all stakeholders
2. Support for the outcomes of the European Clinical Trial Facilitation Group discussions on the regulatory aspects
3. Policies to support Industry to engage closely with regulators
4. Support for ongoing work to increase pathology skills and standardization of pathology services in the UK
5. Support for the ongoing work to improve the clinical trials environment for all trials, including work to streamline approval and start-up processes
6. Strategies to increase the reliability of the NHS workforce to be available to conduct clinical trials.

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