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

Department of Health
Medicines & Healthcare products Regulatory Agency
abpi Bringing medicines to life
NHS National Institute for Health Research
NHS Health Research Authority

Foreword from the Ministerial Industry Strategy Group Clinical Research Working Group

Clinical Research is vital for developing new treatments for patients. It is an area of strategic importance for the UK and this is recognised in the recent Life Science Industrial Strategy. However, Clinical Research is a complex process; it relies on different organisations working effectively to ensure the clinical research is high quality, ethical and scientifically robust. This needs to be as effective and efficient as possible in order to attract commercial research to the UK in a globally competitive environment.

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. This important report brings together many data sources to give a set of insights on the status of clinical research in the UK now and to set a baseline for future activities. These data sources demonstrate that:

- the UK is maintaining a competitive position in relation to Europe, according to the Medicines & Healthcare products Regulatory Agency (MHRA) data on Clinical Trial Applications by phase;

- NIHR support for clinical trials through both the NIHR Clinical Research Network and the NIHR translational infrastructure (NIHR Biomedical Research Centres and Facilities) continues to expand;

- Data on the speed of clinical trial initiation show improved performance; and

- The UK's position is strong relative to its key competitors in key therapeutic areas, according to data commissioned by the Association of the British Pharmaceutical Industry (ABPI).

The CRWG is delighted to have compiled this integrated report which demonstrates an encouraging position for UK clinical trials broadly across all trial phases. The data highlights that the UK's improving trend in life sciences industry clinical trial activity has been maintained and built upon. The CRWG are clear that this improvement reflects the partnership working between the life sciences industry, the UK Government and all the organisations involved in enabling trials to take place in the NHS. Most of all, the CRWG recognises that it is the patients who participate in clinical trials, often for altruistic reasons, who deserve so much credit for their involvement in the development of new and more effective diagnostics and treatments.

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1 Introduction

1.1 Background

This report brings together data on UK clinical trial activity from the MHRA, NIHR, HRA and ABPI. It follows previous reports from the Chief Scientific Advisor at the Department of Health, Professor Chris Whitty, in March 2016 and from the Chief Medical Officer, Professor Dame Sally C Davies, in March 2015.

1.2 Executive Summary

Comparative data from the MHRA and the ABPI[1] continue to indicate an improving and competitive performance by the UK in comparison to Europe, both in terms of clinical trial authorisations and initiation of clinical trials. Where there have been reductions in UK activity they are generally reflected by other competitor countries or by Europe as a whole.

Data on clinical trial activity in the NHS, enabled and supported by the NIHR in England, continues to demonstrate a positive trend across a broad range of indicators such as:

- The proportion of UK Clinical Trial Authorisation (CTA) applications in the context of overall European applications increased to 29% of total EU CTA applications in 2016.
- The NIHR early translational (experimental medicine) centres and facilities are continuing to support a year-on-year increase in the number of clinical trials in 2016/17, up 25% on the previous year.
- The number of life sciences industry commercial contract and collaborative studies supported and facilitated by the NIHR CRN has continued to increase year-on-year. In 2016/17 the NIHR CRN supported delivery of 1241 commerical contract studies - an increase of 11% on the previous year; and 668 commerical collaborative studies, showing an increase of 10% on the previous year.
- The UK is competitive for commercial research across all Phases of clinical research as measured by the number of trials over the period 2010 through 2015, leading European competitors in particular for Phase I trials.

In 2016/17 a new process for the approval of clinical research was introduced – ‘Health Research Authority (HRA) Approval’ - which streamlines research approvals in the NHS.

[1] Sourced from Clarivate Analytics Cortellis Clinical Trial Intelligence

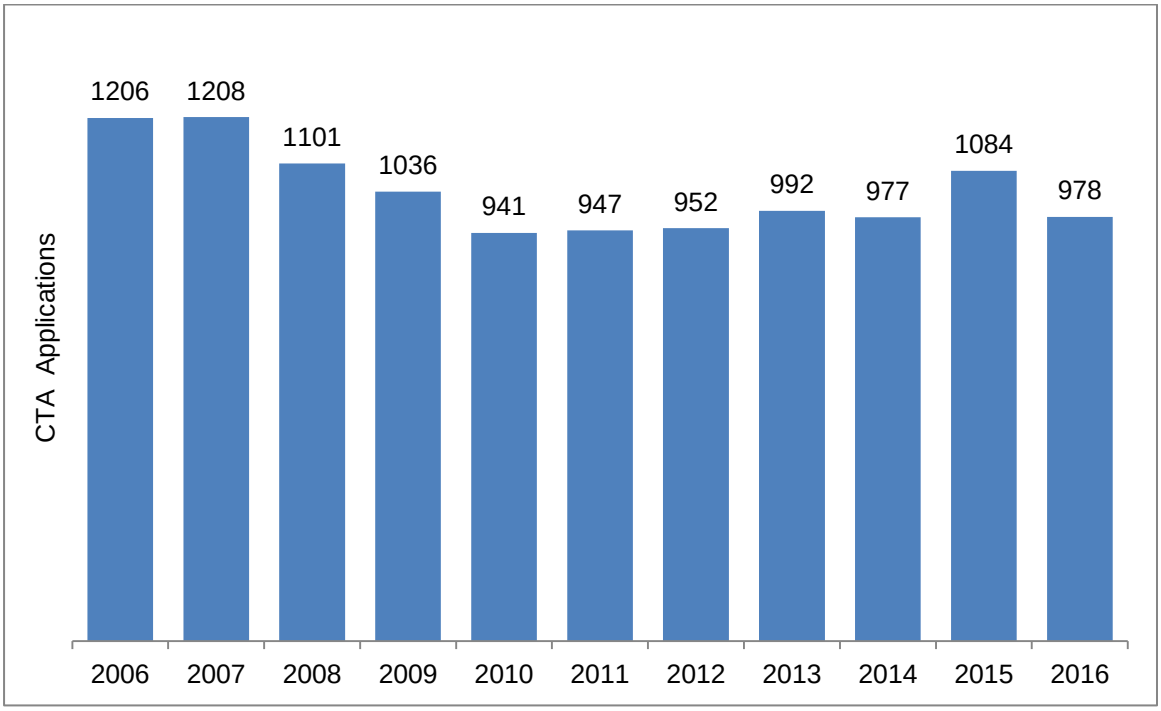
2 MHRA Clinical Trial Authorisations

The MHRA regulates medicines, medical devices and blood components for transfusion in the UK. The MHRA is an executive agency, sponsored by the English Department of Health. As part of its responsibilities the MHRA considers applications for CTA for clinical trials of investigational medicinal products (IMPs) undertaken in the UK.

2.1 CTA applications received by the MHRA

Data from the MHRA indicate that the UK is attracting a generally increasing number of clinical trial applications since 2010. The small decrease in activity in 2016 compared to 2015 reflects a reduction in overall European activity (see figure 2). Early data of UK activity in the first quarter of 2017 shows an increase in clinical trial applications against the same period in 2016 (not represented in the graph).

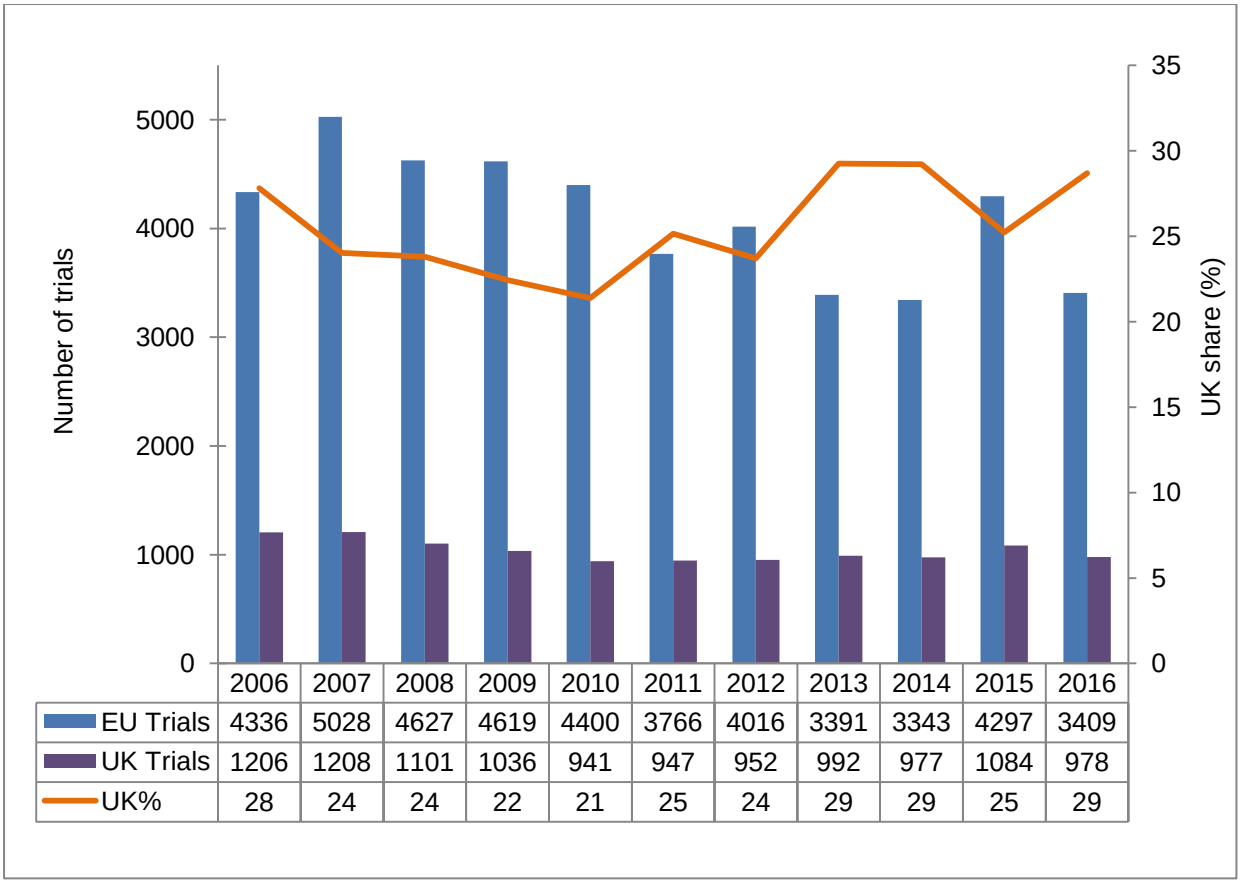
Figure 1. UK CTA Applications by Year



2.2 UK CTA applications as a proportion of EU CTA applications

Figure 2 demonstrates the UK CTA applications in the context of overall European applications. Despite the drop in UK applications against a 2015 peak, the data suggests that the UK's increase in the share of European trials has been maintained, with the UK achieving 29% of total EU CTA applications in 2016. This comparative information is based on data from the EudraCT database[2].

Figure 2. UK CTA Applications as a proportion of EU CTA applications



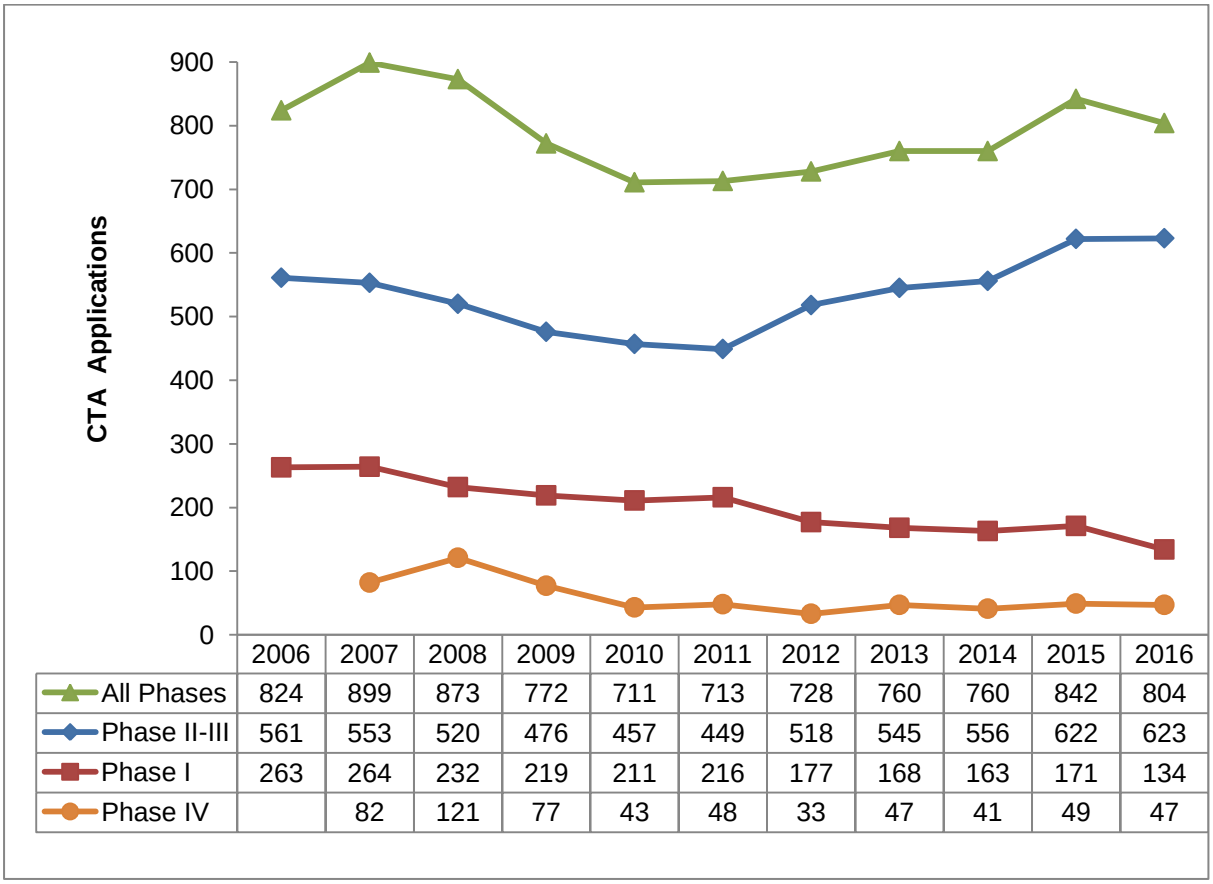
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
EU Trials	4336	5028	4627	4619	4400	3766	4016	3391	3343	4297	3409
UK Trials	1206	1208	1101	1036	941	947	952	992	977	1084	978
UK%	28	24	24	22	21	25	24	29	29	25	29

2.3 Commercial CTA applications received by the MHRA (by Phase)

Figure 3 demonstrates the commercial CTA applications received by MHRA by Phase of clinical research. Analysis of clinical trials shows that Phase I trials account mainly for the slight decrease in overall clinical trial authorisations. It should be noted that an increase in integrated protocol designs may be contributing to the decrease in Phase I only studies (i.e. Phase I protocols that incorporate early Phase II would not be classed as Phase I).

[2] https://eudract.ema.europa.eu/results-web/

Figure 3. UK CTA applications by trial Phase



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
All Phases	824	899	873	772	711	713	728	760	760	842	804
Phase II-III	561	553	520	476	457	449	518	545	556	622	623
Phase I	263	264	232	219	211	216	177	168	163	171	134
Phase IV		82	121	77	43	48	33	47	41	49	47

Further information on the latest MHRA CTA activity is publicly available on Gov.uk here: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/607294/01_Mar_2017.pdf

3 Early Phase commercial research with NIHR translational research infrastructure

Established by the Department of Health in England, the NIHR funds high quality research to improve health, trains and supports health researchers, provides world-class research facilities, works with the life sciences industry and charities to benefit all, and involves patients and the public at every step.

The NIHR provides a range of research infrastructure centres and facilities in the NHS within England to support world-class early translational (experimental medicine) research and clinical and applied health research. It drives faster translation of discoveries from basic/discovery science into tangible benefits for patients and for the health and care system, and to widen economic growth.

The main NIHR-funded research infrastructure in the NHS that supports early translational (experimental medicine) clinical trials are the NIHR Biomedical Research Centres (BRCs). NIHR BRCs are partnerships between England's leading NHS organisations and universities, which conduct people- and patient-focused early translational (experimental medicine) research to transform scientific breakthroughs into life-saving treatments.

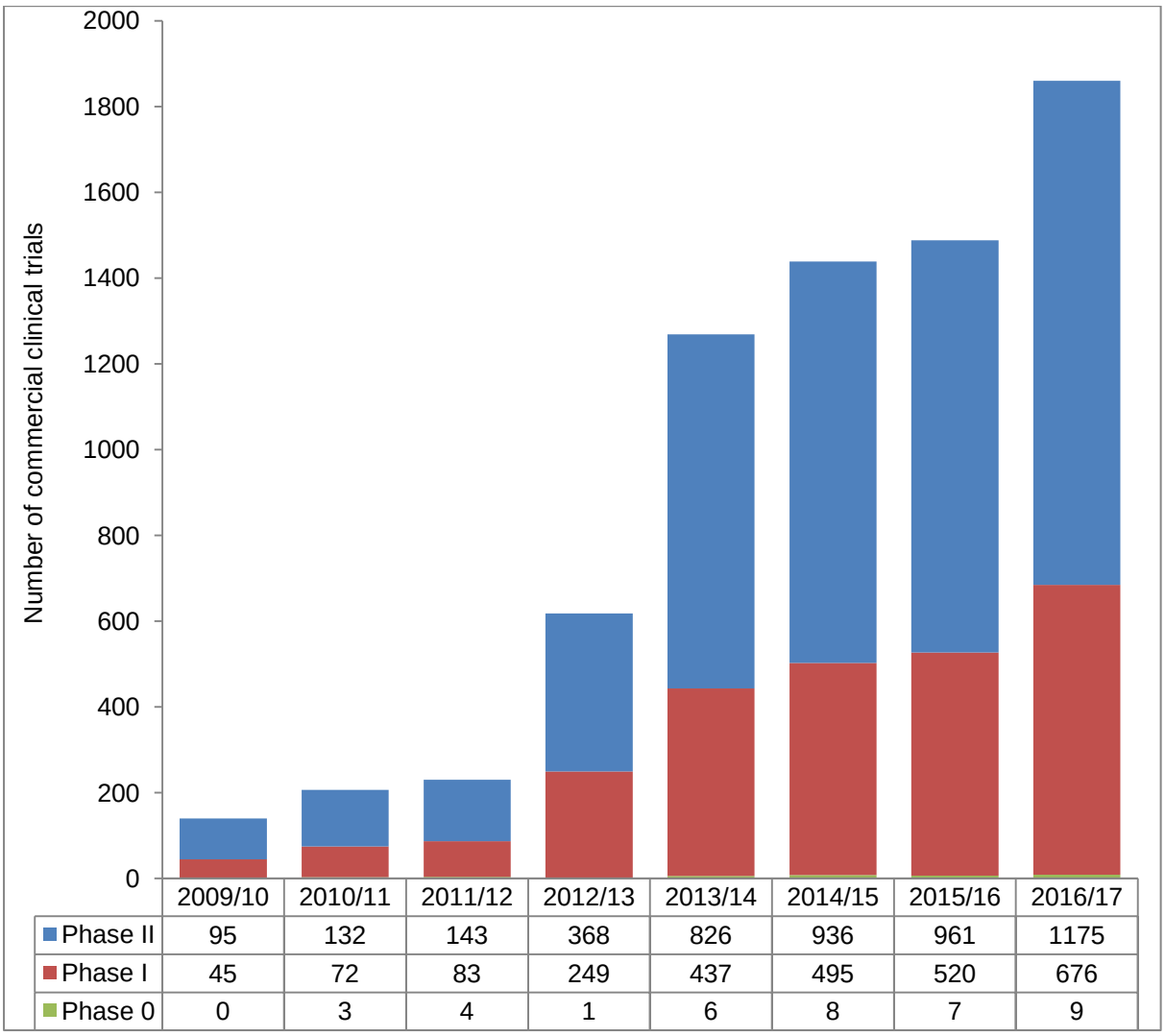
NIHR Clinical Research Facilities (CRFs) are dedicated and purpose built facilities in the NHS in England with specialist clinical research and support staff working together to enable and deliver commercial and non-commercial early translational (experimental medicine) studies.

In 2016/17, NIHR funding of £928 million was announced for new NIHR BRCs and NIHR CRFs for 5 years from April 2017.

3.1 Early Phase Commercial contract and collaborative trials across the translational NIHR infrastructure components

The number of clinical trials undertaken by NIHR-funded infrastructure centres and facilities has increased significantly since 2009/10, as demonstrated in figure 4.

Figure 4. Early Phase commercial contract and collaborative trials active across the NIHR translational infrastructure



	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
Phase II	95	132	143	368	826	936	961	1175
Phase I	45	72	83	249	437	495	520	676
Phase 0	0	3	4	1	6	8	7	9

4 NIHR Clinical Research Network supported commercial research

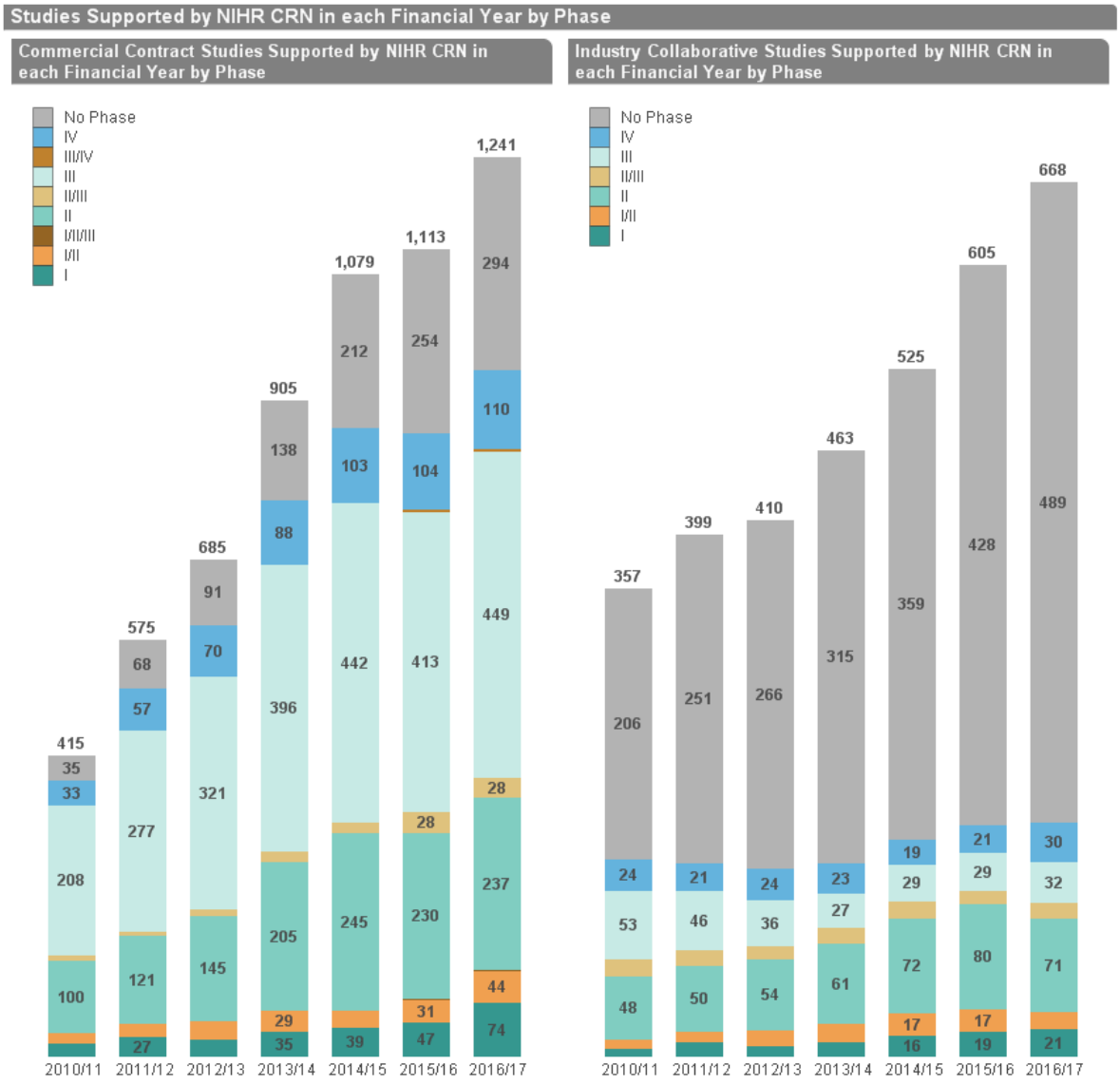
The NIHR CRN makes it possible for patients and health professionals across England to participate in clinical research. The NIHR CRN provides the infrastructure that allows high quality clinical trials and other high quality research funded by the life sciences industry to be undertaken throughout the NHS. It offers a no-cost study support service package to the life sciences industry, comprising of services that spans the lifecycle of a clinical trial. This package includes support focused on study feasibility, site identification, providing enabling tools such as costing templates, model agreements and performance management of trials. This package is designed to help commercial organisations efficiently setup and deliver clinical trials to time and target. It supports clinical research across the pharmaceutical, biotechnology, diagnostics and medical technology industries, as well as the Contract Research Organisations that support them.

Embedded within the NHS, the NIHR CRN provides full geographical and therapeutic coverage across the length and breadth of England, with dedicated staff and support services to assist with study feasibility, rapid setup and study delivery at a site level. Figures 5-8 show the clinical trial activity supported and facilitated by the NIHR CRN in the NHS.

4.1 Commercial contract trials supported by the NIHR CRN

The NIHR CRN supports commercial contract trials, funded and sponsored by the life sciences industry. It also supports industry collaborative trials that are funded but not sponsored by the life sciences industry, and may include investigator initiated trials (IIT's). Figure 5 shows that the NIHR CRN is supporting an increasing number of commercial contract and industry collaborative trials, within the NHS, across all Phases of trials, with a majority between Phase II-IV.

Figure 5. Studies supported by NIHR CRN in each financial year by Phase



Definition of 'No Phase': The types of trials which are incorporated within the 'no phase' category include:

a) clinical investigations or other studies of medical devices (Medtech)

b) Clinical research not involving investigational medicinal products or medical devices. For example, research involving: surgery, radiotherapy, imaging investigations, mental health investigations or therapies, physiological investigations, trials of products not defined as medicines or medical devices (e.g. nutritional), complementary or alternative therapies

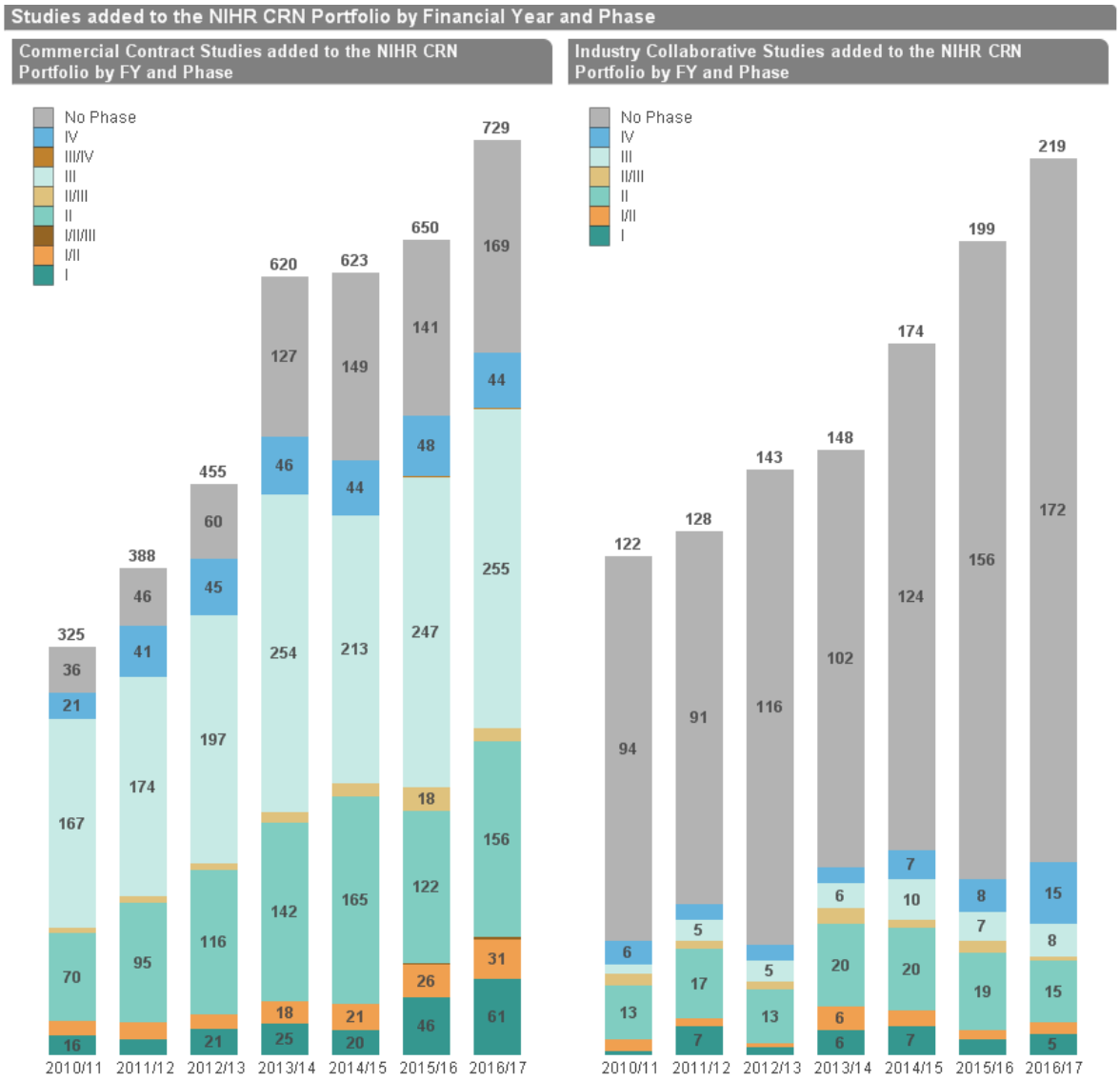
Clinical trials are counted as ‘supported’ by the NIHR CRN for the duration over which they are recruiting participants. If that duration spans financial years, they are counted in each relevant financial year. N.B. All trials also receive support from the NIHR CRN outside of this period (e.g. during feasibility and study setup).

It should be noted that use of strict Phase I to Phase IV terminology does not reflect where within the same protocol the study progresses between Phases, including by expanding cohorts depending on the developing results. This means recording studies by Phase is sometimes difficult.

4.2 New commercial clinical trials added to the NIHR CRN Portfolio

The number of new commercial contract and industry collaborative trials added to the NIHR CRN portfolio shows a strong year-on-year increase as shown in figure 6. For both commercial contract trials and industry collaborative trials, the number of new trials added to the NIHR CRN portfolio has more than doubled since 2010/2011.

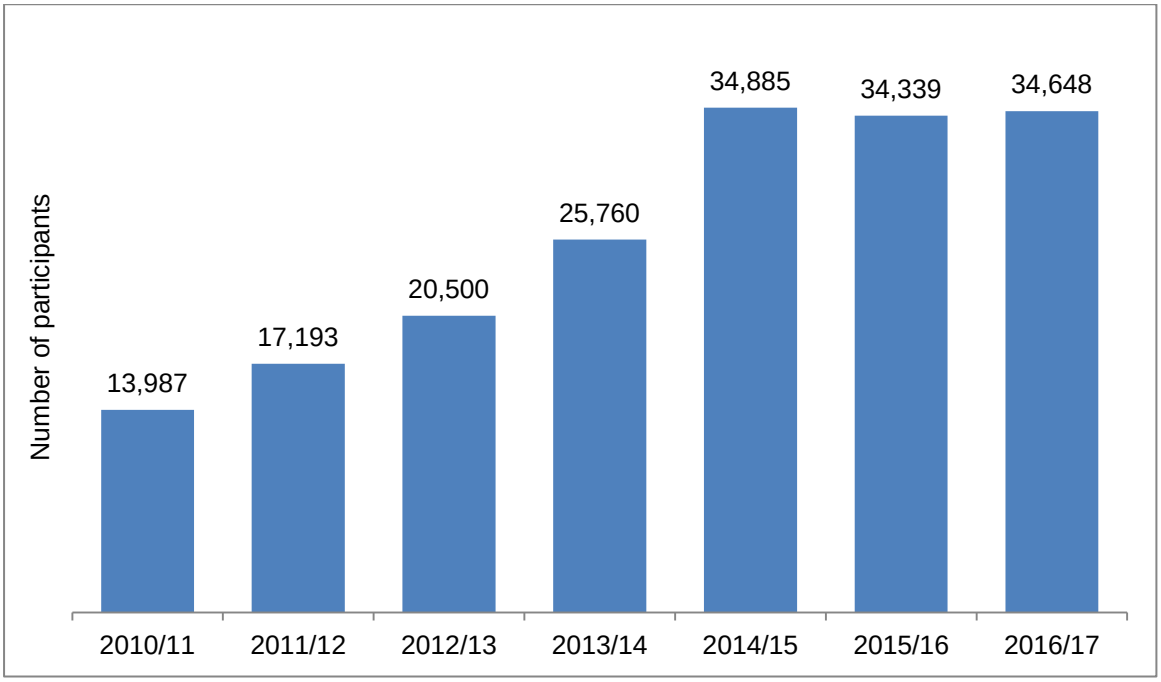
Figure 6. New commercial clinical trials added to the CRN Portfolio



4.3 Number of participants recruited to commercial contract studies supported by the NIHR CRN

The NIHR CRN continues to support the life sciences industry to recruit a significant number of participants to commercial contract trials, recruiting over 180,000 participants since 2010.

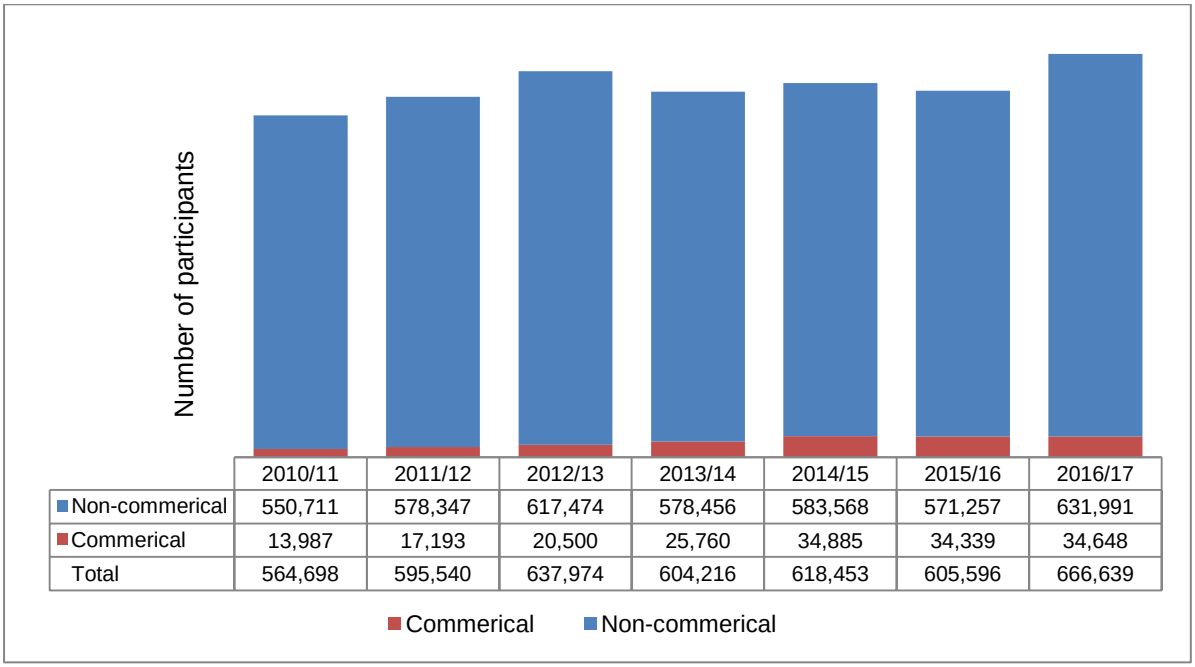
Figure 7. Number of participants recruited to commercial contract clinical trials supported by NIHR CRN



4.4 Number of participants recruited to all NIHR CRN supported studies, including commercial and non-commercial studies

Figure 8 illustrates the number of participants recruited to both commercial (commercial contract) and non-commercial studies, supported by the NIHR CRN. For the past seven years, the NIHR CRN has supported over half a million people year-on-year to take part in clinical research in the NHS, and over 4 million people since 2010.

Figure 8. Number of participants recruited to all studies supported by NIHR CRN



	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
Non-commerical	550,711	578,347	617,474	578,456	583,568	571,257	631,991
Commerical	13,987	17,193	20,500	25,760	34,885	34,339	34,648
Total	564,698	595,540	637,974	604,216	618,453	605,596	666,639

4.5 NIHR CRN supported research

The NIHR CRN has worked closely with the NHS to drive improvements in study setup and delivery. In 2016/17:

- The NIHR CRN delivered 83% of all research funded by charities and other non-commercial funders to time and target. 73 per cent of commercial contract studies were delivered to time and target, which is a 10% improvement on the previous year. Delivery of research to agreed recruitment timelines and targets is an excellent indicator of efficiency and a priority area of focus for the NIHR CRN.
- Over 99% of English NHS trusts recruited into a NIHR CRN Portfolio study, indicating the breadth of opportunities for people to actively participate in clinical research.
- 79% of English NHS trusts recruited to commercial contract NIHR CRN Portfolio studies showing the increasing spread of commercial contract study uptake within the NHS.
- The NIHR CRN continues to demonstrate that the UK is internationally competitive in speed of study setup by recruiting 24 global and four European first patients into multiple specialty areas.

5 Clinical trial initiation: speed and predictability

5.1 Health Research Authority and HRA Approval

The HRA protects and promotes the interests of patients and the public in health and social care research.

HRA Approval is the new research approval process for the NHS in England, which brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent Research Ethics Committee (REC) opinion provided through the UK Health Departments' Research Ethics Service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England, therefore removing the 'R&D approval' step that was regarded as adding an additional step to site setup. It also collates other approvals that may be required depending on the nature of the research, for example MHRA approval of clinical trials of investigational medicinal products (CTIMPs).

The new system simplifies the approvals process for research, making it easier for research studies to be setup. The elimination of duplicate application routes means that the answers to research questions about how to improve patient care or about new treatments will be answered more rapidly.

The HRA Approval system was rolled out in a series of tranches and completed with its adoption for clinical trials in April 2016. It is now the process for application to undertake research in the NHS in England. Modification of the application process through HRA Approval means that some of the historical metrics and their associated timepoints have changed. NIHR and the HRA have collaborated to produce a minimum data set that describes the new process and can be used to consistently monitor the whole of the clinical research initiation from application to first patient recruitment.

5.2 Preliminary analysis of clinical trial initiation under HRA Approval

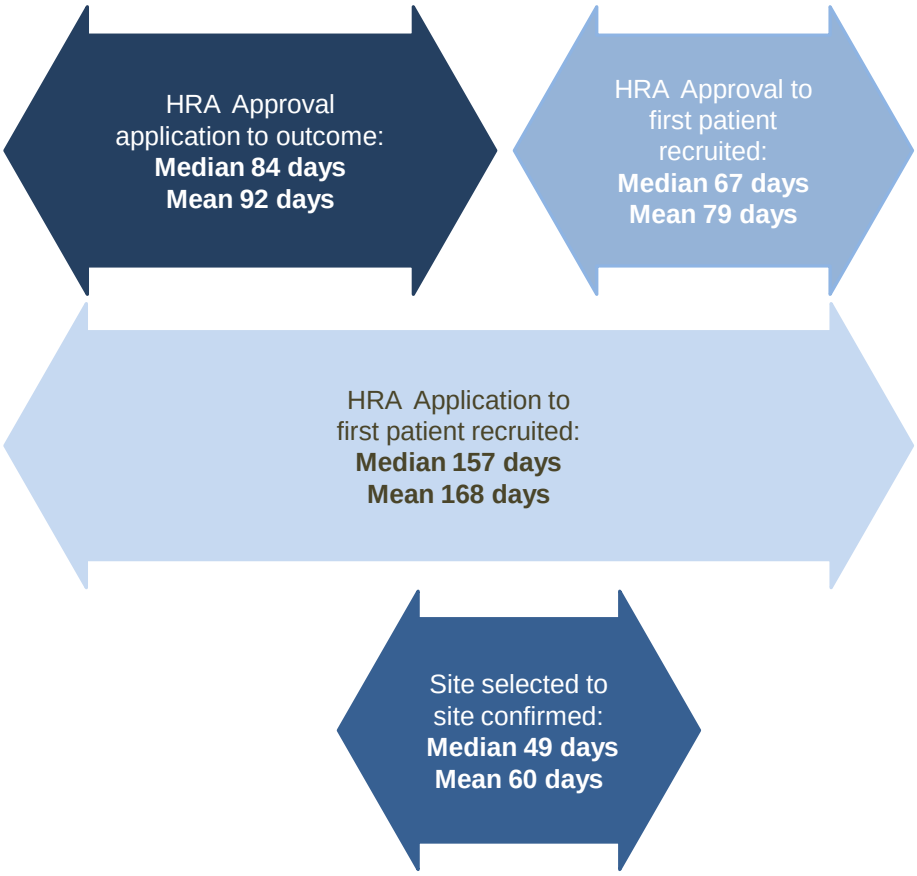
Preliminary analysis of the minimum data set from quarter 4 of 2016/17 shows the following timescales. Note that this information relates to commercial clinical trials going through HRA Approval reported by providers of NHS services.

- HRA Application to first patient in study (aggregated site data) – minimum time 50 days, median 157 days and mean 168 days

- HRA Approval to first patient in study (aggregated site data) – minimum 9 days, median 67 days and mean 79 days
- Site Selected to Site Confirmed (contract completion) – median 49 days and mean 60 days

Please note that these timelines cannot be compared with historic data due to the change in process and the timepoints that are measured. However, the data now represents full elapsed timelines including the time taken for all regulatory approvals and for the applicant to respond to any queries raised.

Figure 9. Median intervals for key parts of the initiation pathway under HRA Approval

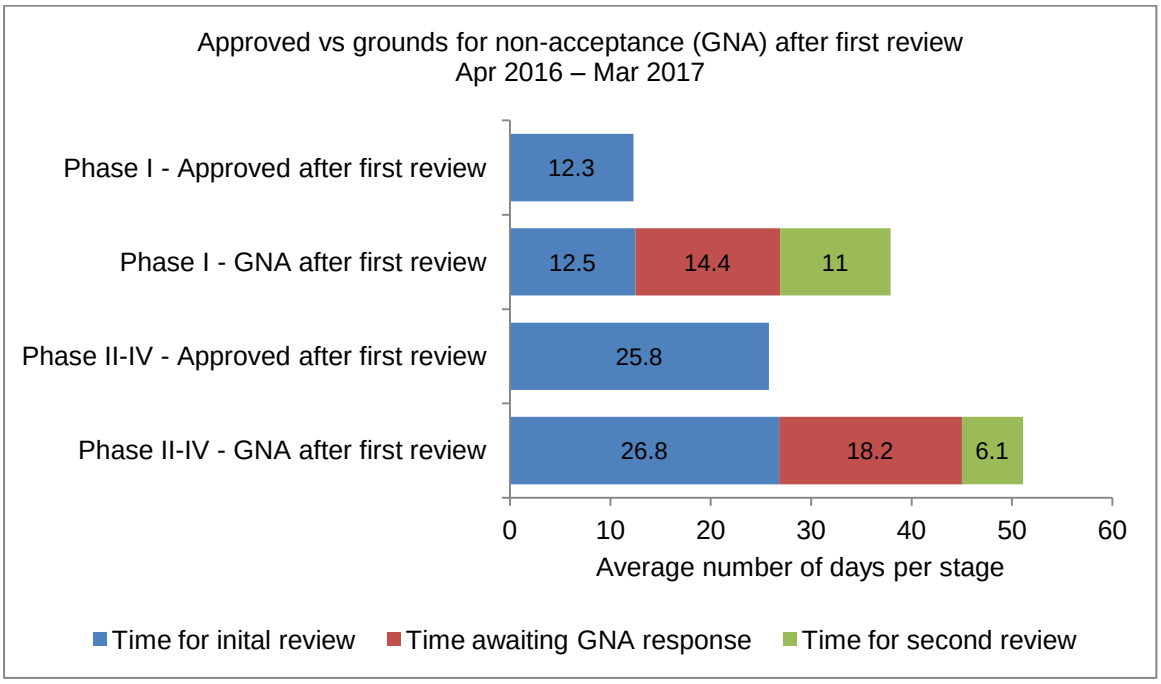


HRA Approval interval is based on all commercial clinical trials going through HRA Approval from April 2016 to April 2017 (not just those reported by providers of NHS services).

5.3 MHRA CTA assessment timeframes

The MHRA conduct an expedited initial assessment of Phase I studies (target of 14 days average) and are also well within the statutory timeframe of 30 days for initial assessment of other Phases. Taking into account when questions need to be asked of the sponsor – when there are grounds for non-acceptance (GNA) after the first review – MHRA are well within the 60 days statutory timeframe for final determination of the application.

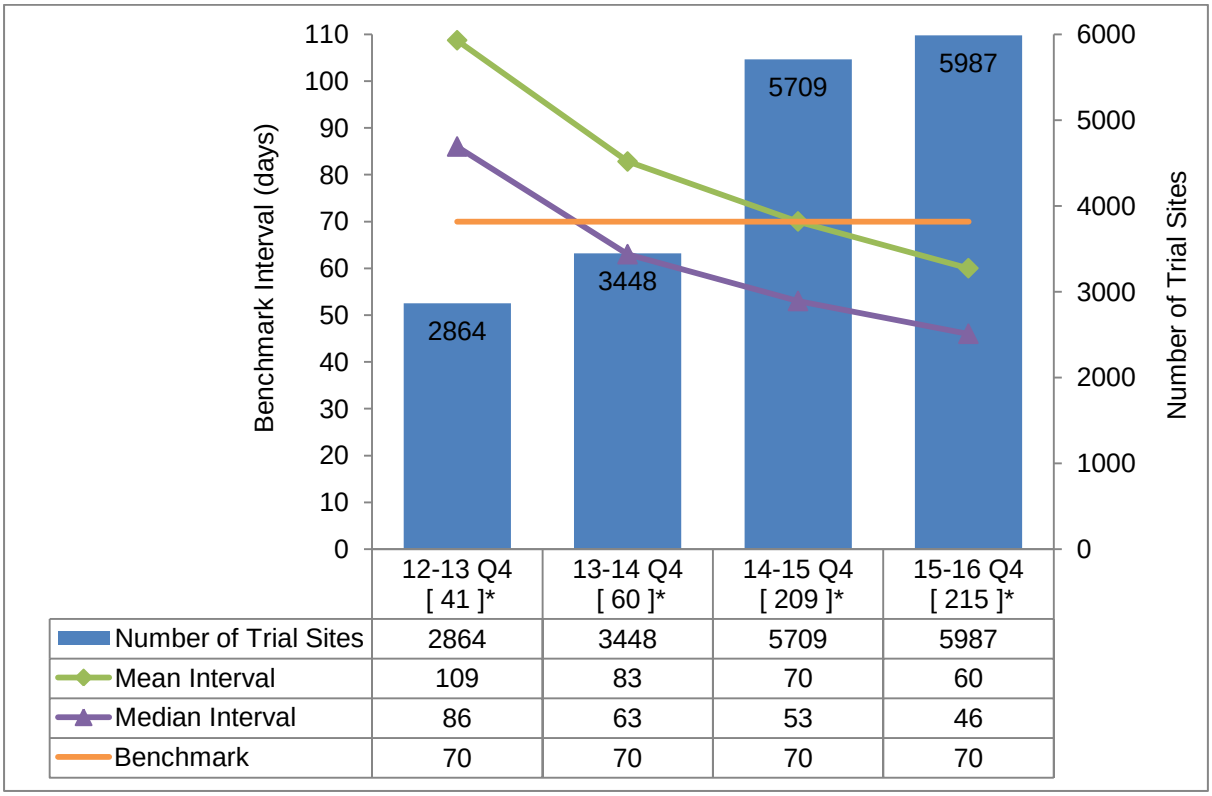
Figure 10. MHRA CTA assessment timeframes



5.4 Clinical trial performance of providers of NHS services

An NIHR '70-day benchmark' for clinical trial initiation in English NHS sites has driven reduction of NHS provider reported site setup times. The 70-day benchmark was measured from a valid research application at a site to the first patient recruitment at that site.

Figure 11. Performance in initiating clinical trials - trend in the average site interval for the 70-day benchmark



	12-13 Q4 [41]*	13-14 Q4 [60]*	14-15 Q4 [209]*	15-16 Q4 [215]*
Number of Trial Sites	2864	3448	5709	5987
Mean Interval	109	83	70	60
Median Interval	86	63	53	46
Benchmark	70	70	70	70

*Number of providers of NHS services (Trusts) submitting data.

Data was collected quarterly, but for a rolling 12 month period. Each provider of NHS services reported on each trial that it hosted. The number of providers subject to the requirement increased over time as new NIHR contracts were issued.

Further information is available on the NIHR website at: https://www.nihr.ac.uk/research-and-impact/nhs-research-performance/performance-in-initiating-and-delivering-research/

6 UK vs other European countries for industry-sponsored clinical trials by Phase

The ABPI publishes an R&D Sourcebook annually, which includes commissioned data from Cortellis Clinical Trials Intelligence from Clarivate Analytics on the position of the UK relative to its key competitors.

The following section presents comparative analysis of the number of commercial clinical trials starting in each year over a six year period, showing those in the UK and in each of a number of core EU comparator countries. Information is presented for each clinical trial Phase from Phase I to III.

6.1 Data Extraction Criteria

Data were collected from Cortellis Clinical Trials Intelligence from Clarivate Analytics™ [3] in July 2016 using the following criteria:

- Trial start date (1st January 2010 – 31st December 2015),
- Phase (I,II,III)
- Country (UK, Germany, France, Belgium, Spain, Poland, Czech Republic and Italy)
- Only trials related to pharmaceutical drug development and molecular/biological entities were included. Only commercial trials were included. Collaborative trials were only included if one or more partners was a commercial organisation.
- All therapeutic areas were included in this analysis.

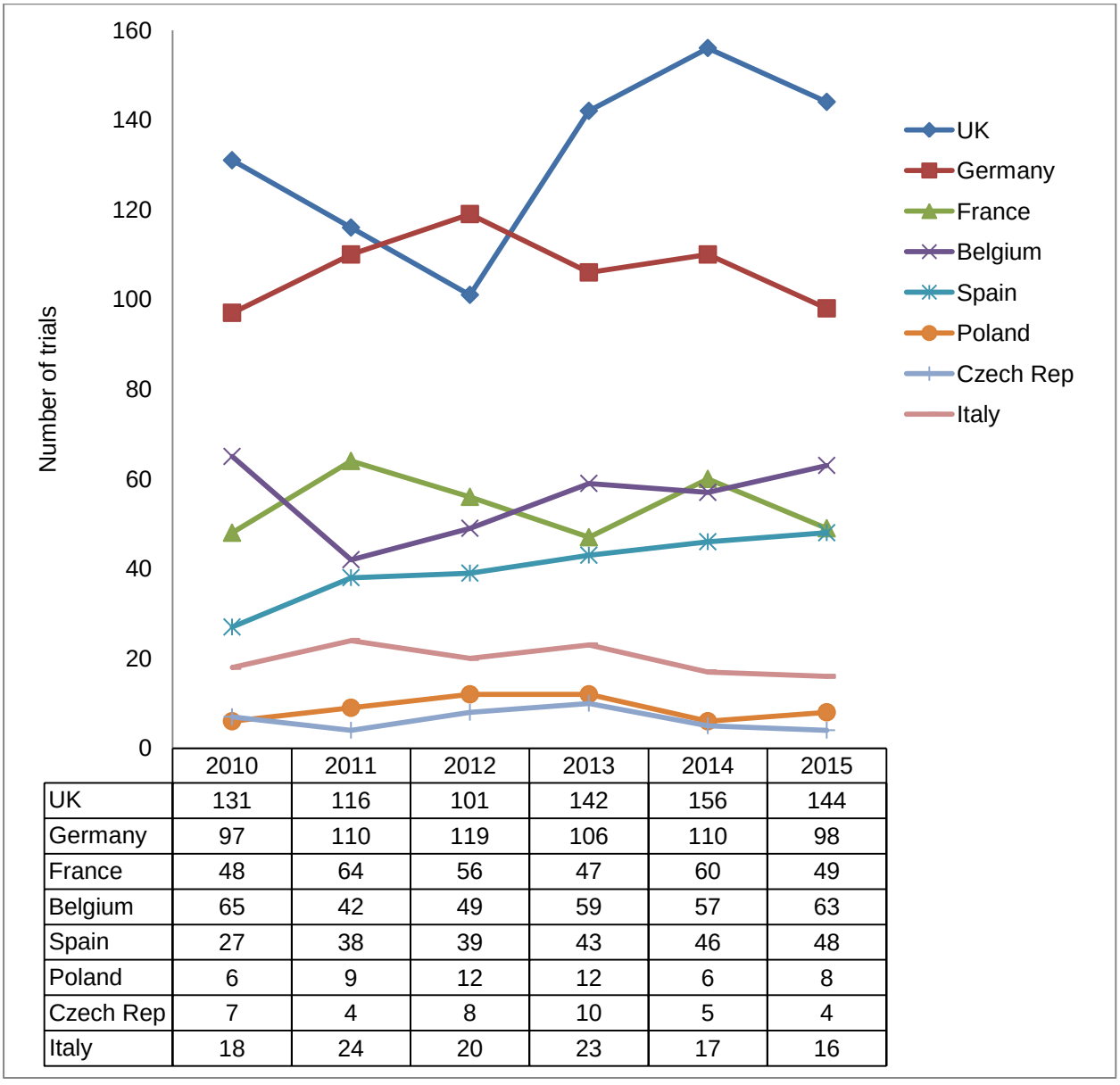
It should be noted that the data source is an active data repository and the exact comparisons may vary according to the state of the data when it is accessed.

[3] Clarivate and Clarivate Analytics are trademarks of the Clarivate Analytics group

6.2 Phase I industry-sponsored clinical trials starting in UK vs European comparator countries

The evidence for the number of trials for Phase I clinical research clearly shows the continued strong performance of the UK, relative to other EU countries including Germany. Although in 2015 both Germany and the UK show a decline from the 2014 performance as do France, Italy and the Czech Republic.

Figure 12. Phase I commercial clinical trials starting in the UK vs in Europe (selected countries)



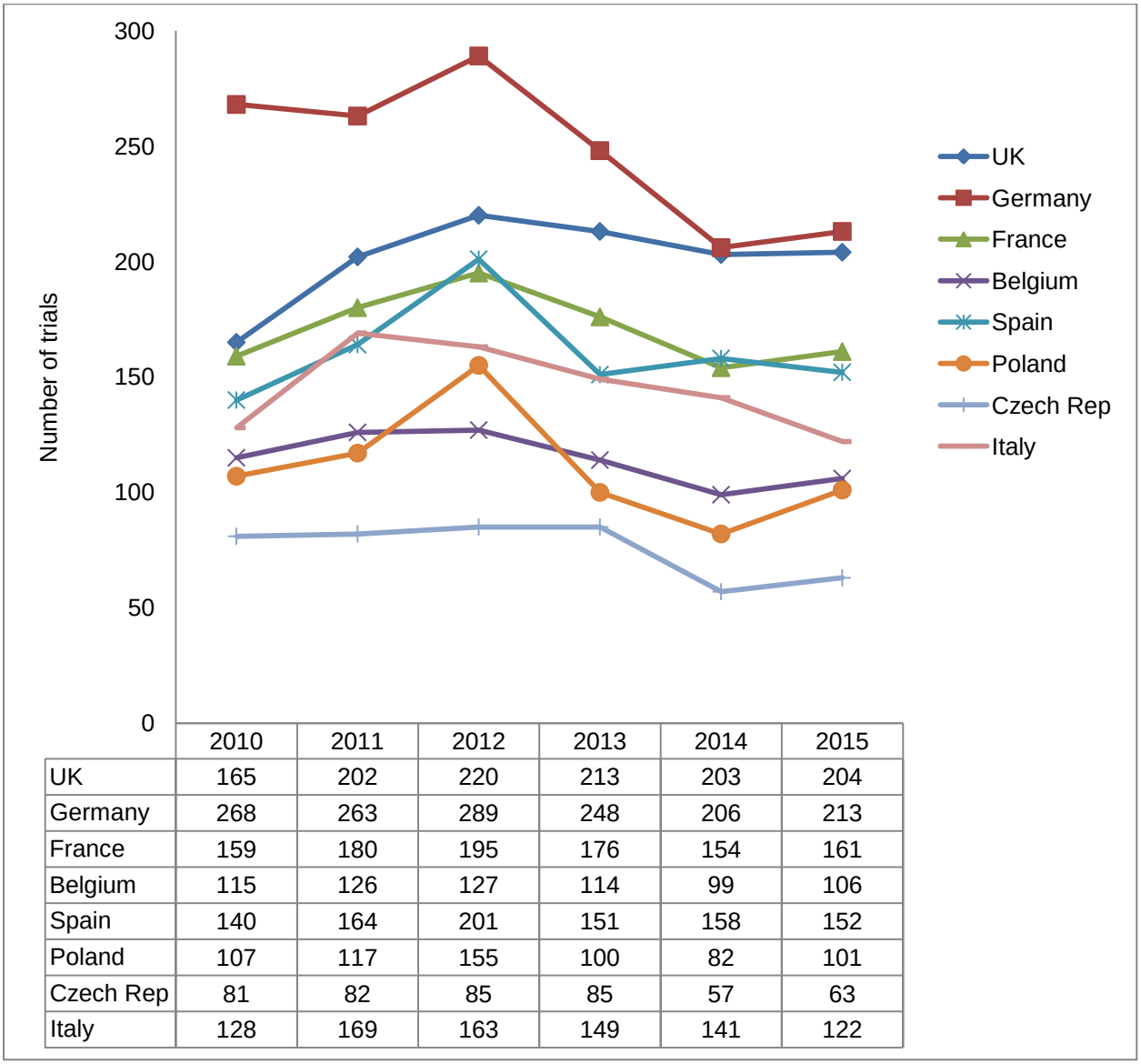
	2010	2011	2012	2013	2014	2015
UK	131	116	101	142	156	144
Germany	97	110	119	106	110	98
France	48	64	56	47	60	49
Belgium	65	42	49	59	57	63
Spain	27	38	39	43	46	48
Poland	6	9	12	12	6	8
Czech Rep	7	4	8	10	5	4
Italy	18	24	20	23	17	16

Source: Cortellis Clinical Trial Intelligence from Clarivate Analytics accessed in July 2016

6.3 Phase II clinical trials starting in UK vs European comparator countries

The UK is competitive for commercial Phase II clinical trials in Europe, according to the Clarivate Analytics Cortellis analysis. By 2015, the number of Phase II trials in the UK is roughly matched to that of the leading country, Germany (which has seen a decline in the number of Phase II clinical trials over the past few years).

Figure 13. Phase II commercial clinical trials starting in the UK vs in Europe (selected countries)



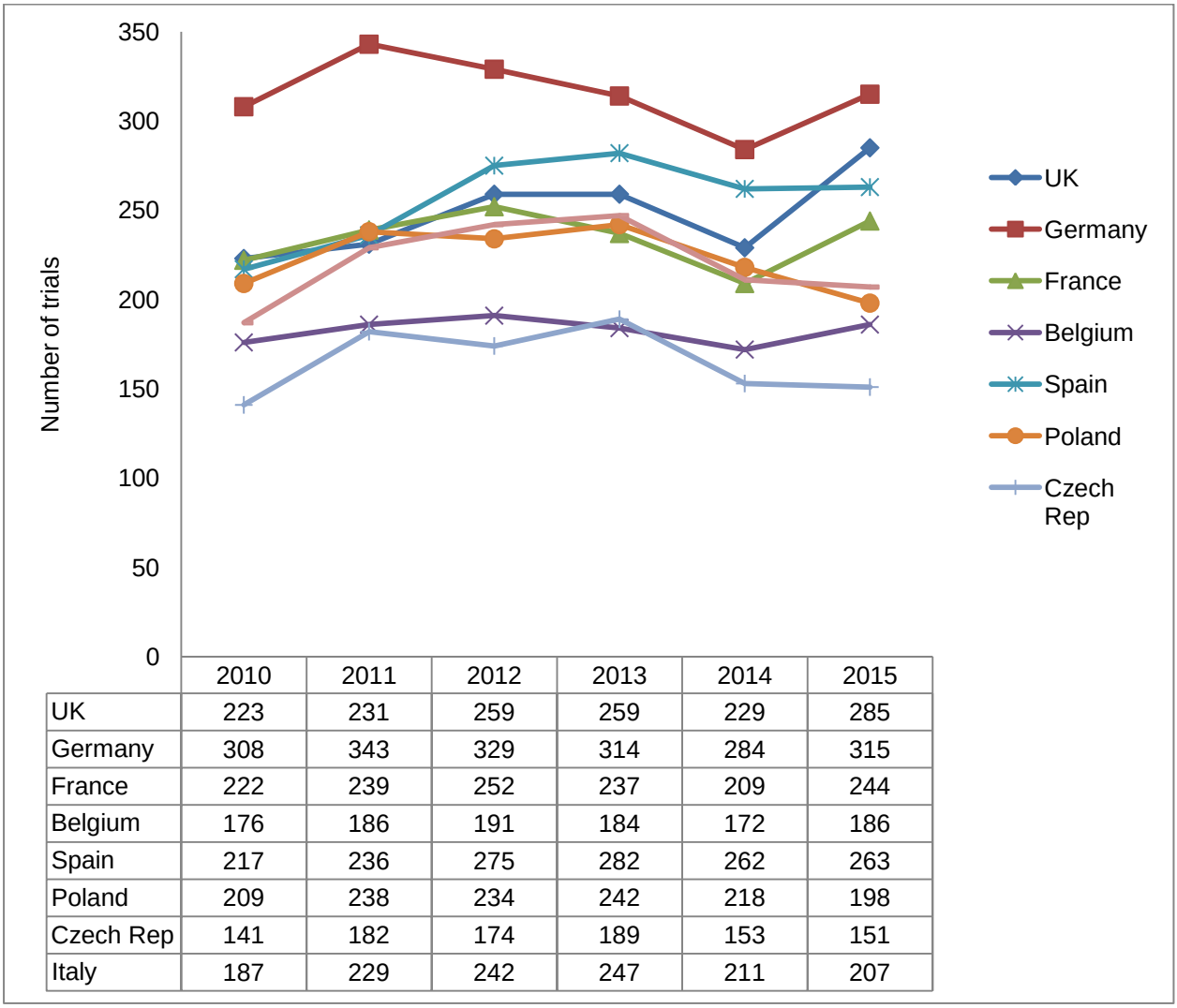
	2010	2011	2012	2013	2014	2015
UK	165	202	220	213	203	204
Germany	268	263	289	248	206	213
France	159	180	195	176	154	161
Belgium	115	126	127	114	99	106
Spain	140	164	201	151	158	152
Poland	107	117	155	100	82	101
Czech Rep	81	82	85	85	57	63
Italy	128	169	163	149	141	122

Source: Cortellis Clinical Trial Intelligence from Clarivate Analytics accessed in July 2016

6.4 Phase III clinical trials starting in UK vs European comparator countries

According to these data, the UK is continuing to demonstrate competitive performance in Europe for commercial Phase III trials and has even moved ahead of Spain this year. What is interesting about this evidence is that the decline, seen in 2014 for all compared countries in Europe, seems to have picked up in 2015. It will be essential over the next few years to monitor whether this is an isolated year or whether it is the beginning of an upward trend for Phase III clinical trials in Europe.

Figure 14. Phase III commercial clinical trials starting in the UK vs in Europe (selected countries)



	2010	2011	2012	2013	2014	2015
UK	223	231	259	259	229	285
Germany	308	343	329	314	284	315
France	222	239	252	237	209	244
Belgium	176	186	191	184	172	186
Spain	217	236	275	282	262	263
Poland	209	238	234	242	218	198
Czech Rep	141	182	174	189	153	151
Italy	187	229	242	247	211	207

Source: Cortellis Clinical Trial Intelligence from Clarivate Analytics accessed in July 2016

7 Conclusion

The various indicators assembled in this document present a promising picture of clinical trials in the UK:

- Clinical Trial Applications and clinical trials starting in the UK are maintaining a competitive aspect in relation to Europe
- NIHR support for clinical trials through both the Clinical Research Network and the translational infrastructure components continues to expand
- The speed of clinical trial initiation has improved and regulatory and NHS processes have been changed to facilitate further improvement
- The MISG CRWG continues to look for areas for further improvement to build on this current position and will continue to monitor progress.

8 Useful Resources

8.1 NIHR Clinical Research Network

www.supportmystudy.nihr.ac.uk

The NIHR CRN provides a range of services across the research pathway that will help study feasibility, setup and delivery to time and target for both commercial and non-commercial studies regardless of the location, study type, study size or therapy area.

Further information about the NIHR Clinical Research Network is available at:
https://www.nihr.ac.uk/about-us/how-we-are-managed/managing-centres/crn/

8.2 NIHR Office for Clinical Research Infrastructure

www.nocri.nihr.ac.uk

The NIHR Office for Clinical Research Infrastructure (NOCRI) simplifies access to the UK's clinical research infrastructure. This includes world-leading science, world-class facilities and expert investigators with access to well characterised groups of patients. For early phase clinical research, NOCRI provides connections to the country's experimental medicine experts who can help companies understand the potential of their developmental drugs, devices and diagnostics, shortening cycle times and enabling earlier go/no go decisions.

8.3 Open for Innovation - UK Biopharma R&D Sourcebook 2016

http://www.abpi.org.uk/our-work/library/industry/Pages/Open-for-Innovation-ABPI-Sourcebook-2016.aspx

The ABPI has published a UK Biopharma R&D Sourcebook 'Open for Innovation' that provides a picture of some of the key measures by which the global pharmaceutical industry develops medicines and the context in which this takes place. The data has been grouped in four sections: Global health and the role of biopharma, Investing in innovation, Driving clinical research to deliver medicines, and Collaborating for innovation.

8.4 MHRA Clinical Trial Authorisation information

Further information on the performance of Clinical Trials Authorisation is publicly available on Gov.uk. The latest report is available here:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/607294/01_Mar_2017.pdf

8.5 Health Research Authority and HRA Approval

Further information about the Health Research Authority is available on their website:
http://www.hra.nhs.uk/
If you would like to understand more about the process of HRA Approval, information is available online at:
http://www.hra.nhs.uk/about-the-hra/our-plans-and-projects/assessment-approval/

8.6 NIHR Clinical Trial Performance

Further information on the management of the performance of providers of NHS services in initiating and delivering clinical research is available at:
https://www.nihr.ac.uk/research-and-impact/nhs-research-performance/performance-in-initiating-and-delivering-research/