Rare Diseases Research Landscape Project Report

September 2023

Authored by the Rare Disease Research Landscape Steering Group

The Rare Disease Research Landscape Steering Group included members from:

- Department of Health & Social Care (DHSC)
- Medical Research Council (MRC)
- National Institute for Health and Care Research (NIHR)
- The Association of Medical Research Charities (AMRC)
- The Association of the British Pharmaceutical Industry (ABPI)
- The Bioindustry Association (BIA)
- LifeArc
- Genomics England
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Institute for Health and Care Excellence (NICE)
- Wellcome Sanger Institute
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- NHS England
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- Northern Ireland Executive
- Office for Rare Conditions Glasgow
- Scottish Government
- Welsh Government

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Executive summary

Pioneering research is an underpinning theme of the 2021 UK Rare Diseases Framework. In support of this theme, in England's 2022 Rare Diseases Action Plan we committed to map the rare disease research landscape to identify gaps and priorities for future funding. Here we present an overall picture of the rare disease research that was taking place across the UK in a 5-year period, from 2016-2021.

We developed a novel search protocol, based on Orphanet-derived search terms, which could be used to identify rare disease research. The limitations of this approach are discussed in the report, but development of the search protocol represented a major step forward in being able to define, identify and classify rare disease research. This protocol was used to search the:

- Medical Research Council (MRC) and National Institute for Health and Care Research (NIHR) research funding portfolios
- Cortellis Competitive Intelligence database (commissioned by the Association of the British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA) to represent organisations involved with the life sciences, pharmaceutical and biotech sectors across the UK)
- The Association of Medical Research Charities (AMRC) members' charitable expenditure portfolios

Information was also gathered from other significant funders of rare disease research and the devolved administrations.

Government, industry and charities all play a significant role in funding and supporting rare disease research. As two major government funders of research, funding for rare disease research accounted for 7% of the total number of awards, and 7% of the total value of award funding, of the overall NIHR Programmes and MRC joint research portfolio in the 5-year timeframe used for this project. This represents an investment of almost £627 million with nearly 700 awards. In addition, a considerable amount of support is provided to rare disease clinical research through investment in infrastructure (research expertise, specialist facilities and a research delivery workforce). MRC, a part of UK Research and Innovation (UKRI), provides funding to universities, research institutes, units and centres across the UK. NIHR supports research through infrastructure schemes such as Biomedical Research Centres and Clinical Research Facilities, as well as the Clinical Research Network in England. Through research supported by the NIHR Clinical Research Network, over 500,000 participants were recruited to take part in rare disease research studies that were open or active between 2016-2021.

There was almost £100 million invested into MRC fellowship and NIHR career development awards over the five-year timeframe, demonstrating the support provided to develop a skilled clinical research workforce with expertise in rare diseases.

When the NIHR programmes and MRC rare disease research portfolio was mapped against the priorities of the UK Rare Diseases Framework, much of the research was mapped against two of the priorities: 'ensuring patients get a final diagnosis faster' and 'improving access to specialist care, treatments and drugs', with far fewer studies on 'increasing awareness of health care professionals' and 'better coordination of care'.

The volume of rare disease research supported by charitable funding was highlighted in the report. Specifically, out of the 171 charities that were AMRC members over the timeframe of this project,

107 charities invested £580 million into over 2,300 rare disease research studies. This funding came from charities that focus on funding research into a specific rare disease, as well as significant funding investments from charities with a broader remit.

The industry research and development (R&D) projects on rare diseases in the UK demonstrated the support provided from industry into rare disease research. There were 254 industry supported rare disease research projects identified. Within these projects, there was an approximately equal split between the development of biologic and small molecule treatments. The greatest number of industry funded projects were at the pre-clinical stage of R&D.

The data in this report shows that there is a significant breadth and depth of rare disease research taking place at sites across the UK, across a range of specialisms. Much of the research is focused on furthering the understanding of the aetiology of rare diseases, pre-clinical work and clinical trials. There are a small number of rare conditions for which there is a large amount of research taking place, but also a large number of rare diseases for which no research was identified. Neurological conditions (including motor neurone disease) and respiratory conditions (namely cystic fibrosis) were among the rare diseases for which the greatest number of research awards were identified across the government, industry and charities portfolios.

The importance of collaborative funding between government, industry and charity was also evident. This included co-funding of specific awards, government funded infrastructure supporting industry or charity funded projects, and the rich research resource provided by charity funded registries and biobanks. International collaboration is of upmost importance for rare disease research. Many conditions are so rare that low patient numbers make transnational collaboration on research essential. Although collecting international data was beyond the scope of this project, consideration of these report findings in the context of the global rare disease research community is important.

Case studies have been used throughout the report to demonstrate the impact of the rare disease research funding identified. For example, the Deciphering Developmental Disorders (DDD) study and the 100,000 Genomes Project, both of which have provided significant advancements in the diagnosis of rare genetic diseases and created valuable resources for use in future research. The devolved administrations have active rare disease research communities across both clinical and non-clinical disciplines, the impact of which are demonstrated through case studies. Additionally, national rare disease registries have significant potential to support UK-wide population health surveillance, health service delivery, and data-driven research.

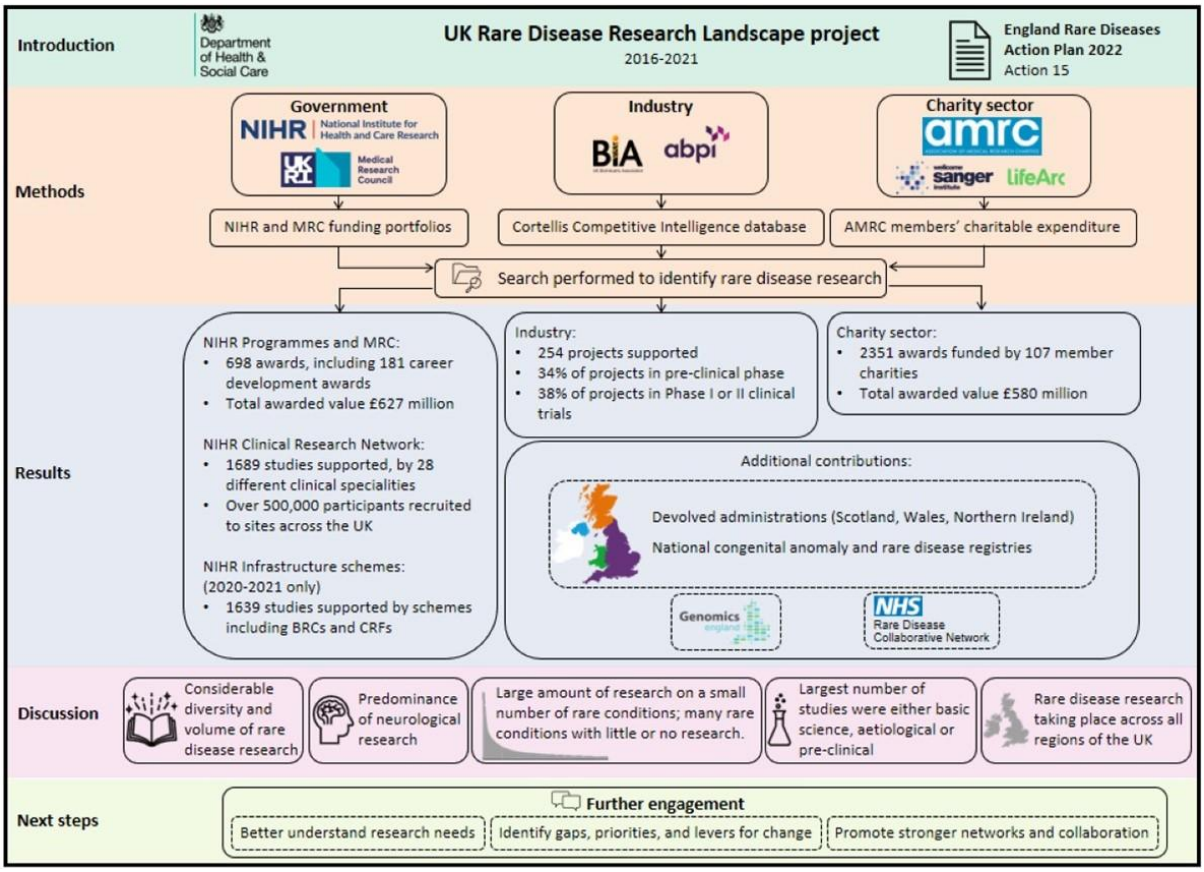
The report displays a significant investment in rare disease research, underpinned by a background of research excellence across the UK. This must be placed in the context of considerable unmet need, with around 95% of rare diseases lacking an effective treatment. The data presented allow questions to be asked about the focus of funding and whether targeted interventions from funders could help to further focus research towards the priorities and unmet needs of the rare diseases community. We intend to use this report as a basis for taking these discussions forward with the rare disease community over the coming year.

Since the collation of data for this report, two significant announcements of rare disease research funding have been made: the £14 million UK Rare Disease Research Platform, co-funded by MRC and NIHR, and the £40 million LifeArc Rare Disease Translational Challenge. These are significant strategic investments that will continue to build, shape and strengthen the rare disease research landscape across the UK. They will build on the diversity and volume of rare disease research

demonstrated in this report to deliver rare disease research with greater impact, and strengthen the UK's rare disease translational capabilities. This will reinforce the UK's position as a leader in global life science research and the ongoing efforts from the research community to improve the lives of those living with a rare disease.

Summary infographic

A summary infographic summarising the key contents of this report is below.



1 Introduction

1.1 The UK Rare Diseases Framework

A rare disease is defined as a disease or condition that affects fewer than 1 in 2,000 people within the general population. Although rare diseases are individually rare, they are collectively common. There are more than 7,000 rare diseases, and this number continues to grow as research advances. One in 17 people will be affected by a rare disease at some point in their lives, which equates to over 3.5 million people in the UK. Research has resulted in scientific advancements that have underpinned many breakthroughs for rare diseases, including improved understanding of causes, mechanisms, diagnosis and treatments to improve frontline clinical care. However, it remains that there is yet no approved treatment for approximately 95% of rare diseases. Due to the nature of rare disease patient cohorts, UK-wide and international collaboration in rare disease research is essential to facilitate progress.

The UK Rare Diseases Framework was published in 2021 and details four key priorities for addressing the challenges faced by people living with rare diseases: helping patients get a final diagnosis faster; increasing awareness of rare diseases among healthcare professionals; better coordination of care; and improving access to specialist care, treatments, and drugs. There are also five underpinning themes running throughout the Framework. Pioneering research is one of these themes and the reason why we undertook this project, to better understand the UK's rare diseases research landscape.

Each nation of the UK has published action plans setting out the steps that will be taken to deliver on the UK Rare Diseases Framework. This project originated as a commitment in England's 2022 Rare Diseases Action Plan to 'map the rare disease research landscape to identify gaps and priorities for future funding' (action 15).

This project is supported by commitments in Northern Ireland's Rare Diseases Action Plan 2022/23 (to "improve awareness of and participation in rare disease research"); Scotland's rare disease action plan (to improve "clinical research for rare diseases"); and Wales Rare Diseases Action Plan 2022 - 2026 (to "ensure access to research studies for rare diseases patients"). We took a UK-wide approach to increase understanding of the distribution and access opportunities of rare disease research across the country.

1.2 The need to identify rare disease research funding

The UK has strengths in rare disease research, which build on its world class research infrastructure and health system. The UK also has world-leading genetic and cohort studies, such as the NIHR BioResource, the UK Biobank, the Avon Longitudinal Study of Parents and Children (ALSPAC), the Born in Bradford study, and the 100,000 Genomes Project (see Section 4.2.3.8 below), all of which include individuals with both rare and common conditions.

With over 7000 rare diseases, it is important to understand the breadth and depth of research activity taking place. Prior to this project, there was not a clear overall picture of what rare disease research was taking place across the UK, where it was happening or who it was funded by. This project aimed to capture a detailed snapshot of research that was being funded across the UK on rare diseases. Herein, this is referred to as the rare disease research landscape.

The purpose of mapping the rare diseases research landscape was to understand the role of research in furthering knowledge, care and treatment of rare diseases, and to build the evidence base to support policy making and decisions around service provision. Through increasing the

baseline understanding of rare disease research that is currently funded, we plan to support the governmental and other funders' continued ambition to invest in pioneering research for rare diseases, and address gaps and priority areas.

1.3 Government funded health research in the UK

The government primarily funds health research through the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR). In addition to government funded research, industry, charities and other organisations provide significant amounts of funding for health research across the UK.

1.3.1 The Medical Research Council (MRC)

The Department for Science, Innovation and Technology sponsors UK Research and Innovation (UKRI), which comprises seven disciplinary research councils, Research England and Innovate UK. The Medical Research Council (MRC) is one of the seven disciplinary councils, and is the key funder of health research in UKRI. Therefore, out of all UKRI councils, only grant funding awarded through MRC was included this project. This project focused on almost all aspects of the MRC portfolio, including research project and programme (group of related projects) awards, funding provided to research institutes, units and centres, and fellowship awards.

The MRC supports research across the biomedical spectrum throughout the UK, from fundamental lab-based science to clinical trials, and in all major disease areas. UKRI has an annual budget of around £8 billion, within which the MRC core budget[1] is around £600 million. The MRC supports cutting-edge science and technology research, as well as training for the next generation of researchers. The MRC works closely with the NHS and the UK health departments to deliver their missions and prioritise research that is likely to make a real difference to clinical practice and the health of the population.

In addition to grant-supported research projects in universities, hospitals and other research organisations, the MRC also provides funding to research institutes, units and centres across the UK. These investments are mission-focused, very long-term, flexible and multidisciplinary. MRC units with a focus on, or with research programmes relevant to, rare diseases include the MRC Human Genetics Unit, the MRC Metabolic Diseases Unit, MRC Mitochondrial Biology Unit and the MRC Biostatistics Unit.

MRC funding is overseen by expert scientific boards and panels, one of which, the MRC Population and Systems Medicine Board has identified rare disease research as a priority. However, rare disease research can be supported through all MRC schemes.

The strategic ambitions of MRC, as part of UKRI, aim to accelerate discovery and translational research to generate impacts for all patients, as set out in the Life Sciences Vision. Additional strategic MRC investments include the MRC Mary Lyon Centre and the MRC National Mouse Genetics Network, which provide national support for the development and use of mouse models for preclinical studies of human diseases. And, in the area of advanced therapeutics, the Nucleic Acid Therapy Accelerator (NATA) and Innovation Hubs for Gene Therapies. There are also relevant UKRI investments for rare disease research outside of MRC, such as the Innovate UK Cell and Gene Therapy Catapult.

[1] *Excluding collective talent funding, across UKRI, of around £600-700 million annually*

1.3.2 The National Institute for Health and Care Research (NIHR)

The Department of Health and Social Care (DHSC) funds health research through the National Institute for Health and Care Research (NIHR). NIHR is the nation's largest funder of health and care research, spending over £1 billion from DHSC on research every year in England. NIHR works closely with devolved administrations in Scotland, Wales and Northern Ireland to co-fund research.

NIHR supports research on all elements of the 'innovation pathway' that involves human participants, from early experimental research into the translation of laboratory discoveries to the clinic; through to clinical research and development; and on to implementation and applied health and social care research. NIHR does not fund basic science or research involving animals.

Different parts of the NIHR portfolio were focused on in this project: NIHR research programmes, and NIHR infrastructure. NIHR research programmes fund defined projects, where funding can be directly attributed to a set of clearly defined research objectives. Here, the NIHR programmes analysis also includes NIHR Academy training and career development awards, which provide support for individual investigators and their teams. NIHR infrastructure invests in research expertise, specialist facilities, a research delivery workforce and support services which support and deliver research. NIHR infrastructure supports research funded by the NIHR itself through its programmes, but also research funded by other partners including UK Research and Innovation, medical research charities and industry. In this report, NIHR infrastructure is divided into two categories: NIHR infrastructure schemes and the NIHR Clinical Research Network (CRN). NIHR infrastructure schemes include the Biomedical Research Centres (BRCs), Clinical Research Facilities (CRFs), Medtech and In Vitro Diagnostics Co-operatives (MICs) and Applied Research Collaborations (ARCs). These are based in NHS Trusts across England. The NIHR Clinical Research Network (CRN) coordinates and supports the delivery of high-quality research across England (CRNs have been established in each of the four nations of the UK, and together the four national CRNs form the UK Clinical Research Network[2]). NIHR infrastructure funding is different to programme funding and cannot be apportioned to specific research projects individually. Therefore, the data set out below reflects the number of studies supported by NIHR Infrastructure, but not funding amounts.

1.4 Non-governmental rare disease research funding in the UK

The government primarily funds research on rare diseases via the MRC and NIHR. Therefore, the initial phase of this project focused on performing a detailed investigation of rare disease research funded by these two organisations. However, the rare disease research funding landscape also extends beyond these two funders, with industry, charities and other organisations playing a significant role in funding rare disease research across the UK. Therefore, alongside the quantitative analysis of the NIHR and MRC portfolio, we also sought to create a more complete picture of the UK-wide rare disease research landscape by gathering information from industry, charities and the devolved administrations.

[2] In England, the Clinical Research Network is funded by NIHR. In Northern Ireland, the Health and Social Care (HSC) R&D Office has established the Northern Ireland Clinical Research Network (NICRN). In Scotland, the Scottish Government Chief Scientist Office (CSO) has established five topic-specific clinical research networks in Scotland to complement the Primary Care and Cancer Networks which already existed. The clinical research infrastructure in Wales is provided by the Welsh Government through Health and Care Research Wales. The CRNs across the UK work collaboratively to ensure the success of studies across all four nations of the UK.

1.5 Aims of the rare disease research landscape project

This project aimed to better understand the current rare disease research landscape and provide an evidence base to support future policy-making decisions on rare diseases. In performing this work, we sought to:

- quantify and analyse the rare disease research landscape funded and supported by NIHR and MRC
- provide a quantitative summary of rare disease research funded by industry and charities
- describe the broader rare disease research landscape, including UK-wide funding
- increase visibility of rare diseases and rare disease research

Although research funding occurs on a continuous basis, it is only possible for a static report of this nature to analyse a fixed timeframe. Therefore, this report aimed to provide a snapshot of rare disease research funding that was awarded or active during a fixed five-year timeframe: from 1 April 2016 until 1 April 2021.

1.6 Future directions

This report concludes the first phase of our work on the UK rare diseases research landscape. We hope that the report, and the datasets published alongside it, will provide a starting point for productive discussions with the rare disease community. As a result of further engagement with stakeholders based upon the findings of this report (see Section 5.7 below for further detail), we will seek to:

- better understand the research needs of the rare disease community
- identify gaps, priorities, and levers for change for future rare disease research
- promote stronger networks and collaboration across the rare disease research community

2 Methods

This section details the governance structure established and methods used to collate the data presented in this report. To aid understanding, definitions of key terminology used throughout are first provided in Table 1 below.

Term	Definition
Rare disease research landscape	The research that was funded across the UK on rare diseases between April 2016 – March 2021
NIHR programmes and MRC rare disease research portfolio	The portfolio containing NIHR programmes and MRC funding for research on rare diseases, from April 2016 – March 2021, as was defined for this report.
NIHR infrastructure rare disease portfolios	The portfolios of NIHR funding that supports research expertise, specialist facilities and a research delivery workforce. This includes: Infrastructure studies supported in 2020/2021 through schemes including Biomedical Research Centres (BRCs), Clinical Research Facilities (CRFs), Medtech and In Vitro Diagnostics Co-operatives (MICs) and Applied Research Collaborations (ARCs). Clinical Research Network (CRN) supported studies, which were open to recruitment April 2016 – March 2021
Programme	A specific research activity, where funding can be directly attributed to a set of clearly defined research objectives.
Award	Funding that is allocated to a specific research programme or research infrastructure.

Table 1: Definition of key terminology used throughout the report.

2.1 Summary of method used in NIHR and MRC portfolio search

There were two main phases of the NIHR and MRC portfolio search: the search phase and the analysis phase. For the search phase, a bespoke search method and algorithm was developed. This aimed to identify research funding relevant to rare diseases in the entire NIHR and MRC portfolios. It is detailed in Annex 1 below and published on NIHR OpenData. A summary is provided here and depicted in Figure 1.

Data held on NIHR Programmes, the NIHR infrastructure schemes, and the NIHR Clinical Research Network (CRN) portfolio differed in format. Therefore, slightly differing approaches had to be taken to searching and analysing these data, the details of which are given in Section 3.6 below.

The selected timeframe for the MRC and NIHR portfolio search included awards that were awarded or active during the fixed five-year timeframe of 1 April 2016 until 1 April 2021. All awards active during this period were eligible for inclusion. Apart from for the data on NIHR infrastructure schemes that reflects a snapshot of active awards supported in the financial year 2020-2021 only.

The search phase involved free text searches of MRC and NIHR databases to identify awards with relevance to rare disease research. Firstly, all awards within the timeframe from the NIHR Programmes and MRC portfolios, including NIHR career development awards, were combined into a joint-funder list. A set of rare disease relevant terms (detailed in Annex 1.1) were used to search within this list to identify all rare disease awards that met the search criteria. The identified awards were then extracted to create an initial dataset, which was manually validated to create the final dataset.

The search algorithm was designed to identify awards mentioning specific rare disease names, as well as awards focused on rare diseases more broadly. Orphanet was used to derive a list of search terms for individual rare disease names. Certain extensions were made to the Orphanet list to account for issues such as alternative UK and US spellings. This list was combined with a curated list of search terms that were used to identify research relevant to rare diseases, that may or may not mention any individual rare disease names in the award description, such as research into groups of rare diseases or research into syndromes without a name. Prior to analysis, the outputs of the search algorithm were manually validated.

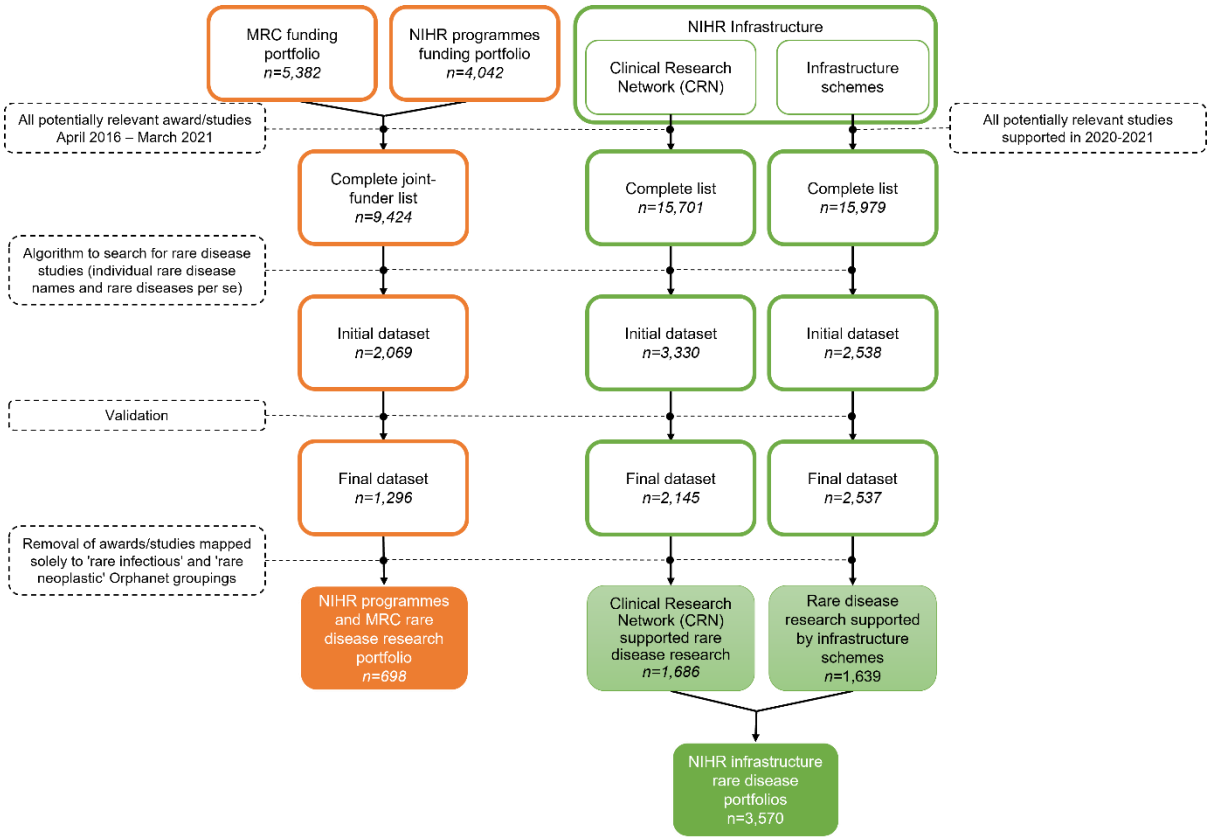


Figure 1: A flowchart summarising the steps taken in the MRC and NIHR portfolio search. Note: awards in the NIHR programmes and MRC rare disease research portfolio (orange in diagram) may have been supported by NIHR infrastructure (green in diagram). Therefore, these awards may appear in both the NIHR infrastructure rare disease portfolios, and the NIHR programmes and MRC rare disease research portfolio. Funding provided to awards through each of these portfolios is distinct.

The search phase was followed by the analysis phase, which aimed to quantify and characterise the rare disease research landscape funded and supported by NIHR and MRC within the five-year timeframe. The search results were analysed with a view to highlight key features of rare disease research funding and understand the variety of rare disease research. The following characteristics of the dataset were analysed:

- Total number of awards
- Total and average values of awards
- Orphanet disease name
- UK Clinical Research Collaboration Health Research Classification System health category (see Annex 1.7.1.1.1)

- UK Clinical Research Collaboration Health Research Classification System research activity codes (see Annex 1.7.1.1.2)
- Postcode data (the lead or contracted research organisation only)

As part of the analysis, we also aimed to map the NIHR programmes and MRC rare disease research portfolio against the priorities of the UK Rare Diseases Framework. Further details of the approach taken to do this are described in Annex 1.7.3.

2.1.1 Rare neoplastic diseases and rare infectious diseases

Rare cancers and rare infectious diseases are two groups of diseases that fall outside of the remit of the UK Rare Diseases Framework, and so were not included in the detailed analysis phase of this project. A large amount of research is funded on rare cancers and infectious disease and their inclusion would also have made it difficult to see patterns in the wider data set. Although we have not analysed these data for this report, the whole dataset, including rare cancers and rare infectious diseases has been made available alongside this report (see Section 2.4 below). Therefore, it would be possible for interested parties to analyse these data independently.

Orphanet groupings were used to remove rare neoplastic and rare infectious diseases from the data set. After removal of these awards, the portfolio contained 698 awards. Herein, the analysed portfolio, that did not include awards mapped solely to the rare neoplastic and rare infectious awards Orphanet groupings, is referred to as the NIHR programmes and MRC rare disease research portfolio. Further detail of the approach taken is given in Annex 1.6.

2.2 Methods used to provide information on other research funding

As part of this project, it was also important to engage with organisations that are involved with rare disease research beyond MRC and NIHR. Therefore, several organisations were approached for involvement in this project, many of whom were able to provide contributions (Figure 2). Contributions were received from the devolved administrations in Scotland, Wales and Northern Ireland; the Association of The British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA); the Association of Medical Research Charities (AMRC); the Wellcome Sanger Institute; LifeArc; and Genomics England. The contributions provided included: a quantitative analysis of charitable rare disease research based upon the search protocol; a quantitative analysis of the industry supported rare disease research and development (R&D) pipeline; narrative summaries; case studies.

Further detail of the quantitative approach taken by the ABPI and BIA, and the AMRC are detailed in Annex 2.2 below. The AMRC were able to adapt and use the search protocol the Project Group developed for the MRC and NIHR portfolio search (detailed in Annex 1) to generate a charity-funded rare disease research portfolio. The ABPI and BIA jointly commissioned a search of the Cortellis Competitive Intelligence database, which used the same principles as the Project Group's protocol, to extract industry R&D projects on rare diseases in the UK.

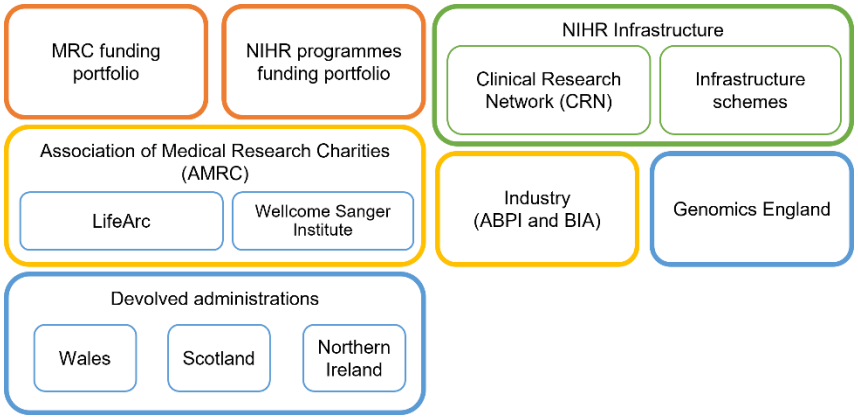


Figure 2: A diagram representing the different organisations that were included in this project. The different box outline colours represent the different approaches taken to searching and analysis of the portfolios. Orange, green and yellow represent quantitative approaches, and blue represents a qualitative approach taken.

2.3 Governance

The governance structure established to deliver this project included three groups: the project, expert and Steering Groups.

The Project Group was composed of representatives from the Department of Health and Social Care (DHSC), the National Institute for Health and Care Research (NIHR) and the Medical Research Council (MRC). This group was responsible for the design and delivery of the project, establishing the search protocol, performing database searches, overseeing the validation and analysis of the search results, and preparing this report.

The Expert Group was composed of rare disease and research systems experts, including researchers and clinicians active in rare disease research with a strong understanding of research systems, and system leaders from NIHR and MRC. This group informed and advised on the practical parameters of the project, including definitions and scope. Members of this group also played a vital role in the validation and analysis of the NIHR and MRC rare disease research portfolios.

The Steering Group was composed of representatives from research funders, commissioners and end users of rare disease research, as well as representatives of the rare disease community. This group shaped the direction of the project and helped identify the output that would be most valuable to research funders. This group co-created and signed off this report for publication and are jointly considered its authors.

The membership of these three governance groups is listed in Annex 3.

2.4 Data availability

The data that underpins the analyses presented in this report have been made available via NIHR OpenData, unless stated otherwise in the relevant methods section. It is important to note that for datasets 1, 2 and 4, a 6-year period (from 1 April 2016 – 1 April 2022) has been published, however, only a 5-year period (from 1 April 2016 – 1 April 2021) of these data was analysed in this report, unless stated otherwise. The following datasets are available to view and download:

- Dataset 1: NIHR Programmes & MRC rare diseases research portfolio
- Dataset 2: NIHR Programmes & MRC rare diseases research portfolio, including awards assigned to the 'rare neoplastic diseases' and 'rare infectious diseases' Orphanet groupings, which were not analysed as part of the report.
- Dataset 3: NIHR infrastructure schemes supported studies

- Dataset 4: NIHR Clinical Research Network supported studies
- Dataset 5: Industry research and development (R&D) projects on rare diseases in the UK
- Dataset 6: LifeArc rare disease research portfolio

3 Results from the MRC and NIHR portfolio search

3.1 Overview of the NIHR programmes and MRC rare disease research portfolio

Together the NIHR programmes and MRC rare disease research portfolio (available as Dataset 1 via NIHR OpenData) comprised 698 awards within a five-year snapshot. The total awarded value of these awards was almost £627 million, equating to approximately £125 million annually. Of all MRC and NIHR awards within the timeframe, the rare disease research portfolio accounted for around 7% of the total number of awards and 7% of the total value of award funding[3]. Within the rare disease research portfolio, the mean value of an award was £898,163 and the median was £427,220.

The identified awards corresponded to 689 search terms from the 'individual rare disease names' list (Annex 1.1.1) and matches to 38 search terms from the 'rare diseases per se' list (Annex 1.1.2). The portfolio is analysed by several features below, such as UK Clinical Research Collaboration Health Research Classification System (HRCS) health category (Annex 1.7.1.1.1), HRCS research activity code (Annex 1.7.1.1.2) and geographical distribution (Annex 1.7.2).

Table 2 below shows the breakdown of research by funder, including number and total value of awards. Due to differences in how database records are held by funders, these figures include large grants from MRC to support Units, but do not include awards in the NIHR infrastructure rare disease portfolios (described separately in Section 3.6 below). Therefore, these data reflect only a subsection of NIHR's total funding and support of rare disease research.

Funder	Number of awards	Total value of awards
MRC	425	£472,772,226
NIHR Programmes	273	£154,145,849
Total	**698**	**£626,918,074**

Table 2: Breakdown of the combined rare disease research portfolio by funder. Award value is the total award budget over the lifetime of the award, for awards active between April 2016 and March 2021 including award years before and after those dates if awards were active before or after. Includes MRC Fellowships, Institutes, P&Cs, Research Grants and Units, and NIHR Research Programmes and Career Development. Excludes NIHR's global health research programmes, ESP Infrastructure (Cochrane Groups), and NIHR Infrastructure.

3.1.1 Career development awards

The NIHR programmes and MRC rare disease research portfolio included 181 career development awards to support the development of a skilled clinical research workforce with expertise in rare diseases. When NIHR Programmes and MRC data were aggregated, the total value of these career development awards was over £99 million with a mean value of £551,027, and a median of £309,129. Career development awards accounted for 26% of the total number of awards, and 16% of the total value of awards, in the NIHR programmes and MRC rare disease research portfolio.

Table 3 below shows the number of career development awards, and value, including the average values of awards.

[3] *Total award number was 10,734 and total award value was just over £10 billion.*

Type of award	Number of awards	Value of awards
MRC Fellowship	103	£54,337,753
NIHR Career Development	78	£45,398,101
Total	181	£99,735,854

Table 3: Breakdown of the career development awards included in rare disease research portfolio. Award value is the total award budget over the lifetime of the award, for awards active between April 2016 and March 2021 including award years before and after those dates if awards were active before or after. Includes MRC Fellowships and NIHR Career Development awards. Does not include NIHR's global health research professorships.

3.2 The NIHR programmes and MRC rare disease research portfolio presented by Orphanet disease names

Figure 3 shows the 30 Orphanet disease names that had the highest number of awards within the rare disease research portfolio associated with them. It was possible for a single award to be identified by more than one rare disease search term, and therefore possible for a single award to appear under more than one category in Figure 3 below (see Annex 1.6 for detailed explanation).

These data show that amyotrophic lateral sclerosis (ALS) was associated with the highest number of awards in the portfolio (n=44), followed by Huntington's disease (n=35), motor neuron disease (MND) (n=32), preeclampsia (n=32), cystic fibrosis (n=30), and frontotemporal dementia (n=28).

ALS is the most common type of MND, however ALS and MND were listed as separate search terms (see Annex 1.1), and so awards mapped to each of these search terms are listed independently in Figure 3. Accounting for this overlap, a total of 53 awards were linked to ALS, MND or both, which is around 8% of the portfolio, by number of awards. Since only 22 of these awards mapped to both search terms, these search terms cannot be treated entirely as synonyms, as the use of either phrase alone would have led to the omission of relevant awards. Importantly, when the portfolio is analysed by award (e.g., in Sections 3.1, 3.3 and 3.4), the awards that appeared in more than one category here are not double counted.

Awards linked to Huntington disease and preeclampsia each comprised around 5% of the portfolio, and cystic fibrosis and frontotemporal dementia each comprised approximately 4% of the portfolio. The predominance of neurological conditions seen in Figure 3 is consistent with the large proportion of awards on neurological research shown in Figure 4 below. Whilst these data are one helpful way of understanding the portfolio, it must also be noted there are several caveats in using Orphanet in this way. Firstly, some conditions, such as preeclampsia, are included although they have a prevalence of above 1 in 2000 in the general UK population. Secondly Orphanet disease names include both broader and specific diseases as separate entities, such as 'Muscular Dystrophy' and 'Duchenne Muscular Dystrophy'.

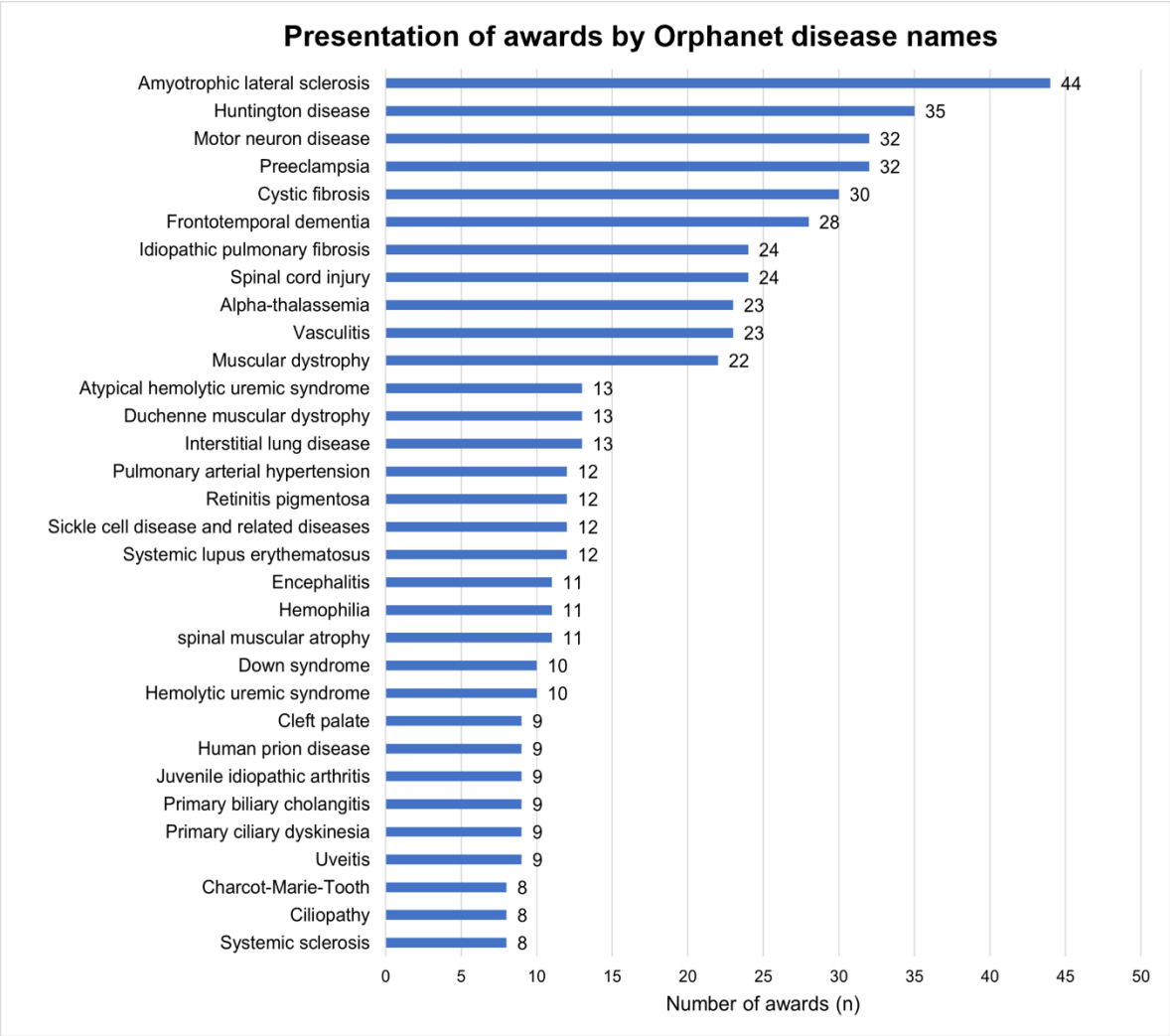


Figure 3: The 30 Orphanet disease names associated with the highest number of awards in the rare disease research portfolio. Includes awards active between April 2016 and March 2021. To note: does not include awards mapped to rare infectious disease and rare neoplastic disease Orphanet groupings.

Awards in the NIHR programmes and MRC rare disease research portfolio were associated with just 362 different rare disease names listed in Orphanet. Of the rare disease names listed in Orphanet that had research associated with them, most were only associated with between one and three awards within the NIHR Programmes and MRC rare disease research portfolio (n = 287). Only 75 rare disease names listed in Orphanet were associated with four or more awards in the NIHR Programmes and MRC rare disease research portfolio. Most rare diseases listed in Orphanet had zero awards associated with them in the NIHR Programmes and MRC rare disease research portfolio (n = 9,278). However, it must be noted that the total number of Orphanet listed disease names includes those in the rare neoplastic diseases and rare infectious diseases groupings, which were not included in the NIHR Programmes and MRC rare disease research portfolio. Table 4 shows the breakdown of the number of awards associated with different rare disease names listed in Orphanet.

Number of Awards	Count of Orphanet Diseases
0	9,278
1	186
2 to 3	101
4 to 5	34
6 to 9	18
10 or more	23
Total	9640

Table 4: The number of awards associated with each Orphanet disease name searched for. Includes awards active between April 2016 and March 2021 matched to at least one or more individual rare diseases (n=1,823). To note: includes diseases listed under all Orphanet Groupings including rare neoplastic diseases and rare infectious diseases.

3.3 The NIHR programmes and MRC rare disease research portfolio analysed using the Health Research Classification System (HRCS)

Collectively, the databases searched contained awards that fund or support research across a wide range of disciplines, including:

- basic and discovery science; cell and animal models; experimental medicine in rare diseases (e.g., mechanistic studies in human participants); functional genomics
- preventative and treatment interventions, identification and screening programmes
- diagnostic testing, identification of clinical thresholds and care pathways for rare diseases
- data science and bioinformatics
- methodology, research design
- health and care services, organization and workforce issues, including leadership and training
- infrastructure

As detailed in Annex 1.7.1.1, the Health Research Classification System (HRCS), consisting of health category and research activity classifications, provides a common language across funders to capture and analyse the focus and type of research that is funded. The NIHR programmes and MRC rare disease research portfolio was analysed by both the health categories and research activities that awards within this portfolio were coded to.

HRCS health categories capture the area of health or disease being studied. Figure 4 shows the total number of awards, and corresponding total funding value, of the awards within the NIHR programmes and MRC rare disease research portfolio distributed by HRCS health category. These data show that awards within the NIHR programmes and MRC rare disease research portfolio cut across all 21 health categories. Some rare diseases fall under more than one health category; an individual award can be assigned to up to 5 HRCS health categories, with the assignment apportioned.

Within the rare disease research portfolio, the neurological category had the largest proportion of awards (n=178) and the largest apportioned funding value (just over £222 million) assigned. The congenital disorders category had the second largest proportion of awards (n= 56) and the fourth largest apportioned value (over £36 million). The health categories with the lowest proportion of awards within the rare disease research portfolio associated with them were stroke (n=2), 'disputed aetiology and other' (n=2) and ear (n=1).

The HRCS system is an established cross-funder basis for classifying research. This is distinct, and therefore not directly comparable to Orphanet grouping classification, which has a different foundation and serves a different purpose. In this project, Orphanet groupings were used to identify

and remove rare neoplastic and infectious disease awards from the analysed portfolio. However, a small number of studies remain that were classified as 'cancer and neoplasms' or as 'infection' using the HRCS system, but not assigned to either of the Orphanet groupings that were removed. This could be due to intricacies of the HRCS system, where some diseases are categorised to multiple Health Categories. This must be considered when interpreting data shown both Figure 4 and Figure 5.

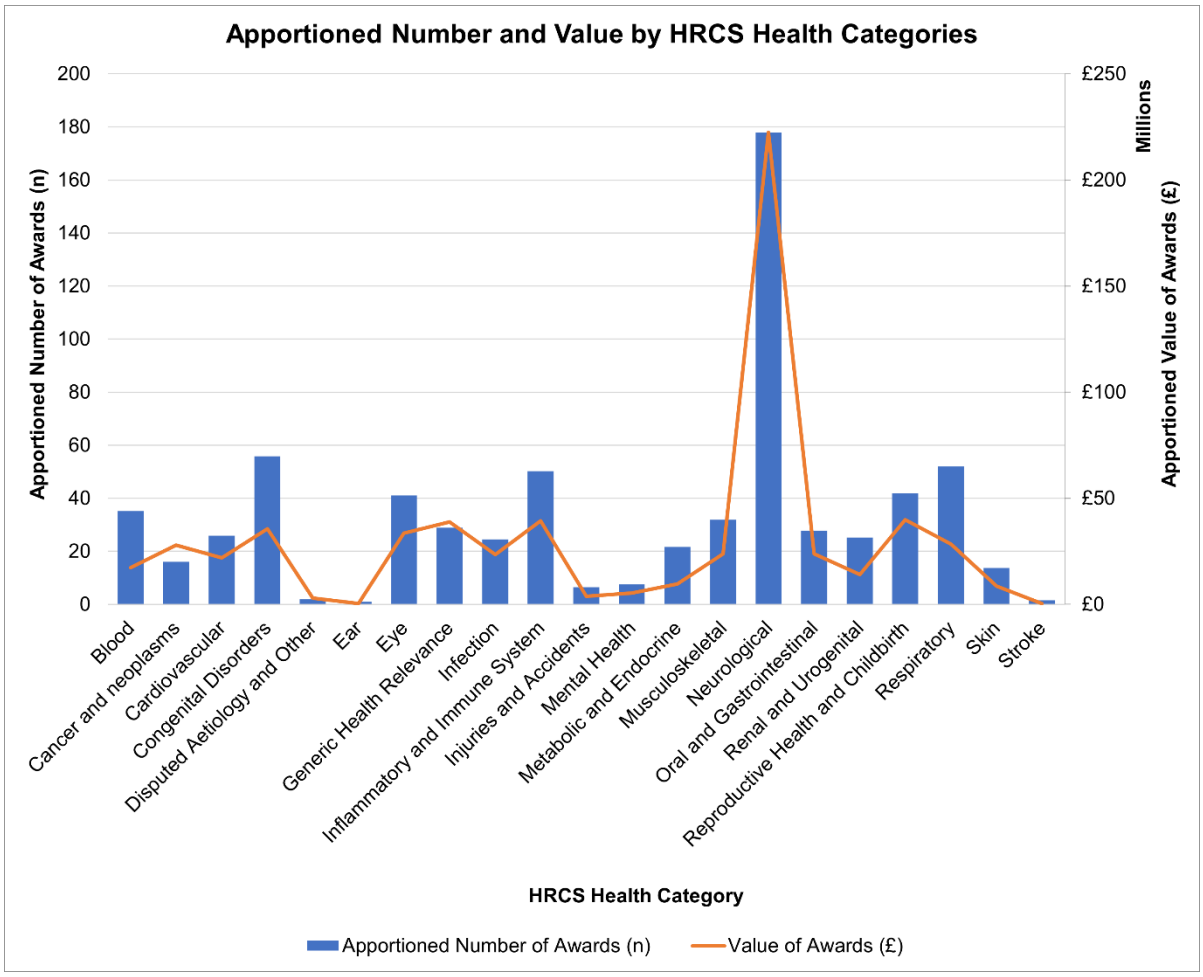


Figure 4: The number and value of awards active between April 2016 and March 2021 by HRCS Health Category for the rare disease research portfolio, where HRCS categorisation has been applied (n=688 awards). A small proportion (n=10) awards in the portfolio are uncoded (n=3 awaiting coding, n=7 uncodeable). A small number of studies on cancer and neoplasms and infection are present owing to differences between the Orphanet and HRCS coding systems. Had Orphanet disease names not been used to remove the majority of these studies, the dataset would have been dominated by the cancer and neoplasms and infection categories.

HRCS Research Activity Codes (RAC) capture the type of research taking place. Figure 5 shows how awards within the NIHR programmes and MRC rare disease research portfolio are distributed across the eight overarching groups of RACs. These data show that the research within the portfolio covers all eight of the overarching groups of RACs. Aetiology has is the largest proportion (n=234) with the highest apportioned value (over £255 million). Evaluation of treatments and therapeutic interventions is the second largest proportion (n=189) and the second largest apportioned value (over £123 million). Prevention of disease and conditions is the lowest proportion (n=11) and the lowest apportioned value (just over £8 million).

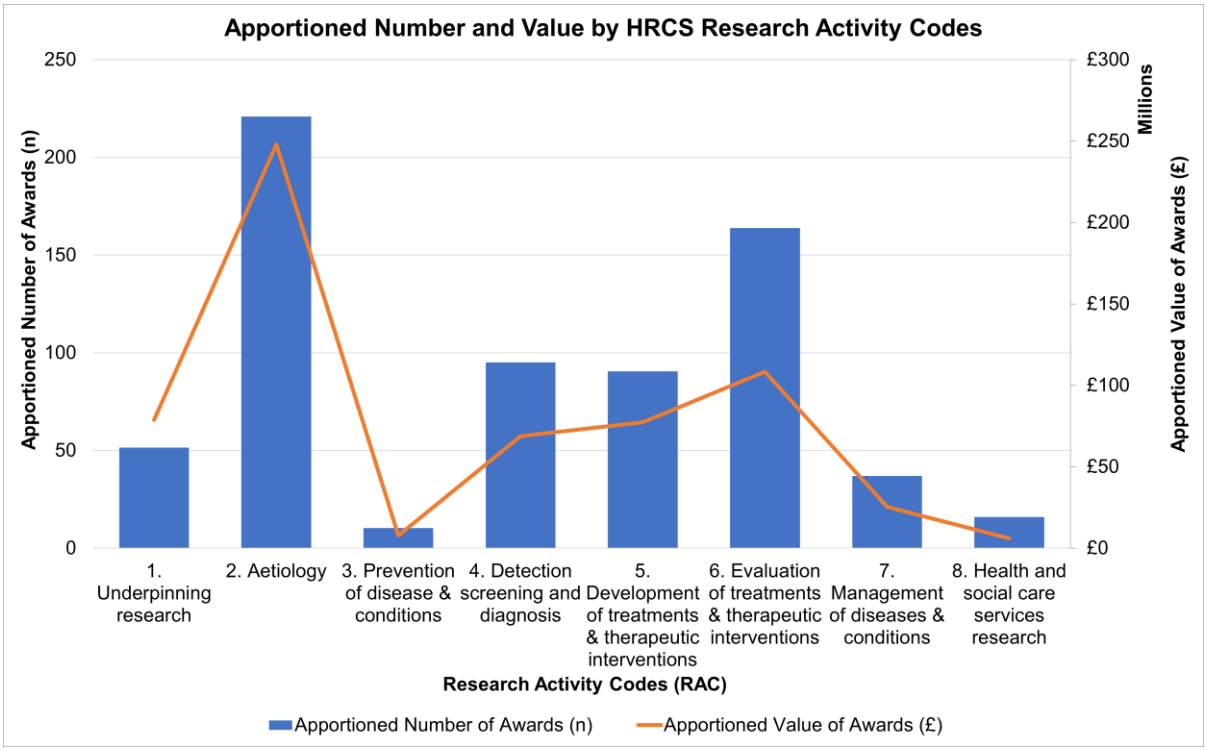


Figure 5: The number and value of awards active between April 2016 and March 2021 by HRCS Research Activity Code (RAC) for the rare disease research portfolio, where HRCS coding has been applied (n=685 awards). A small proportion (n=13) awards in the combined portfolio are uncoded (n=3 awaiting coding, n=10 uncodeable) and are not included in the above chart.

A detailed breakdown of the rare disease research portfolio by the full list of 48 Research Activity Codes is provided in Annex 6.1. These data show that the rare disease research portfolio includes research across 46 of the 48 codes. The highest proportion of awards in the portfolio were coded as biological and endogenous factors (RAC 2.1; n=198). The pharmaceuticals code (RAC 6.1; n=103) accounts for the second highest proportion of awards in the portfolio. There were no awards in the portfolio that were assigned to either the 'complementary' code (RAC 5.8) or the 'policy, ethics and research governance' code (RAC 8.3), and therefore these codes are not shown in Annex 6.1.

3.4 Geographical distribution of awards within the rare disease research portfolio

The NIHR programmes and MRC rare disease research portfolio included postcode data for the lead or contracted research organisation for each award. These data were used to aggregate the total number and value of NIHR Programmes and MRC awards that were led by or contracted to research organisations within each region of England and devolved administrations. Figure 6 shows a map of these data as percentages of the portfolio totals, by award number (Figure 6, left) and award value (Figure 6, right). This shows that the NIHR programmes and MRC rare disease research portfolio consisted of awards led by, or contracted to, research organisations across all regions of England, as well as Scotland, Wales and Northern Ireland. Most awards were led by, or contracted to, research organisations within England, with the greatest number of research awards led by or contracted to organisations in London (35.8%). These research organisations included University College London, King's College London, Imperial College London, Guy's and St Thomas' NHS Foundation Trust, and Great Ormond Street Hospital for Children NHS Foundation Trust.

The second greatest number of research awards were led by or contracted to organisations in the South East (13.5%), such as the University of Oxford and the University of Cambridge. This was closely followed by Yorkshire and the Humber (11.6%), which included the University of Sheffield,

The University of York and the University of Leeds. Research organisations located in Wales (1.6%) and Northern Ireland (0.9%) led or contracted the lowest number of awards active in the period. When the award values are analysed, the greatest total value of research award funding was to awards led by or contracted to organisations in London (£282 million). The second greatest value of research awards were led by or contracted to organisations in the Southeast (£97 million), and third highest value is East of England (£62 million). Research organisations located in Wales (£9 million) and Northern Ireland (£2 million) had the lowest total value of funding for lead or contracted awards active in the NIHR programmes and MRC rare disease research portfolio.

Out of the 181 career development awards contained within the NIHR Programmes and MRC Rare Disease Research portfolio (Section 3.1 above), 75 of these awards were led or contacted by research organisations in London. Research organisations in the South East, Yorkshire and The Humber, East and North West led or contracted 25, 15, 13 and 12 career development awards respectively. There were only 5 career development awards led or contracted by research organisations in Scotland, and 1 career development award led or contracted by a research organisation in Wales. There were no career development awards in this portfolio led or contracted by research organisations in Northern Ireland. The geographical distribution of the NIHR Programmes and MRC rare disease research career development awards is largely reflective of the overall geographical distribution of awards in this portfolio. Collecting data on career development awards funded in the devolved administrations was beyond the scope of this project.

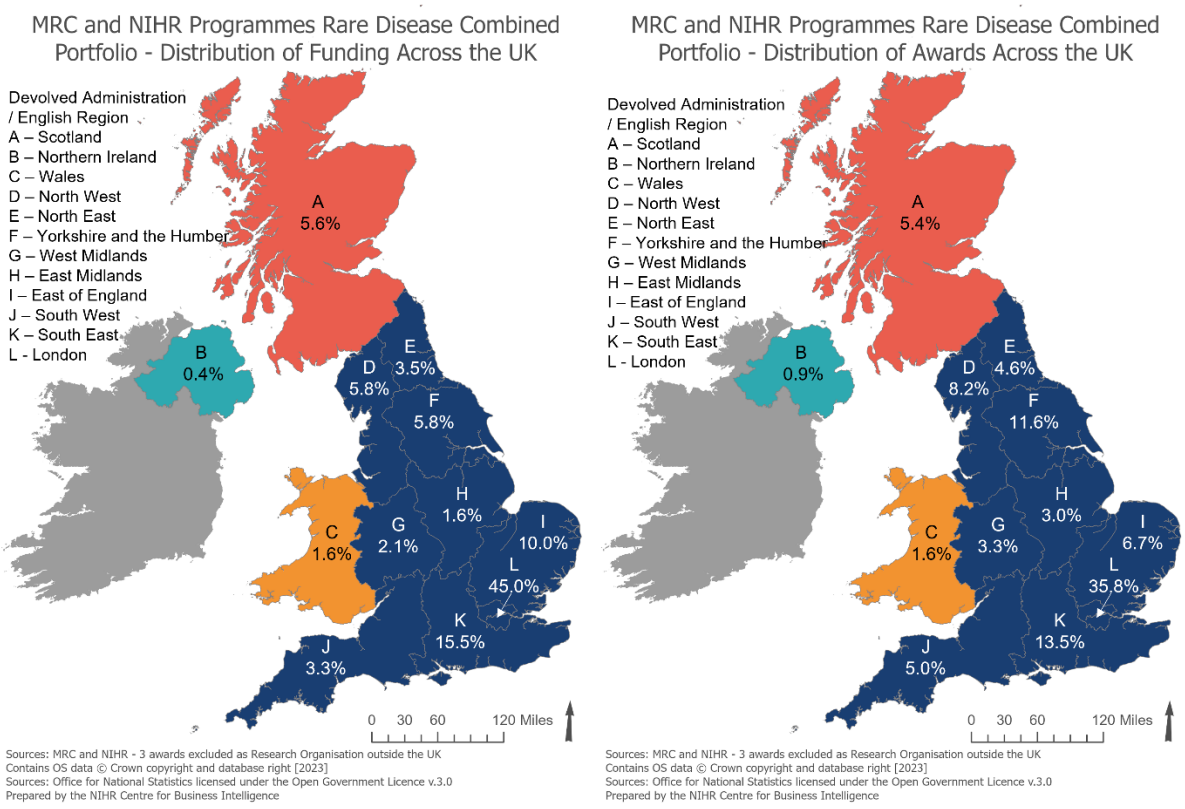


Figure 6: Map showing the number (A) and value (B) of NIHR Programmes and MRC research awards active between 2016-2021 by English region/devolved nation based on the lead research organisation the award was awarded to.

In the NIHR programmes and MRC rare disease research portfolio, there were also three awards led by or contracted to organisations outside of the UK[4] (not shown in Figure 6).

These data only reflect the lead or contracted research organisation for each award in the portfolio. Particularly for rare disease research, many programmes are undertaken collaboratively across different organisations, and participants involved in clinical studies are often widely dispersed geographically. Therefore, the lead or contracted organisations may not reflect the physical location(s) of where research in the NIHR programmes and MRC rare disease research portfolio was undertaken (see Section 3.6.2.2 for information on participant recruitment).

3.5 Mapping of awards within the NIHR programmes and MRC rare disease research portfolio to the UK Rare Diseases Framework

The 2021 UK Rare Diseases Framework lists four key priorities: helping patients get a final diagnosis faster; increasing awareness of rare diseases among healthcare professionals; better coordination of care; and improving access to specialist care, treatments, and drugs. To better understand how research funded by MRC and NIHR might contribute to advancing these priority areas, experts were asked to manually assign each award to at least one of six categories: the four priority areas, basic science research, or 'no priority' (definitions detailed in Annex 5). These assignments were therefore based primarily on experts' own knowledge and experience, and their interpretation of the definitions provided.

To get a broader picture for this analysis, an extra year of funded research programmes was included, so the period ran for six years from April 2016 until April 2022. All 787 awards in this extended NIHR programmes and MRC rare disease research portfolio were reviewed. Table 5 shows the number of awards assigned to each of the six categories. It must be noted that as awards were assigned to at least one category, several awards were mapped to more than one of the six categories. As a result, the total number of awards in Table 5 exceeds 787.

Basic science research had the largest number of awards assigned (n=358), followed by priority 4 ('improved access to specialist care, treatment and drugs') (n=319). Priority 3 ('better coordination of care') had the lowest number of awards assigned (n=34). Experts were able to assign most awards to at least one priority, with only 31 awards categorised as 'no priority'.

Category	Number of awards
Priority 1: Faster Diagnosis	120
Priority 2: Increased awareness of rare diseases among healthcare professionals	56
Priority 3: Better coordination of care	34
Priority 4: Improved access to specialist care, treatment and drugs	319
Basic Science Research	358
No Priority	31

Table 5: Assignment of awards in the NIHR programmes and MRC rare disease research portfolio against six categories.

The majority of awards (over 70%) were mapped to a single category (either one of the four Framework priorities, or basic science research).

[4] *These were two awards funded via the NIHR Evidence Synthesis Programme and one award funded via the NIHR Health Technology Assessment Programme.*

3.5.1 Priority 1: Faster Diagnosis

Research relevant to priority 1 was defined as being specifically focused on improving the rate or process of detection, screening or diagnosis of rare diseases, or on understanding the diagnostic pathway (see Annex 5 for full definition). There were 120 awards mapped to this priority, with a similar number of awards from the MRC portfolio and the NIHR programmes portfolio.

Many of the studies mapped to this priority aimed to establish or evaluate new diagnostic technologies, tools or screening tests, or to improve existing diagnostic tests, particularly where this could result in a reduction in the need for invasive procedures. Many studies also focused on the identification of novel biomarkers, to enable earlier and more rapid diagnosis of disease, including at a pre-symptomatic stage.

Several studies referenced the use of genomic techniques, including whole genome sequencing and next generation sequencing, to identify novel genetic causes of disease. Some studies also involved the use of large datasets to understand the causal effects of known and novel variants. This could lead to new confirmed diagnoses, by improving understanding of how variants identified through genomic techniques cause disease.

Research under this priority also included studies aimed at improving risk prediction or disease detection using artificial intelligence, and those aimed at improving clinical phenotyping, to aid in the diagnosis of patients with previously unclassifiable disease.

High value awards under this priority included the 'UK GENetic Frontotemporal dementia Initiative (UK GENFI)', which aimed to identify markers which could enable early detection and tracking of the condition, and the 'Disorders of Sex Development' study, which combined a strong basic science component with research to identify novel genes causing disorders of sex development in humans.

Other notable awards mapped to priority 1 included:

- Awards to support the Wales and Northern Ireland Genomic Medicine Centres, whose aims are to bring benefit to patients through improved diagnosis, together with improved understanding of rare diseases through the contribution of samples from patients in Wales and Northern Ireland.
- Rethinking Strategies for Positive Newborn Screening Result Delivery (ReSPoND) - a process evaluation of co-designing interventions to minimise impact on parental emotional well-being and stress
- Research to support rapid exome sequencing for the diagnosis of critically ill children in the NHS Genomic Medicine Service. This study aimed to ensure that rapid exome sequencing delivered through the Genomic Medicine Service is offered in a manner that is acceptable to parents and professionals, efficient to the NHS and maximises benefits to patients and parents across the country.
- A study to define patient priorities and preferences when consenting to whole genome sequencing to ensure informed choice, which seeks to identify whether patients are making informed decisions to undergo whole genome sequencing, how informed consent can be best facilitated, what the barriers are to informed consent and how these can be addressed

3.5.2 Priority 2: Increased awareness among healthcare professionals

For the purposes of this project, priority 2 was interpreted as addressing 'increased awareness amongst healthcare professionals' as a specific goal, over and above dissemination of research

findings (see Annex 5 for full definition). This included studies which outlined structured approaches to engaging with healthcare professionals, such as arranging focus groups, training, and education; producing educational or training materials; or seeking to influence professional colleagues or policy. Studies which referenced the development of guidelines or engaging with communities of experts were also included.

Many of the awards in the NIHR programmes and MRC rare disease research portfolio included references to improving knowledge of rare diseases. This is likely to reflect funder application processes, which require detailed dissemination plans and impact statements. These studies were not included under the definition of priority 2 used for this project.

According to this definition, there were only 56 studies mapped to priority 2, including 9 fellowships. Most awards under this priority were also mapped to at least one other priority, suggesting the proportion of research that is solely focused on increasing awareness of rare diseases among healthcare professionals is small. Included within these awards were multi-centre studies, awards supporting national and international clinical and research networks of excellence, and studies where findings will be translated into educational or supportive resources that can be utilised by healthcare professionals.

High value awards mapped to this priority included 'harnessing routinely collected UK health data to improve access to care for under-researched medical conditions such as sleep disorders, which included in its outcomes the development of materials for GPs and sleep specialists; and 'delivering genomic sequencing in clinical practice: a patient-centred evaluation of the new NHS Genomic Medicine Service', which sought to understand patient-provider communication around offering whole genome sequencing for paediatric rare disease and around return of results, and deliver recommendations for enhancing this communication process.

3.5.3 Priority 3: Coordination of care

Awards relevant to priority 3 were defined as 'social or economic research into the needs of rare disease patients for coordinated care; how care for people living with rare diseases could be better coordinated within a health or social care setting, or how technology or innovation could improve coordination of care for people living with rare diseases' (see Annex 5 for full definition). There were 34 awards mapped to this priority, the majority of which were funded by the NIHR programmes portfolio. This included studies focused on evaluating care coordination, studies that focused on developing strategies or interventions to potentially improve care coordination, and studies where improved care coordination was a likely linked outcome.

Several studies explored ways of delivering care remotely, or improving the services people with rare diseases were able to access from their own home. At least 6 studies included a focus on the provision of mental health support. Importantly, several studies mentioned the involvement of patients and carers in designing new services or interventions.

Awards mapped to this priority were typically multidisciplinary or multi-site, and involved multiple interventions, which inherently required some aspect of coordination of care. Most of the awards under this priority were also mapped to at least one other priority, suggesting there is currently not a high volume of research which is primarily or entirely focused on coordination of care.

A high-value awards under this priority was *the '*development and evaluation of an intervention to support adherence to treatment in adults with Cystic Fibrosis (ACtiF)*'* study. This study aimed to enable the development and evaluation of a behaviour change intervention to support adherence to medication in adults with Cystic Fibrosis, including a web-portal to display adherence data. Another

high-value award was 'Using digital health to transform the management of long-term conditions [including rare diseases] in the NHS: Assessing real-world patient experience and empowerment and improvements to productivity and capacity', which aimed to evaluate how a remote digital monitoring platform impacts long-term condition management, hospital capacity and productivity and patient experience, to then support procurement, commercialisation and scale up of the platform. 'Better outcomes for patients living with motor neuron disease' was also a high-value award that investigated whether highly specialised personalised evidence-based multidisciplinary care for people living with MND could be delivered effectively close to home, and whether technology and patient centred outcome measures could reduce burden and increase participation in clinical trials.

Other notable awards mapped to priority 3 included:

- CONCORD: CO-ordiNated Care Of Rare Diseases, which looked at how care for people with rare diseases is coordinated, and how they would like it to be coordinated.
- Transitions from paediatric to adult services for sickle cell disease (SCD): a study bringing together a multidisciplinary team to understand the experiences of young people living with SCD, and their perspectives on how transition could be improved.

3.5.4 Priority 4: Access to specialist care, treatment and drugs

Research mapped to this priority was defined as being focused on 'the discovery and development of therapeutic interventions for rare diseases, and testing in preclinical, clinical, community or applied settings' (see Annex 5 for full definition). It also included research into improving access to specialist care and treatments. There were 319 awards mapped to this priority.

Most of the awards mapped to priority 4 were clinical studies, in particular phase I and II clinical trials into novel advanced therapies, including gene therapies for rare diseases, which address unmet needs for diseases that currently have no or limited treatment options. Several of the later stage trials also aimed to inform evidence-based clinical guidelines. These trials often demonstrated innovative methodological approaches, including the use of real-world evidence, to overcome traditional barriers to rare disease research, such as small sample sizes. Many of these awards mentioned the contribution of patient voice as being central to their design.

Several studies involved the development of stratified approaches to treatment and management of rare conditions, to enable personalised approaches to be taken to achieve optimal clinical outcomes. Often the stratified approaches used, or were informed using data, digital health tools or machine learning.

Several studies took multidisciplinary approaches, involving clinicians, molecular scientists, geneticists, immunologists, statisticians, computer scientists, economists and more. Studies commonly involved partnerships between academia, industry and charities, as well as national and international collaborations.

High value awards under this priority included 'MAximizing SLE ThERapeutic PotentiaL by Application of Novel and Stratified approaches (MASTERPLANS)', which aimed to identify features of systemic lupus erythematosus that could be used to predict responses to different treatments in order to develop an approach that enables the right patient, to be treated with the right drug, at the right time. 'MICA: Childhood arthritis and its associated uveitis: stratification through endotypes and mechanism to deliver benefit; the CLUSTER Consortium', aimed to identify subgroups of juvenile idiopathic arthritis (JIA) and JIA-uveitis, to facilitate more accurate predictions of likely treatment response and disease course, enabling targeted treatment decisions to be made. Whilst

'development of PEGylated Domain I of beta-2-glycoprotein I as a new therapeutic agent for the antiphospholipid syndrome', involved development of a new therapy for antiphospholipid syndrome that avoids side effects associated with existing therapies.

3.5.5 Basic science research

Experts reviewing the portfolio were also asked to consider mapping to a fifth category, 'basic science research'. This was defined as 'any basic science research where rare disease is the primary focus, including the development of *in vitro* and *in vivo* models of rare diseases, and research into understanding the cause and development of rare diseases' (see Annex 5 for full definition). 'Basic science research' was the largest category in portfolio, with 358 awards mapped to this category. Almost all the awards mapped to this category were funded by MRC. This reflects the UK's strength in discovery science. Most awards in this category did not additionally map to any of the 4 Framework priorities.

As expected, most awards in the basic science category were preclinical studies underpinning the development of new therapies; studies aimed at understanding the molecular causes of rare diseases; or studies focused on the identification of possible therapeutic targets. In keeping with patterns identified across the NIHR programmes and MRC rare disease research portfolio, neurodegeneration appeared to be a key theme ('neurological' was the HRCS health category with the largest proportion of awards and apportioned funding value; amyotrophic lateral sclerosis (ALS) and Huntington's disease were among the Orphanet individual disease names with the largest number of associated awards; see Sections 3.3 and 3.2 respectively). Novel therapeutic approaches being explored experimentally included studies that would support the development of oligonucleotide therapies, gene therapies and gene editing.

High value awards in this category included 'Defining defective DNA repair in Fanconi Anaemia', which outlined genetic and biochemical approaches to define the DNA repair pathway in which the Fanconi Anaemia proteins participate, as well as a number of awards on prion diseases (including several programmes at the MRC Prion Unit). Note that several of these award values are inflated due to the much longer funding period of these awards (over 20 years for some, compared to the 6-year window for this analysis), which gives rise to a higher cumulative award value. This could be handled in future analyses by considering research spend rather than award values, or by normalising the award values by the award length.

Other notable awards in this category included:

- A large award to the MRC Centre for Neuromuscular Disease, whose mission is to translate science into experimental medicine & new treatments for children & adults with neuromuscular diseases
- An award to the Scottish Genomes Partnership (SGP), to support SGP's sequencing of genomes of individuals with rare diseases, and to support the development of federated analysis solutions for distributed genomic data, including through joint working with Genomics England. This represents the MRC's investment in the Scottish Genomes Partnership, complementing partnership funding from the Scottish Government, and Scottish Enterprise, awarded separately.

3.6 NIHR Infrastructure portfolio

As noted in Annex 1.3, the data held on the NIHR infrastructure schemes portfolio was less detailed than for programmes ('title' was the only input field). The data held on NIHR Clinical Research Network (CRN) supported studies was more detailed, but differed in input fields from the

programmes data. Therefore, the analyses below take a less quantitative approach than we took for the analysis of the NIHR programmes and MRC rare disease research portfolio. Because of how NIHR provides infrastructure support to studies, it was not possible to analyse the NIHR Infrastructure portfolios by the same parameters at the NIHR programmes and MRC rare disease research portfolio. The data for the NIHR Infrastructure schemes reflects a snapshot of active studies supported in the year 2020/2021 (available as Dataset 3 via NIHR OpenData), whereas the NIHR CRN portfolio spans from April 2016-April 2021 (available as Dataset 4 via NIHR OpenData).

3.6.1 NIHR Infrastructure schemes

NIHR Infrastructure schemes identified through the search protocol as being involved in rare diseases research were Biomedical Research Centres (BRCs); Clinical Research Facilities (CRFs); Medtech and In vitro diagnostics Co-operatives (MICs); and Applied Research Collaborations (ARCs). These schemes provide support for research funded by the NIHR itself, but also research funded by other partners including UK Research and Innovation (UKRI), medical research charities and industry. There were 1639 rare disease research studies supported by these schemes in the year 2020/2021 identified through the search protocol.

NIHR Biomedical Research Centres (BRCs) facilitate collaboration between universities and NHS organisations to translate scientific advancements into clinical benefits. There were 20 NIHR BRCs active throughout England in 2020/21. In total, there were 819 rare disease research studies supported by BRCs during this time. The Great Ormond Street BRC and the University College London Hospitals BRC supported the greatest number of rare disease related studies active during 2020/2021. The number of studies supported reflects the research focus of the BRCs during this time (further information about the research themes of individual BRCs can be found on their websites). The full distribution of rare disease research studies supported by BRCs is shown in Figure 7.

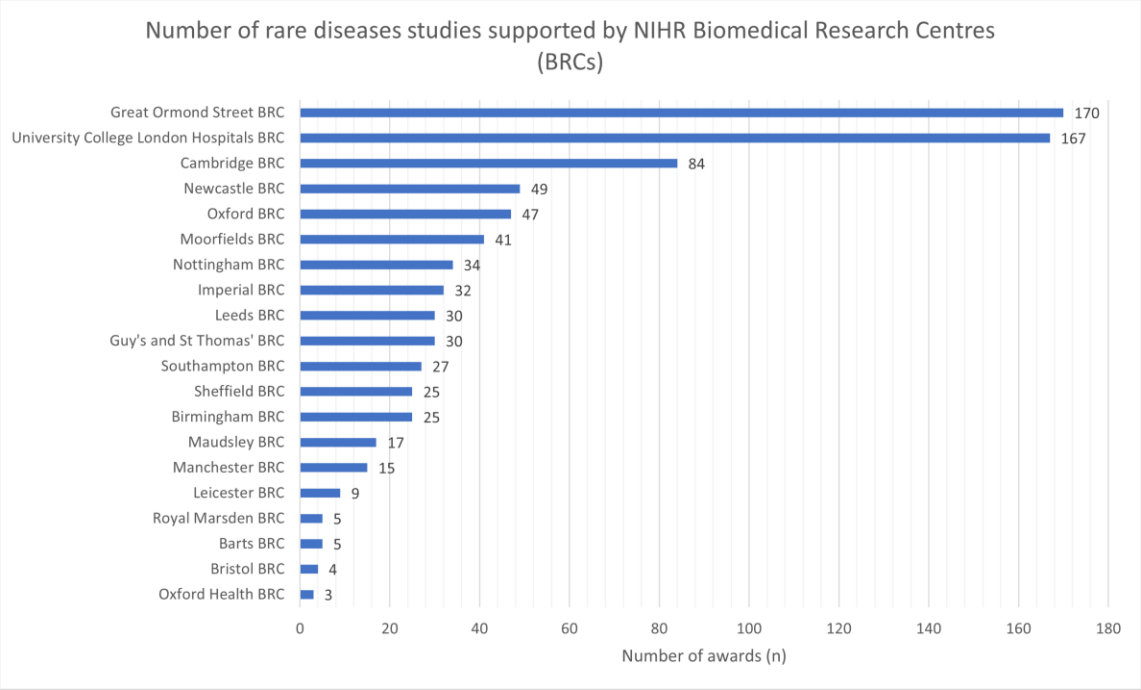


Figure 7: The number of research studies on rare diseases supported in 2020/2021 by the NIHR Biomedical Research Centres (BRCs).

Case study: NIHR Leeds Biomedical Research Centre

Improving genetic diagnosis and treatment of patients with primary immunodeficiencies (PID)

Primary immunodeficiencies (PID) are rare disorders, however these conditions cause significant ill health and in some cases are associated with a shortened life span. In most cases PID are sporadic (no known family history), and until recently the cause in the majority was unknown. Consequently, the management has been difficult, and treatment options limited. The Leeds BRC and BioResource has contributed to a national study looking at genetic causes of PID.

This is the largest cohort of patients with PID in the world who were investigated using the latest genetic techniques such as whole genome sequencing. Through this research it was possible to not only identify a disease-causing mutation in a significant portion of patients, but also identify numerous new candidate genes as likely cause of PID.

The findings of this study have significantly advanced the field of PID and will certainly have a positive impact on future diagnosis and clinical management. One of the immediate benefits of achieving a genetic diagnosis for some PID patients is that prospect of bone marrow transplant, which is potentially a curative procedure, becomes a realistic option. This is not only the case for children but increasingly also for adults. In addition, with advancement of genetic therapies, establishing a genetic diagnosis early and accurately will become a necessary part of routine clinical practice, so that these patients can access ever increasing number of effective treatment options.

NIHR Clinical Research Facilities (CRFs) are purpose-built facilities in NHS hospitals that enable cutting-edge research to take place. There are 28 NIHR CRFs spread throughout England. In total, there were 801 rare disease research studies supported by CRFs during 2020/2021, spread across 21 different CRFs. The Birmingham CRF and Manchester CRF supported the greatest number of rare disease related studies active during 2020/2021, with 118 and 104 studies supported respectively. The full distribution of rare disease research studies supported by CRFs is shown in Figure 8.

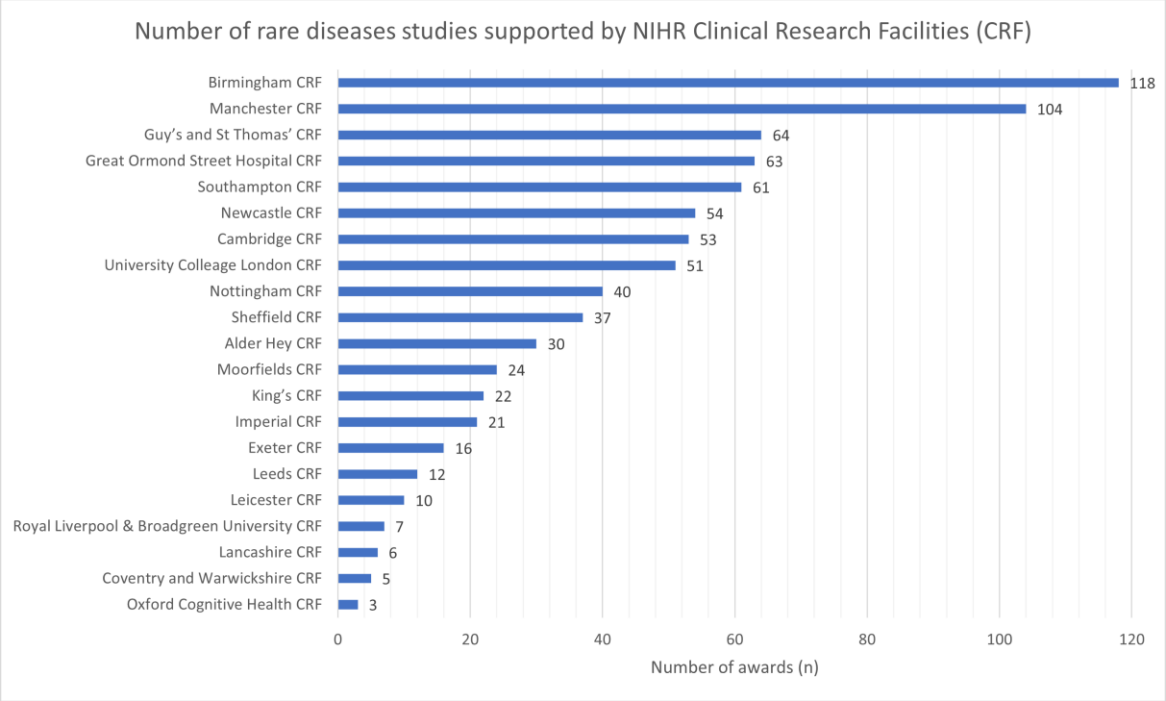


Figure 8: The number of research studies on rare diseases supported in 2020/2021 by the NIHR Clinical Research Facilities (CRFs). CRFs where rare disease research was not taking place are not displayed.

Case study: NIHR Manchester Clinical Research Facility

Transforming the lives of people with cystic fibrosis: CF modulator therapies, from trial to patient

Cystic fibrosis (CF) is a rare genetic disease caused by mutations in the CFTR gene, that affects around 10,000 people in the UK. Manchester Clinical Research Facility (MCRF) has been involved in CF clinical trials for almost 10 years and played a key role during a period that has seen rapid evolution of life-changing therapies. Researchers from MACFC have served as national and global leads on several pivotal studies.

MCRF has hosted a range of clinical trials of different modulator therapies from several industry partners, including those from the successful Vertex range of compounds. Early dual-therapy combinations, such as Ivacaftor/tezacaftor (symkevi) were trialled at MCRF, and later licensed and funded in the UK (November 2019).

MCRF has been at the forefront of trials of the most recent and most powerful triple combination therapies. These compounds have progressed along the MCRF translational pathway from Phase 1 (with SME, Medicines Evaluation Unit) to Phases 2 and 3, which continue to be supported through MCRF infrastructure, including experienced research nurses and staff from laboratory services and physiology.

The Phase 3 studies continued during the COVID-19 pandemic with patient safety the primary driver; MACFC and MCRF staff conducted study visits at alternative clinical sites, and the use of home spirometry was increased to reduce patient visits to the MCRF. Participants continued to be provided with-highly effective CFTR modulators that were only available as part of the trial.

These trials included the Vertex triple combination therapy, Kaftrio – a breakthrough therapy that has been shown to be effective in 90 per cent of CF patients with an average improvement in lung function of over 20%. MCRF has been central to the development of these therapies,

Following the trials at MCRF, the novel therapies were rapidly rolled out to more than 280 adult CF patients across Manchester, the first in Europe to receive these transformative medications. This has resulted in life-changing improvements, including eight patients who no longer require long-term oxygen support, and eight patients who are now considered well enough to no longer require a lung transplant.

MCRF continues to support new developments in CF therapies, including the next generation of triple therapy studies.

MACFC is also a European CF Society Clinical Trials site and will be playing a key role in delivery of NIHR supported initiatives, including the i CF-STORM study and the NIHR Rare Diseases Bioresource (see Section 3.6.1.1 below).

NIHR Medtech and In vitro diagnostics Co-operatives (MICs) are centres of expertise within leading NHS organisations that assist with the development and adoption of new medical devices, digital technologies or diagnostics in the NHS. There are 11 NIHR MICs in England, three of which were identified as having supported rare disease research studies within 2020/2021. These were the Leeds In Vitro Diagnostics Co-operative (7 studies supported), the Children and Young People MedTech Co-operative (6 studies supported) and the Trauma Management MedTech Co-operative (1 study supported). Examples of these projects include using artificial intelligence to enhance rare disease diagnosis, and investigating the use of virtual reality in rehabilitation.

NIHR Applied Research Collaborations (ARCs) support local collaborations in applied health and care research to transform evidence into practice that addresses the needs of the local populations in a way that is sustainable for the local heath and care system. There are 15 ARCs that collectively cover all geographical regions in England. The search identified five rare disease research studies supported by ARCs within 2020/2021, across four of the ARCs: ARC East of England (2 studies supported); ARC Northwest Coast (1 study supported); ARC Southwest Peninsula (1 study supported); and ARC West Midlands (1 study supported). These studies included epidemiological and non-clinical research projects, such as health economic analyses and development of family-focused interventions for rare disease.

3.6.1.1 The NIHR BioResource

The NIHR also supports the NIHR BioResource. There are currently 18 local BioResource Centres across England. Each BioResource Centre is connected to the corresponding local Biomedical Research Centre (BRC). As well as the 18 local BioResource centres, there are also NIHR BioResource national programmes, which are major initiatives between BioResource Centres and partners to tackle specific health conditions. The Rare Diseases BioResource is one of these national programmes. Funding for national programmes is not allocated to an individual infrastructure centre, but is rather coordinated across several. England's 2022 Rare Diseases Action Plan included an announcement of £40 million of funding to the NIHR BioResource, to further work in characterising and understanding rare diseases. The case study below highlights the impact of one of the research projects undertaken by the NIHR Rare Diseases BioResource.

Case study: NIHR BioResource

Improving the safety of blood transfusions

Patients with conditions such as thalassemia or sickle cell disease require regular blood transfusions, but these transfusions can sometimes cause dangerous side effects because of inadequately matched blood. The main source of blood for transfusions are people with European ancestry, but sickle cell disease predominantly affects people from African and Caribbean backgrounds, and approximately 17,000 people in the UK have the disease. Thalassemia mainly affects people of Mediterranean, south Asian, southeast Asian and Middle Eastern origin. Over 800 people in the UK are living with thalassemia.

Working with NHS Blood and Transplant (NHSBT) and an international Blood Transfusion Genomics Consortium, the NIHR BioResource is developing new methods of blood matching and supporting clinical trials using red blood cells grown from human blood cells in the laboratory. This will reduce the risk of potentially dangerous side effects occurring during blood transfusions.

3.6.2 NIHR Clinical Research Network (CRN)

As detailed in Section 1.3.2 above, NIHR Infrastructure support also includes clinical research studies that are supported by NIHR's Clinical Research Network (CRN), which were open to recruitment of participants during April 2016 – April 2021. The NIHR CRN is comprised of 15 Local Clinical Research Networks (LCRNs), which together, coordinate and support the delivery of high-quality health and care research throughout England. Within each LCRN, there are several sites where research takes place, including NHS Trusts, Integrated Care Boards and other local organisations. Each LCRN is responsible for the support of studies that span 30 specialties.

The CRN supports studies funded by the NIHR itself, but also research funded by other partners including UK Research and Innovation (UKRI), medical research charities and industry, through the

provision of staff and facilities essential for the delivery of the research. To receive this support, studies must meet specific criteria and be registered on the NIHR CRN Portfolio.

In total, the NIHR CRN supported 1686 rare disease studies during the report's timeframe. The NIHR CRN portfolio was analysed to determine the funder type, lead administration, lead Local Clinical Research Network (LCRN), participant recruitment, and managing specialty.

3.6.2.1 Funder type

In some instances, studies were supported by a single funder, but many rare disease studies were funded by more than one organization. Just under half (49.3%) of all rare disease studies supported by NIHR CRN were funded commercially by industry. Funding from charities based in England and Wales that are registered with The Charity Commission for England & Wales (referred to as 'charity-England' in Figure 9) accounted for 19.5% of the NIHR CRN supported studies. There were eight studies that received funding from charities that are registered with the Scottish Charity Regulator (comprised <0.6%, and therefore fall under the 'other' category in Figure 9). There were no studies supported by CRN in the portfolio that received funding from charities registered with The Charity Commission for Northern Ireland. Further information on rare disease research funded by industry and charity is provided in Sections 4.1 and 4.2 respectively.

NIHR was the primary funder for 7.2% of NIHR CRN supported studies; and Research Councils funded 5.5% of the NIHR CRN supported studies. Overseas funders supported just over 4% of NIHR CRN supported studies, of which the majority (3.1%) were funded by governmental organizations. Figure 9 below details the distribution of funder types present in the NIHR CRN rare disease portfolio, by number of studies funded by each funder type expressed as a percentage. The 'other' category includes organisations whose funded studies accounted for less than 0.6% of NIHR CRN supported studies. Whilst indicative, the breakdown shown in Figure 9 may not fully reflect the mixed nature of funding for many of the studies, as it was not possible to precisely determine the number of studies funded by single or multiple organisations.

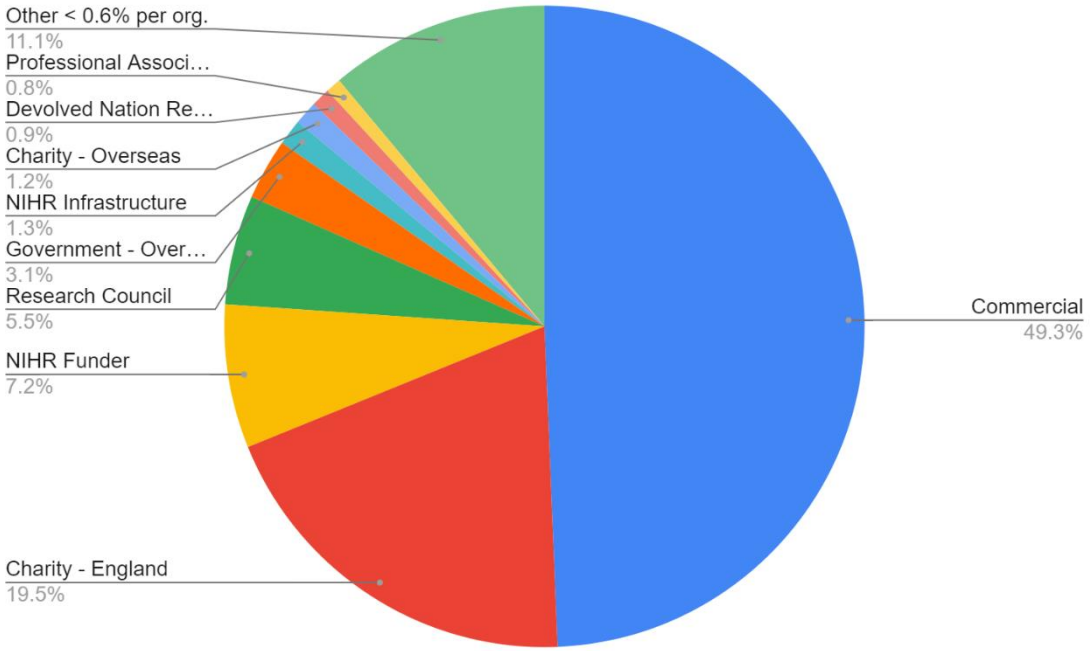


Figure 9: Pie chart detailing the funder type of rare disease studies active between 2016-2021 on the NIHR CRN portfolio. The number of studies in the portfolio is expressed as percentage by funder type.

3.6.2.2 Lead Local Clinical Research Network (LCRN) and participant recruitment

Research studies supported by the NIHR CRN have a designated Lead LCRN. All 15 LCRNs were engaged in hosting studies on rare diseases. There were over 500,000 participants recruited to take part in CRN supported rare disease research studies that were open or active during the 5-year period. Just over 45% of rare disease studies were led by the three London LCRNs (North Thames, South London, Northwest London), with North Thames LCRN accounting for 27.1% of studies (data not shown). The pattern of participant recruitment by LCRN (Figure 10, right) broadly reflects the number of studies led by each LCRN. The number of studies that these participants were recruited to is shown in Annex 6.3.

The map in Figure 10 (left) shows that there are several sites that recruited participants to take part in rare disease research within each LCRN. Importantly, the sites where people are going to participate in rare disease research are distributed across the UK. Although the NIHR only supports the CRN in England, a study can be NIHR CRN supported but also recruit participants in the devolved administrations. In these instances, the study will receive NIHR CRN support for study sites in England, and equivalent support from CRNs in the devolved administrations for sites in Scotland, Wales or Northern Ireland.

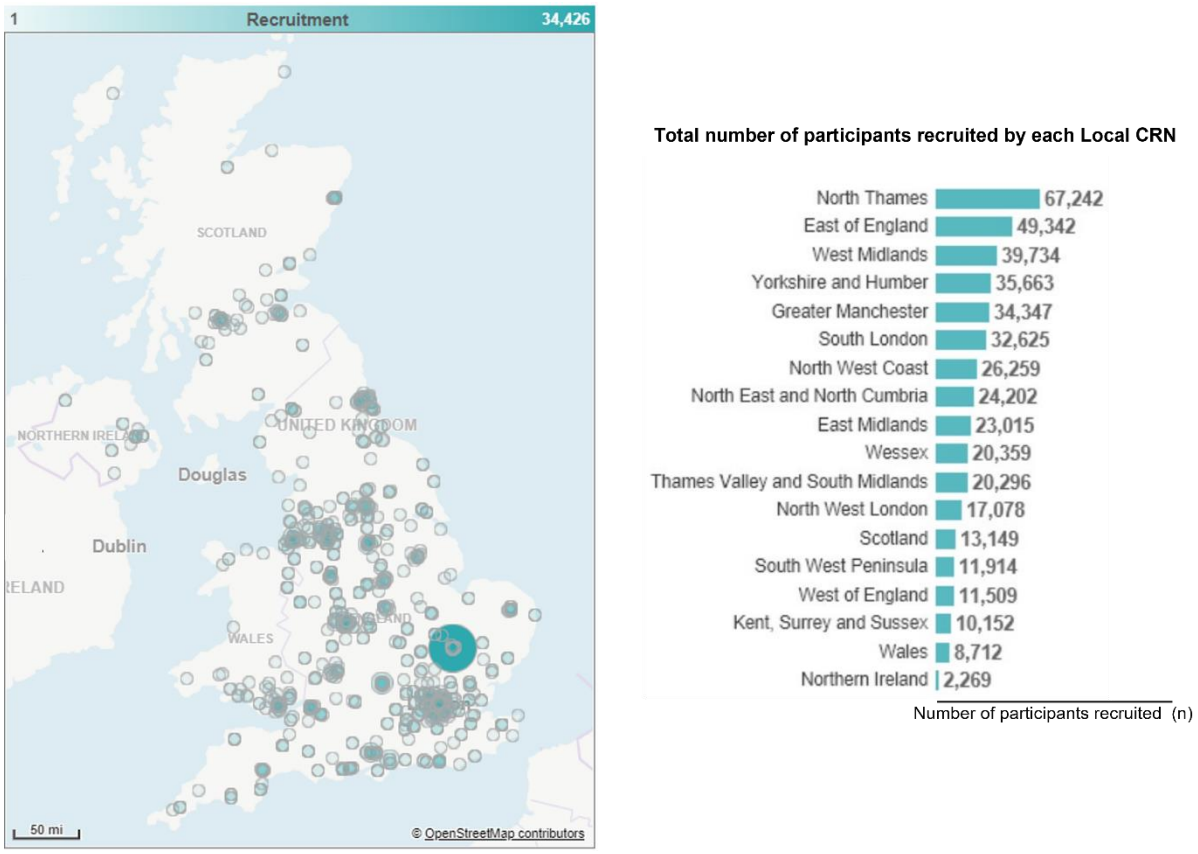


Figure 10: Total numbers of participants that were recruited to NIHR CRN supported rare disease research studies that were open or active between 1 April 2016 – 1 April 2021. The map (left) shows the number of participants recruited by each site (each circle represents a single research site), with the colour intensity and the size of the circle indicating participant number. The darker the colour intensity (see scale bar at the top of the map), and the larger the circle size, the greater the number of participants recruited by that site. The bar chart (right) shows the total number of participants recruited by each Local CRN region (each LCRN is a network of several research sites).

When recruitment data were looked at over time (data not shown) it was found that although there were spikes in recruitment as new studies began, rare disease research activity across LCRN sites remained relatively stable across the five-year period.

3.6.2.3 *Managing Specialty*

The NIHR CRN co-ordinates and enables the delivery of research across 30 clinical speciality areas. The NIHR CRN rare disease portfolio includes research supported by 28 of these specialties. The Children Specialty supports the largest proportion (18%) of studies and together with the Haematology (10.2%), Respiratory Disorders (10%), Musculoskeletal Disorders (7.6%) and Dementias and Neurodegeneration (8.0%) specialties support over half of studies in rare diseases in the NIHR CRN portfolio. Figure 11 below details the distribution of managing specialities present in the NIHR CRN portfolio, by number of studies supported by each speciality expressed as a percentage. The 'other' category includes specialities which supported less than 0.4% of studies on the NIHR CRN portfolio.

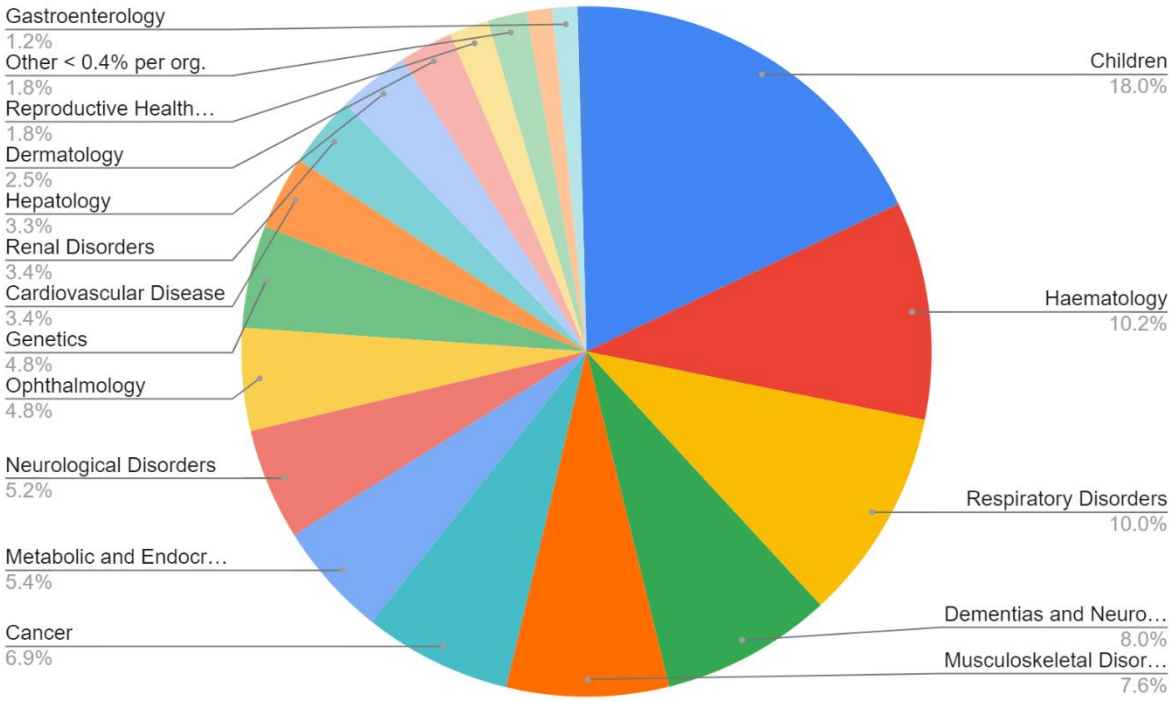


Figure 11 Pie chart detailing the speciality of rare disease studies active between 2016-2021 on the NIHR CRN portfolio. The number of studies in the portfolio is expressed as percentage by managing speciality.

The NIHR musketeers memorandum

Populations of people living with each rare condition are small and scattered throughout the UK. To reach as many people as possible it is important that research studies can take place across multiple centres. The NIHR musketeers memorandum has been an important tool in making this happen for rare disease studies where recruitment happens in the NHS. Rather than needing governance and ethics approvals for multiple centres, one approval is signed up to by multiple recruiting centres. This has enabled UK-wide involvement in studies that might not otherwise have been able to recruit adequate numbers of patients. It speeds up the protocol review and negotiation process and enables fair and even access to patients with rare disease across the UK.

4 Wider funders of rare disease research

In developing and testing the search protocol, NIHR and MRC were focused on as the two major government funders of rare disease research. The analysis presented above is based upon the data

collected from the searches performed on the NIHR and MRC portfolios. However, other funders also make a very significant contribution to funding rare disease research. The following sections of this report present data on research funded by industry, charities (including the Wellcome Sanger Institute), LifeArc, Genomics England and the devolved administrations. Research funded by these funders may have been supported by NIHR infrastructure. Therefore, this research may have been counted in the NIHR infrastructure rare disease portfolios. However, NIHR infrastructure support is distinct from the funding provided by other funders detailed below.

4.1 Industry funded rare disease research

The global life sciences industry is a significant contributor to rare disease research; the pharmaceutical industry invested £5 billion in UK Research and Development in 2020[5]. Industry works to better understand drivers of rare disease and develop new treatments, such as gene therapies, which address unmet needs for patients who currently have no or limited treatment options.

As representative trade bodies, the Association of the British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA) collectively represent over 650 member organisations involved with the life sciences, pharmaceutical and biotech sectors across the UK. The ABPI and BIA champion the work of their member organisations, provide their members with a wide range of services and support, and represent the interests of their members to a broad range of stakeholders, both within the UK and globally. In this project, the ABPI and BIA were able to represent the voice of the UK life sciences industry.

4.1.1 Method for extracting industry funded rare disease research data

To characterise industry research in rare diseases in the UK, the ABPI and BIA commissioned Clarivate™ to perform a search of the Cortellis Competitive Intelligence database. The search was performed using the same definitions and timeframe as the protocol developed by the Project Group (see Annex 2.1 for detailed methods). The information contained in this database represents industry research in general, and is not limited to the ABPI and BIA member organisations. The timeframe used for this search was 1 April 2016 – 1 April 2021, to align with the NIHR Programmes and MRC portfolio search. The results of this search represent industry research and development (R&D) projects on rare diseases in the UK. These results are analysed below (available as Dataset 5 via NIHR OpenData).

Term	Definition
Project	Research on a specific drug, to treat a specific condition, sponsored by a single company. Each project is at a specific phase in the R&D pipeline (discovery, preclinical, phase I clinical trial, phase II clinical trial, phase III clinical trial).
Industry research and development (R&D) projects on rare diseases in the UK	The number of industry drug projects at all stages of R&D within the UK for rare diseases between 1 April 2016 and 1 April 2021.

Table 6: Definition of terminology used in the industry funding section of the report

[5] Office for National Statistics, 2021. *Business enterprise research and development, UK: 2020.* Available online here: https://www.ons.gov.uk/economy/governmentpublicsectorandtaxes/researchanddevelopmentexpenditure/bulletins/businessenterpriseresearchanddevelopment/2020

4.1.2 Data on Industry research and development (R&D) projects on rare diseases in the UK

Of the 530 projects identified, 267 were in rare cancers, 9 in rare infectious diseases and 254 in other rare diseases. It was found that 54.6% of the projects related to the development of biologic treatments and 45.4% of the projects related to the development of small molecule treatments. Given the scope of this project, rare cancers and rare infectious diseases were excluded from the analyses shown below, in line with the other analyses conducted for this project.

Focussing on other rare diseases, Figure 12 shows the top 30 conditions being researched by industry in the UK between 2016-2021. In a similar fashion to the non-industry research described in this report, cystic fibrosis, motor neuron disease, and Duchenne muscular dystrophy are amongst the top conditions. Members of the ABPI and BIA overall felt this was an accurate representation of the industry R&D underway in rare diseases. There are some diseases, such as haemophilia, which were listed as one of the top conditions being researched in individual years, but do not feature in the list of the top 30 diseases for industry projects (Figure 12). Some of the ABPI and BIA members expected haemophilia to be listed more highly given the composition of the global industry R&D pipeline, and it may be the case that R&D into treatments for haemophilia is primarily being conducted elsewhere globally.

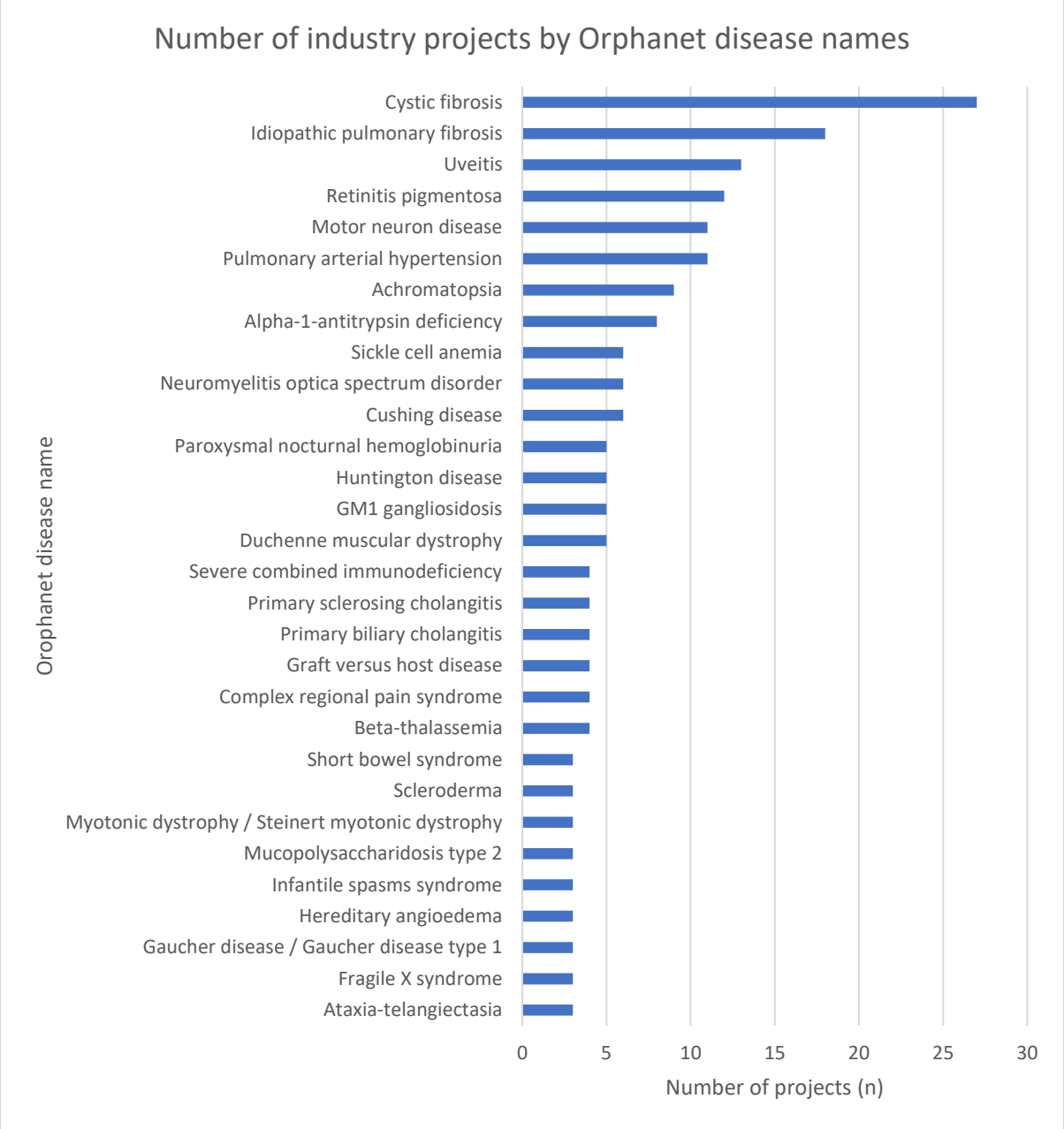


Figure 12: Top 30 diseases for industry projects in rare disease research and development (2016-2021)

In terms of the type of R&D being conducted, Figure 13 shows that industry is active in the UK across all stages of R&D, with 55.1% on industry projects in discovery and pre-clinical development, and 44.9% in clinical trials. As for the phase of clinical trials, during the 5-year time period used in this report, there were a greater number of projects in early phase clinical trials (Phase I and Phase II), than in later phase (Phase III), with 44 projects in Phase I, 52 in Phase II and 18 in Phase III.

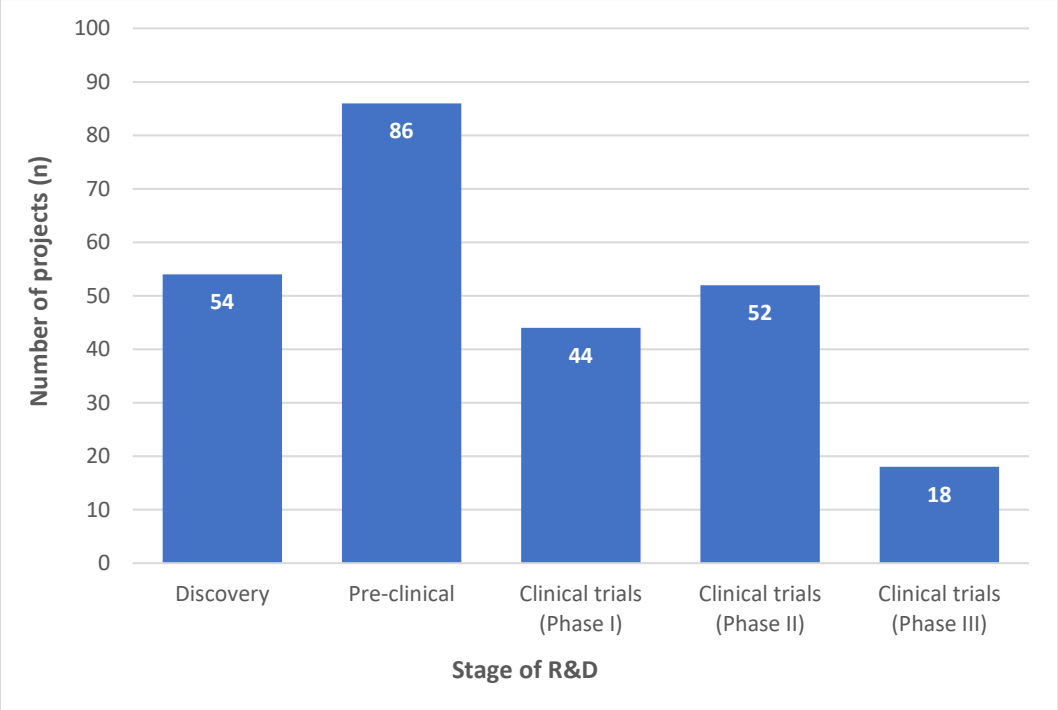


Figure 13: Number of industry projects in rare disease research and development, by stage (2016-2021)

4.1.3 Industry research aligned with delivering the priorities of the UK Rare Diseases Framework

Industry funding of specific research projects detailed here collectively demonstrate industry's contribution to basic science research and to improving patient access to treatment (Priority 4 of the UK Rare Diseases Framework), through the discovery and development of new medicines. In addition to these specific projects, the life sciences industry also develops better diagnostics (Priority 1 of the UK Rare Diseases Framework), increases awareness among healthcare professionals (Priority 2 of the UK Rare Diseases Framework), and generates real-world evidence to demonstrate the impact of treatments for patients, working closely with patient organisations. This activity is not captured in the data presented here, however the following case study is an example of how companies are working from bench to bedside.

Case study: Mendelian's MendelScan technology

Mendelian's MendelScan: Empowering Rare Disease Diagnosis in the NHS with artificial intelligence (AI) Technology

Mendelian is a UK-based digital health company and recipient of the NHS AI Award for MendelScan, an innovative AI-powered platform designed to accelerate the diagnosis of rare diseases.

MendelScan utilises intelligent case-finding algorithms to analyse patients' electronic health records and identify individuals exhibiting clinical indicators suggestive of rare diseases. MendelScan is currently implemented in over 50 NHS primary care practices across England, with the aim of optimising how patients with unrecognised or undiagnosed rare diseases are moved towards possible diagnoses on a large scale – minimising the burden on the health system and ensuring patients are matched with the best available management and treatment.

In March 2023, Mendelian was awarded £1.4 million of funding through the AI in Health and Care Award, an NHS AI Lab programme run by the Accelerated Access Collaborative in partnership with the NIHR. The funding will support a real-world evidence generation project, including the deployment of MendelScan into clinical care across the UK, covering approximately 750,000 patients. This will be done with the support of a number of primary care GP practices, primary care networks and the Central and South Genomic Medicine Service Alliance. Additionally, Mendelian is engaging with NHS Highly Specialised Services to keep them informed on their progress and outcomes.

The aim of the project is to gather sufficient evidence to drive nationwide adoption and rollout of MendelScan in the future. The evaluation will assess feasibility, efficacy, patient and clinical acceptance, and impact, encompassing a large-scale retrospective validation on 23 million electronic health records, implementation research, real-world deployment as part of a prospective research study.

Mendelian's MendelScan technology represents significant advances in using technology to expedite diagnosis and improve patient care. The AI Award further demonstrate the platform's effectiveness and potential for nationwide adoption. MendelScan's impact on rare disease diagnosis and the continuous research efforts contribute to advancing rare disease care in the UK healthcare system.

4.2 Charity funded rare disease research

4.2.1 The Association of Medical Research Charities (AMRC)

The Association of Medical Research Charities (AMRC) is a membership organisation dedicated to supporting medical research charities in saving and improving lives through research and innovation. The AMRC membership consists of over 150 medical research charities of a variety of sizes, from household names such as Cancer Research UK, Wellcome and the British Heart Foundation to smaller charities who invest in specific areas of unmet need. Over the past 10 years, AMRC member charities have spent £15.7 billion on research in the UK, supporting research at all stages and in all areas of health and disease, throughout the UK.

Annually, the AMRC asks member organisations to provide detail of their research expenditure and award portfolio. For the purposes of this project, all active awards funded by AMRC members during the five-year timeframe (defined in Table 7 below; 1st January 2016 – 31st December 2020) were identified and used to generate an AMRC award portfolio. It should be noted that the AMRC portfolio reflected a 5-year timeframe based on calendar years, rather than financial years.

Term	Definition
AMRC award portfolio	All active awards funded by AMRC members across the UK between 1st January 2016 – 31st December 2020
AMRC rare disease research portfolio (all awards)	The research that was funded by AMRC members across the UK on rare diseases within the five-year timeframe
AMRC rare disease research portfolio	AMRC rare disease research portfolio (all awards) with 'rare infectious' and 'rare neoplastic' disease search terms removed

Table 7: Definition of terminology used in the charity funding section of the report

4.2.2 Methods used by the AMRC to generate the AMRC rare disease research portfolio

The AMRC was able to use the search protocol developed by the Project Group (see Annex 1) with minimal adaptions (detailed in Annex 2.2), to generate a rare disease research portfolio that contained all rare disease awards funded and supported by AMRC member organisations during the five-year timeframe (1st January 2016 – 31st December 2020).

4.2.3 The AMRC rare disease research portfolio

4.2.3.1 Overview of rare disease research funded by AMRC members

Over the 5-year timeframe used for this project, AMRC members funded awards to a value of over £11.5 billion. Within this dataset, 4,421 awards were on rare diseases, with a total funding value of over £1.8 billion, with funding from 133 different charities. This represented 16% of total award value and 17% of the total number of awards from the five-year period.

For the purpose of this report, rare infectious and rare neoplastic diseases were excluded from the analysis. This removed 2,070 rare disease awards from the AMRC dataset, and the research funded by 26 charities, including research funded by rare disease focused charities, including Meningitis Now, Myeloma UK, Neuroblastoma UK and Solving Kids' Cancer.

Using the definitions of this report, and for the rest of the analysis below, AMRC members funded 2,351 research awards on rare diseases (10% of all awards) to a value of over £580 million (5% of the portfolio value) (Table 8). The mean value of an award within this dataset was £248,436 and the median was £99,973. 15% (374) of awards funded by charities were co-funded with another organisation.

	Number of awards (n)	Number of awards (%)	Award value (£)	Award value (%)	Number of charities (n)
All awards	26,236		11,543,216,651		171
AMRC rare disease research portfolio (all awards)	4,421	17	1,845,385,995	16	133
AMRC rare disease research portfolio	2,351	10	584,073,569	5	107

Table 8: Summary of AMRC member awards 01.01.2016-31.12.2021

4.2.3.2 Overview of which medical research charities are funding research into rare diseases

Overall, 107 charities (out of a total of 171 current and former members during the reporting timeframe) funded one or more awards focusing on a rare disease within the definition used in this report, representing a majority. This includes a subset of charities whose mission is to focus on a rare disease (Figure 14).

Figure 14: AMRC members focusing on rare disease in the rare disease research portfolio.

However, it is not just rare disease charities that are investing in rare disease research. 84% of investment from AMRC members in this dataset came from other charities with a focus beyond rare diseases. Figure 15 lists non rare disease charities that invested more than £1 million on rare disease, within the timeframe.

Figure 15: Non-rare disease focused AMRC members with over £1M investment in rare disease over the five-year timeframe

We examined the distribution of rare disease charities based on their size, using the 2022 UK research expenditure from each charity. Across the AMRC membership portfolio, the majority of charities with a focus on rare disease spend under £1 million on research per annum (78%).

Figure 16 shows the distribution of members by value of annual research funding investment. 50% of member charities with research spend under £1m funded rare disease research, as defined in this report. All the member charities with research spend over £15 million and 80% of member charities spending between £1 and £15 million funded one or more studies focusing on rare disease during the timeframe of this study.

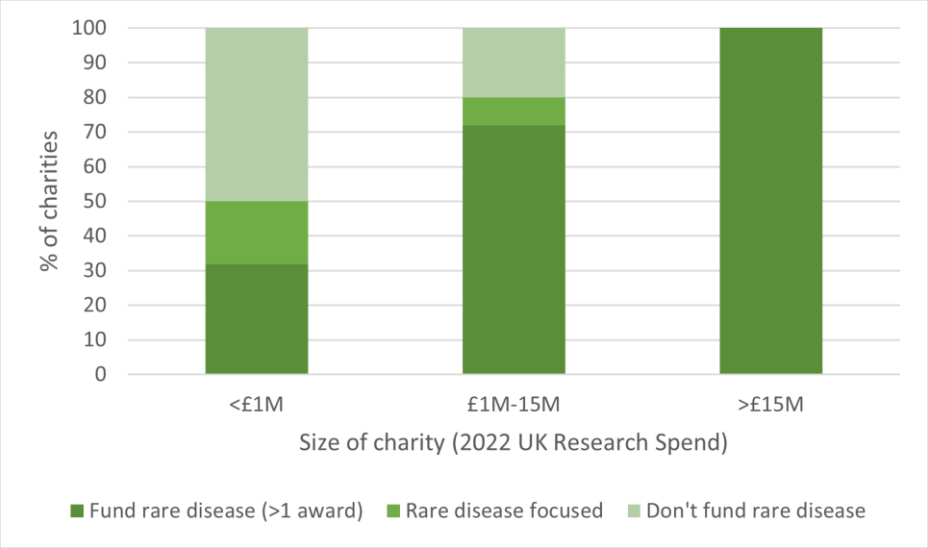


Figure 16: Distribution of AMRC members that fund rare disease by size, based on 2022 UK research spend

4.2.3.3 Distribution of awards by disease

429 rare diseases from Orphanet were identified within the portfolio of rare disease awards funded by AMRC members (Table 9). Approximately half of awards with a focus on rare disease focused on a single rare disease (44%) (Table 9). This is made up of 499 search terms (data not shown) from the 'individual rare disease names' list, and 42 additional terms manually curated by the AMRC (Annex 4).

Number of Awards	Count of Orphanet Diseases
0	8626
1	192
2 to 3	106
4 or more	131

Table 9: number of rare disease awards per Orphanet Disease category

Figure 17 shows the 30 Orphanet disease names that had the highest number of awards by Orphanet Disease classification (identified by rare disease terms in abstract). The areas containing the greatest number of awards across the portfolio were motor neurone disease and cystic fibrosis (n=154 and 140 respectively).

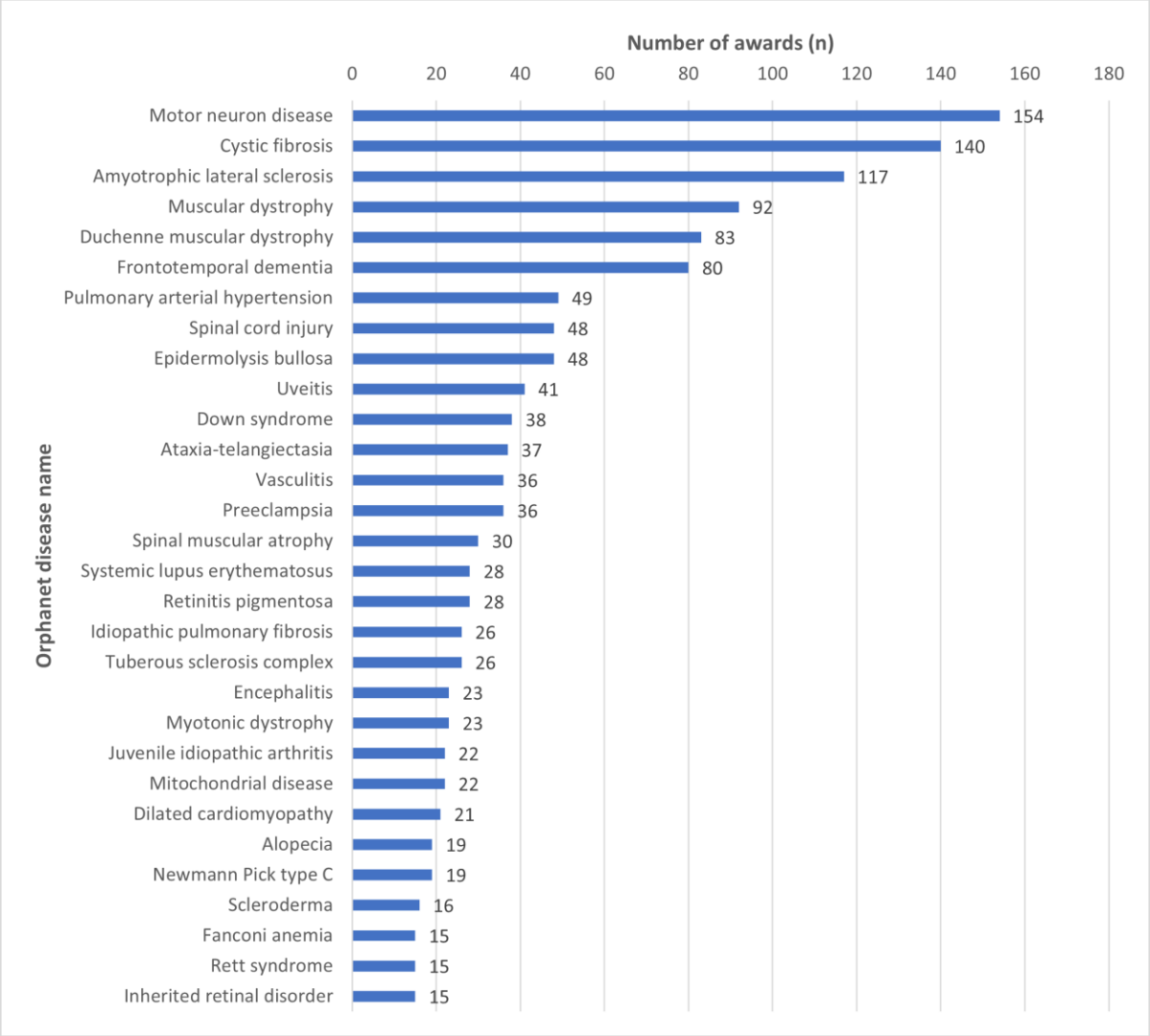


Figure 17: Top 30 Orphanet disease names in the AMRC rare disease research portfolio

4.2.3.4 Health Research Classification System (HRCS) Health Categories and Research Activity Codes (RAC)

Within the AMRC rare disease research portfolio, 458 awards (19%) were coded with Health Category (HRCS) codes. The neurological category had the highest number of awards in the AMRC portfolio (n=139) (Figure 18). Greatest funding was in Cancer and Neoplasms category, which also had the 2nd highest number of awards. This is despite the removal of awards within the Orphanet Groupings for 'rare neoplastic' and 'rare infectious' disease search terms prior to analysis using the HRCS categories.

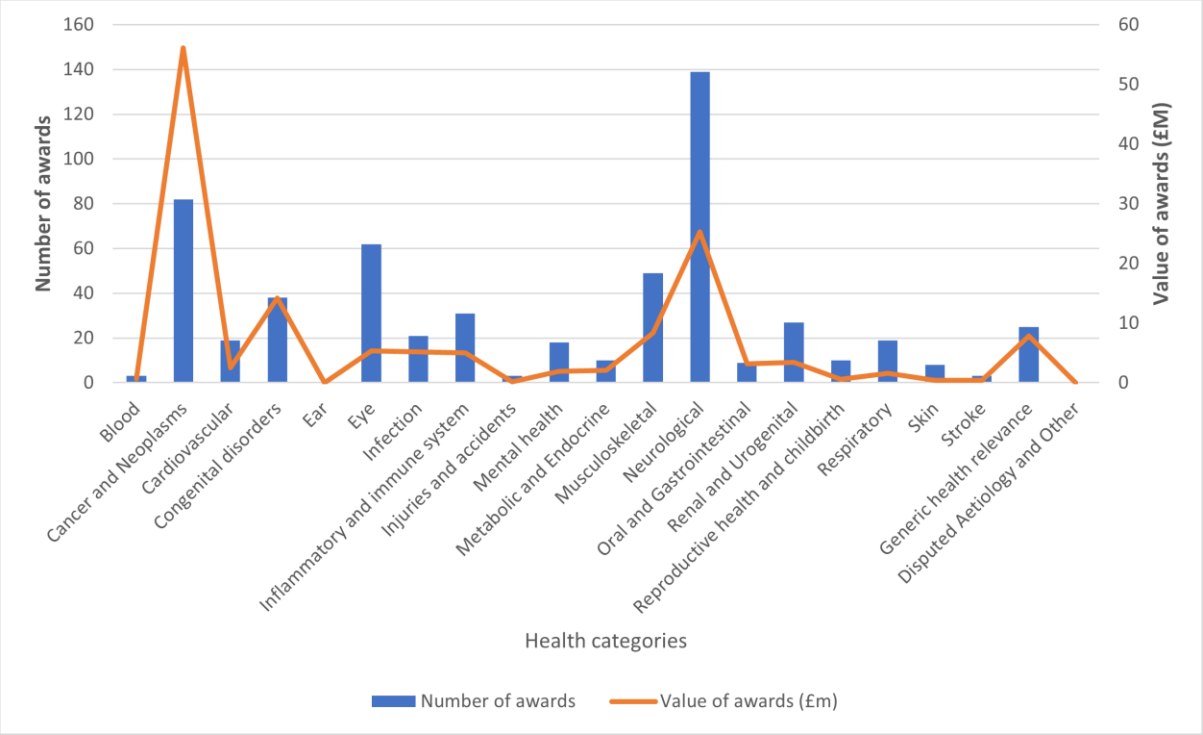


Figure 18: Distribution of AMRC member rare disease awards by HRCS Health Categories

Within the AMRC rare disease research portfolio, 416 awards (18%) were coded with Research Activity Codes (RAC). The most frequent category was 'Aetiology', followed by 'Development of treatments and therapeutic interventions' (Figure 19).

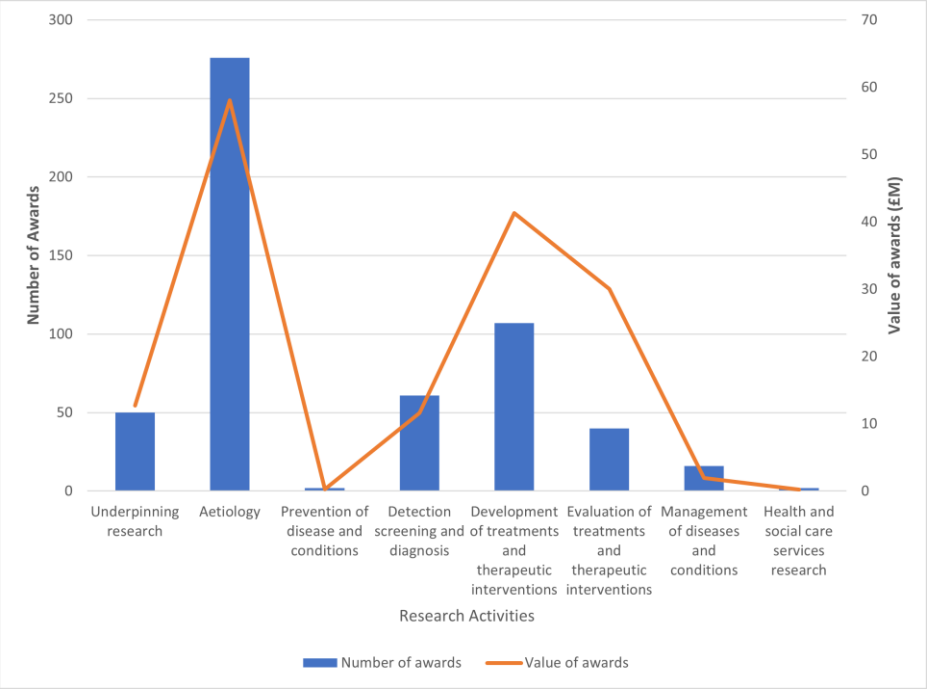


Figure 19: Distribution of AMRC member rare disease awards by Research Activity

4.2.3.5 Geographical location of awards

We examined the geographical distribution of rare disease awards across the UK using the postcode of the host institution to which the award was awarded. The region with the largest proportion of

rare disease award funding was Greater London, accounting for over a third of rare disease funding from AMRC members, followed by East of England and Scotland.

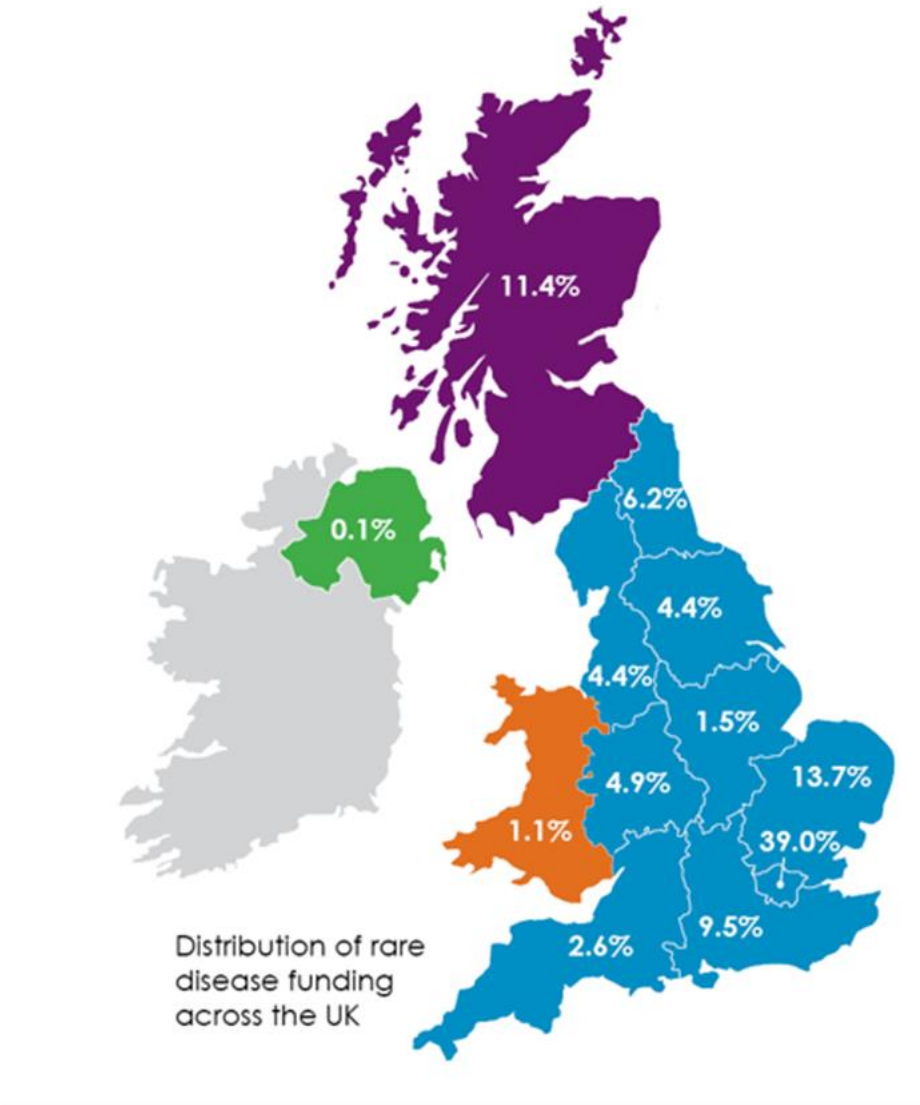


Figure 20: Geographical distribution of rare disease awards across the UK funded by AMRC members[6]

4.2.3.6 AMRC member organisation case studies

The case studies below demonstrate the impact of the research carried out by four of the AMRC member organisations.

[6] *There is an additional 1.2% of awards where the location within the UK is unknown*

Case study: Tuberous Sclerosis Association

Repurposing mTOR inhibitors as first line therapy for Tuberous Sclerosis Complex-associated kidney disease

Tuberous Sclerosis Complex (TSC) affects around 1 in every 10,000 people. It is characterised by the growth of benign tumours in different organs of the body, most commonly in the brain, kidneys and skin. Although these tumours are non-malignant, TSC is a life-changing condition with life-threatening co-morbidities, including renal defects due to angiomyolipomas (kidney tumours, the leading cause of death in adults from TSC). Other common and debilitating symptoms of TSC include refractory epilepsy, developmental delay and learning difficulties.

Recent research into the underlying mechanisms of TSC identified a link between disease-causing mutations, mTOR signalling and tumour growth. This presented the possibility that TSC tumours could be treated with existing therapies that inhibit the mTOR pathway, such as rapamycin. Research funded by the Tuberous Sclerosis Association into the application of mTOR inhibitors in TSC confirmed these therapies as a novel treatment for TSC, shrinking renal tumour growth and alleviating wider disease manifestations. Standard treatment options for TSC-related renal tumours include invasive surgery, which carries risks of immediate complications and permanent renal damage. The use of mTOR inhibitors such as rapamycin provides a safer, more effective treatment method which targets the mechanisms of the disease, thereby significantly increasing the quality of life of TSC patients.

This research has led to the worldwide approval of mTOR inhibitors as a frontline therapy for the clinical management of TSC, improving treatment options for this rare disease and resulting in changes to international disease management guidelines. This work has also provided the basis for a successful lobbying campaign by the Tuberous Sclerosis Association for the NHS to commission mTOR inhibitors for TSC patients, leading to NHS England announcing in 2016 that it would allow the treatment for children aged three and above and adults living with TSC. Following this, the UK Clinical Guidelines for Management and Surveillance of TSC – the first clinical guidelines published with a complete focus on UK care settings – was published in 2019, improving the healthcare provision that TSC patients receive from the NHS.

Overall, these advances have greatly increased the quality of care and life for the approximate 11,000 people in the UK that live with this challenging and often life-limiting condition.

Case study: Cystic Fibrosis Trust

Clinical Trials Accelerator Platform (CTAP)

Cystic fibrosis (CF) is a life-limiting, recessively inherited disease, affecting about 10,900 people in the UK (1 in 2,500 live births). There have been significant advances in CF care and treatment, with a host of new treatments in the pipeline.

Cystic Fibrosis Trust's Clinical Trials Accelerator Platform (CTAP) was launched in 2017 after a need to improve access to clinical trials for people with CF in the UK was identified. This nationwide initiative brings together CF centres to support delivery of CF clinical trials.

CTAP provides the infrastructure to support sponsors with delivery of CF clinical trials (commercial and academic) through a network of centres, and a platform to enable people with CF to gain access to these trials. Centralised support for sponsors is available across all stages of clinical trials, with involvement of people with CF at its centre. Peer support and training is also provided through the network.

The CTAP network has brought together 27 CF centres across the UK and funded a national team of 25 Trial Coordinators based at these centres. A wealth of information for people with CF interested in taking part in clinical trials has been made available. The network currently reaches about 89% of the UK CF population and CTAP centres are encouraged to accept referrals from elsewhere.

Since the CTAP network began over 3,500 people with CF have been screened for a trial. 2,300 have been enrolled in 50 trials supported by CTAP. Together, these studies are advancing the quality of care for people with CF across the UK. The CTAP has increased the number of clinical trial opportunities and improved access to the newest therapies for people living with CF.

Case study: Progressive Supranuclear Palsy (PSP) Association

PROSPECT Study Network improving diagnosis and care of rare neurological disorders

Progressive Supranuclear Palsy (PSP), CorticoBasal degeneration (CBD) and Multiple System Atrophy (MSA) are rare neurological conditions that progressively impact balance, movement, vision, speech, and cognition. Although there are similarities between the disorders, the classical clinical picture of each condition is distinct.

The rarity of PSP, CBD and MSA necessitated a collaborative approach to research, which led to the creation of the PROgressive Supranuclear Palsy CorTico-Basal Syndrome Multiple System Atrophy Longitudinal Study UK (PROSPECT-M-UK) study network. This brings together leading experts from many areas of biomedical research, including neuroimaging, clinical analysis, pathology and genetics. The network involves seven primary centres, with an aim to develop a UK wide network for future clinical trials.

The PROSPECT-M-UK study aims to find ways of tracking disease progression and improving diagnosis. The study found that the different forms of PSP, CBD and MSA have distinct patterns of clinical, cognitive and scientific results that can be used to improve early and accurate diagnosis in the clinic. It was also found that 50% of people living with PSP had a delayed diagnosis (an average of 3 years) because they initially presented with symptoms similar to other neurodegenerative conditions. A similar delay in diagnosis was also typical in MSA. These findings will help increase awareness of the conditions among clinicians, and provide better diagnosis and improved care to those living with these conditions. PROSPECT-M-UK created a participant registry, forming a unique collection of people that could be stratified and be asked to participate in future clinical trials.

This work is funded by the PSP Association and MSA Trust to a value of £2.7 million, over eight years. Funding from the UK Rare Disease Research Platform has been awarded to a follow-on study, to map the journey of people at early stages of atypical parkinsonian disorders, which will involve the PROSPECT-M-UK study network working in collaboration with patient-centric charities.

Case study: Great Ormond Street Hospital (GOSH) Charity

Pioneering new curative therapies for rare diseases

Great Ormond Street Hospital (GOSH) Charity provides funding to drive the development of pioneering interventions for rare conditions, such as gene therapies. GOSH Charity funding ranges from early seed-funding to support researchers in scientific discovery, to building world-class infrastructure. This funding has enabled the delivery of personalised medicine to families affected by rare diseases around the world, transforming their treatment.

In 2001, the only long-term treatment Severe Combined Immunodeficiency (SCID), a rare genetic condition, was a bone marrow transplant. At that time, GOSH was the first hospital to administer a gene therapy to a child in the UK with SCID, and this individual is now a young healthy adult.

Since 2013, GOSH Charity have supported work to develop gene therapy approaches for degenerative and eventually fatal neuromuscular conditions, such as spinal muscular atrophy (SMA). Children with SMA can now receive a gene therapy called Zolgensma® to improve their movement and breathing. A team supported by GOSH Charity also facilitated the implementation of Spinraza®, another drug for SMA, in the UK. Since its NHS adoption in 2019, 300 patients have already gained access to Spinraza®.

With the establishment of the Zayed Centre for Research into Rare Diseases in Children, GOSH Charity has further been able to support the development of therapies for recently identified rare diseases. The degenerative brain disorder, called Dopamine Transporter Deficiency Syndrome (DTDS), is a rare, progressive neurological condition, with no known cure and a high rate of mortality before adulthood. In 2021, GOSH Charity funded research to develop a gene therapy for DTDS, which has proved successful in both *in vivo* and *in vitro* experiments thus far. A future clinical trial of this treatment is in the planning stages at GOSH.

4.2.3.7 Wellcome Sanger Institute

Wellcome is a global charitable foundation that funds research, leads policy and advocacy campaigns and builds global partnerships. Wellcome funds discovery research across a range of academic disciplines that advances scientific discovery and leads to new insights into life, health and wellbeing. Wellcome's current strategy focuses on three urgent global health challenges: mental health, infectious disease, and climate and health. Wellcome also play a significant role in funding rare disease research, for example as a co-funder with NIHR of many of the Clinical Research Facilities described above (Figure 8).

The Wellcome Sanger Institute's is a wholly owned subsidiary of Wellcome, and its mission is to 'use information from genome sequences to advance understanding of biology and improve health'. In addition to the core funding from Wellcome, the Wellcome Sanger Institute is supported by a number of external grants from funders including UK Research Councils, charities, philanthropic organisations and the European Union. Quantitative data from both Wellcome and the Wellcome Sanger Institute are included within the AMRC rare disease research portfolio above. Here we provide an example of a significant study in the rare disease space that took place at the Wellcome Sanger Institute: the Deciphering Developmental Disorders (DDD) project (see case study box below).

The DDD study brought together Regional Genetics Services throughout the UK and Republic of Ireland with scientists at the Wellcome Sanger Institute. It was funded initially by the Health

Innovation Challenge Fund, a funding partnership between the Wellcome Trust and the Department of Health and Social Care, and latterly by the Wellcome Sanger Institute. DECIPHER was used to collate data from the DDD project (see case study box below), this was initially funded by the Wellcome Sanger Institute's core funding from the Wellcome Trust, and latterly by a Wellcome Biomedical Resource Grant.

Case study: Deciphering Developmental Disorders and DECIPHER

Deciphering Developmental Disorders (DDD) was established in 2010 as a partnership of the 24 Regional Genetics Services throughout the UK and Republic of Ireland, and scientists at the Wellcome Sanger Institute. The project aimed to advance clinical genetic practice for children with developmental disorders using sequencing technologies while addressing the ethical challenges raised.

DDD recruited 13,500 individuals with severe undiagnosed developmental disorders and their parents, from the UK and Ireland. Scotland, Northern Ireland and Wales recruited over 1200, 700 and 370 individuals respectively to the DDD project.

The individuals recruited to DDD had extremely rare developmental disorders which have remained undiagnosed with conventional diagnostic approaches. The lack of a diagnosis has a significant impact on families who may not know if future children will also have the same disorder, and they may struggle to access beneficial treatments and therapies for their child or to identify appropriate support groups for people living with the condition.

As of April 2023, the study had provided genetic diagnoses for around 5,500 children in the study, representing 40% of the cohort. The diagnoses were in over 800 genes, and included 60 new conditions discovered by the DDD study. The study has also resulted in medication or treatment changes for around a quarter of the children participating due to a clearer diagnosis.

The DDD project is ongoing and will continue to seek to provide diagnoses for the 13,500 participants in the original cohort, but it has already had significant impact across the UK. Some of the technologies and approaches developed by the DDD team have been adopted by Genomics England in the 100,000 genomes project (see case study below) and by the NHS within the Genomic Medicine Service, the Scottish Genomics Laboratories Network Whole Genome Sequencing Service, and the Rapid Genome Sequencing Service.

Northern Ireland is undertaking a DDD complementary analysis project on muscle and movement disorders for all 13,500 families across the UK and Ireland. Although recruitment to the project closed in April 2015, analysis and re-analysis is ongoing.

The sequencing and clinical data generated by DDD contribute to the knowledge resource in DECIPHER, a free-to-access database sharing phenotypic and genotypic data to support clinical diagnosis globally. Academic centres of clinical genomics around the world can become affiliated to DECIPHER to deposit their data, collaborate and facilitate diagnosis. DECIPHER contains 46,000 open-access patient records, and hundreds of thousands of phenotypic observations and genetic variants, and has resulted in 4,864 collaboration requests since 2014. DECIPHER data has contributed to more than 3,000 papers in the peer-reviewed scientific literature.

Congenica, spun-out from the work of DECIPHER in 2012, has become the exclusive clinical decision support partner for the NHS Genomic Medicine Service, and works with clinical organisations globally, to support analysis of large-scale genomic data. In 2020, Congenica raised $50M in funding.

4.2.3.8 LifeArc

LifeArc is a self-funded, not-for-profit medical research organisation. LifeArc takes science ideas out of the lab and helps to turn them into medical breakthroughs that can be life-changing for patients. LifeArc have been doing this for more than 25 years and their work has contributed to five licensed

medicines, including cancer drug pembrolizumab (Keytruda®), lecanemab for Alzheimer's (Leqembi), and a diagnostic for antibiotic resistance.

LifeArc's work is in translational science, bridging the gap between academic research and clinical development, providing funding, research and expert knowledge, all with a clear and unwavering commitment to having a positive impact on patient lives. LifeArc is committed to spending £1.3 billion by 2030 in areas of high unmet medical need.

LifeArc identified 16 projects in their Philanthropic Fund portfolio that were related to rare disease research in the 2016-2021 timeframe, not including one in a neoplastic cancer (available as Dataset 6 via NIHR OpenData). The Philanthropic Fund provides grants to academic researchers working to advance new treatments and diagnostics for rare diseases.

LifeArc contributed ~£6.3 million across these 16 projects and ~£1.3 million was contributed by other organisations. Of these 16 projects, four were awarded via funding calls run in partnership with another organisation (Action Medical Research (n=2) and the Great Ormond Street Hospital Charity (n=2). Three awards were co-funded by at least one additional external partner (The Aplastic Anaemia Trust, Cystic Fibrosis Trust + Rosetrees Trust and DEBRA Austria).

Since April 2021, LifeArc has continued to run the Philanthropic Fund supporting projects in rare diseases, contributed to the Innovation Hubs for Gene Therapy together with the MRC and the UKRI Biotechnology and Biological Sciences Research Council (BBSRC), created six Pathfinder awards and recently launched a £40 million fund for creating Translational Rare Disease Centres as part of the Rare Disease Translational Challenge. Motor Neurone Disease (MND) research has been supported via a MND Translational Research Fund (a joint fund with the MND Association the My Name'5 Doddie Foundation) and a MND Primer Fund (to support projects which seek to develop solutions to accelerate MND diagnosis). In addition, a collaborative partnership aimed at speeding up the development of effective MND treatments has been established, and a LifeArc- UK Dementia Research Institute Partnership Translation Fund was launched in 2023, and will provide funding opportunities for MND focused projects.

4.3 Genomics England

Genomics England, a company wholly owned by the Department of Health and Social Care, was formed in 2013 to guide the 100,000 Genomes Project in partnership with the NHS (see case study box below). A decade on from its establishment, Genomics England continues its mission to bring the benefits of genomic healthcare to everyone by connecting healthcare and research in genomics.

Case study: 100,000 Genomes Project: building foundations for the future

In 2013, Genomics England was set up to deliver the 100,000 Genomes Project. This moon-shot project had the goal of harnessing WGS technology to uncover new diagnoses and improve treatments for patients with rare inherited conditions and cancer.

Just 5 years later, the project reached its target: the 100,000th genome was sequenced.

The impact continues

Many patients and their families consented to add their genomic and health data to a secure library, where approved researchers could analyse it. This analysis continues to contribute to the development of new diagnostic tests, treatments and therapies for a range of conditions.

A foundation of clinical care

The 100,000 Genomes Project laid the foundations for the NHS GMS – the first healthcare system in the world to offer WGS as part of routine clinical care.

Through the 100,000 Genomes Project:

- 6,625 participants with rare conditions received a diagnosis that had not been possible through routine care
- 50% of participants with cancer received diagnostic results or changed treatment course

100,000 Genomes Project and the devolved administrations

The Scottish Genomes Project (SGP) recruited 1000 patients to 100,000 Genomes, under a bespoke but aligned ethics protocol, with sequencing done at University of Edinburgh. A rare disease diagnosis was made in 22% of families that took part, and an in-depth value-based health economics assessment is ongoing.

The 100,000 Genomes Project in Wales recruited 441 individuals from 154 families. The initial diagnostic rate in the Welsh cohort was 23%, and this has been increased following further research analysis and clinical review.

In Northern Ireland, the 100,000 Genomes Project recruited 442 people from across the region, and sequenced around 1,700 samples from patients and relatives. A diagnosis has been returned to over 150 families to date. A reanalysis of the data in 2022 increased the initial diagnostic yield from 20% to 35%.

Genomics England supports the NHS to offer whole genome sequencing to patients who might have genetic conditions and help to interpret results before they go back to a patient's clinician. Many patients and their families opt to share their genomic and health data for research. The data they collect is stored in the National Genomic Research Library, a platform built by Genomics England and NHS England that allows approved researchers to access samples, genomic data, and other associated health data via a secure research environment. Through this approach, Genomics England helps to ensure that healthcare data feeds into research, and in turn, that research generates new insights to improve diagnoses and treatments for NHS patients (see Infinity Loop diagram in Figure 21 below).

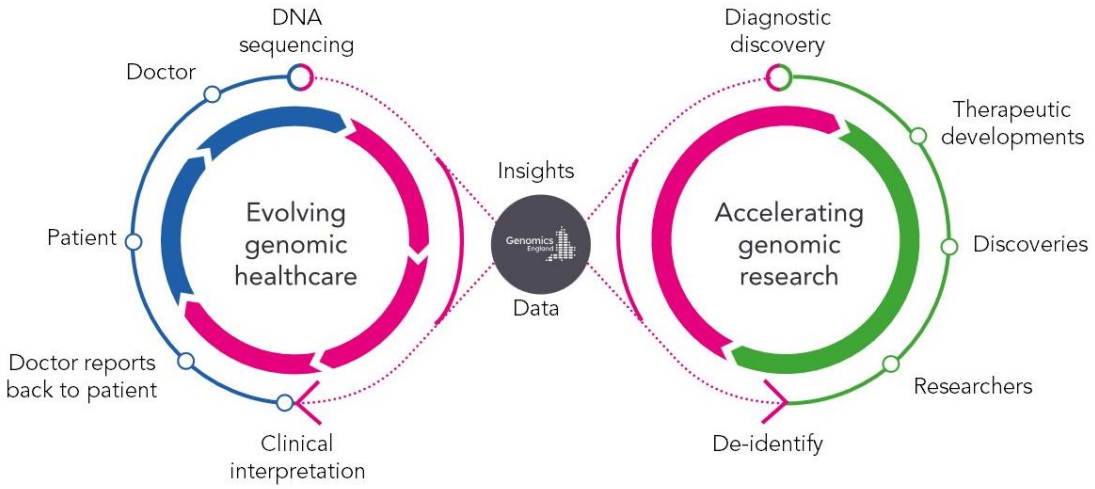


Figure 21: Genomics England Infinity Loop: demonstrating how healthcare data feeds into research, and how that research generates new insights to improve diagnoses and treatments for NHS patients.

The Clinical Research Interface (CRI) provides a safe and effective pathway for insights and data to be exchanged between researchers and NHS clinical teams to bring research findings into clinical care and benefit research. This means that when researchers find information of potential relevance to an individual's health in whole genome sequences in the National Genomic Research Library, it can be passed back to the NHS Genomic Medicine Service (GMS). This helps to:

- Provide research-identified diagnoses to participants through their healthcare professionals. In 2022, 1,518 research-identified potential diagnoses were returned to NHS Genomic Laboratory Hubs.
- Facilitate collaboration to enable fundamental and translational research in diagnostics and therapeutics. In 2022, 604 collaboration requests were sent to clinicians.

4.4 Rare disease research funded in devolved administrations

The devolved administrations play a pivotal role in cross-UK research initiatives. The advancement of rare disease research is highly dependent on coherent working across the four nations of the UK. Research in the devolved administrations of the UK is funded by similar mechanisms to those in England. The central government-funded health research opportunities, primarily through the MRC and NIHR, as described in Section 1.3, were accessible to researchers in the devolved administrations, as are charitable funding opportunities. Other smaller funding streams from the devolved health departments are administered via the Health and Social Care Research and Development Division of the Public Health Agency in Northern Ireland, the Chief Scientist's Office in Scotland, and both the Welsh Government Office for Science, and Health and Care Research Wales in Wales. Access to NIHR funding streams is facilitated via agreed financial contributions to the programmes, which allows researchers from those nations to lead applications. Funding from other major national and international research funders is also accessible to researchers from devolved administrations, and regardless of where lead site or sponsor organisation is located, care organisations in the devolved administrations can become sites for studies and recruit patients to research studies where the lead site is in another nation. Patients can also be referred to other sites for research study participation, particularly in conditions with small numbers of eligible participants, as is often the case with rare diseases.

The infrastructure required to support the management and delivery of research is similarly government-funded with support from charitable organisations, and ensures the ability to plan,

govern, manage and deliver health and care research. This includes research offices within care delivery organisations, clinical research networks, clinical research facilities and clinical trials units, biorepositories, and genetics networks and centres. In partnership with academic researchers and patient and public representatives, rare disease research is delivered across Health Boards and Trusts, specialist genetics centres and in primary care settings.

All four nations of the UK have established formal structures for the implementation of rare disease action plans which align to the UK Rare Diseases Framework document. In Scotland, the Rare Disease Implementation Board (RDIB) research subgroup has formed two working groups; Enhanced use of Registries and Data for Clinical Research, and One Scotland for Clinical Research, which are tasked with taking forward recommendations from the Rare Disease Action Plan for Scotland. Similarly in Northern Ireland, the Rare Disease Research (RDR) working group of the Northern Ireland Rare Disease Implementation Group has four key work areas: Establishing Baselines and Needs; Improving Accessibility and Uptake; Enhancing Communication and Awareness; and Improving Future Systems and Initiatives. In Wales, the Rare Diseases Implementation Group oversees the national plan and supports health boards to deliver their local plans. Wales' rare disease action plan includes specific research commitments to develop a consent strategy to enable researchers to securely and safely access routine genomic data and to engage with HCRW to help increase access to research studies for rare diseases patients. In England, the Rare Disease Framework Delivery Group consists of delivery partners across the health and care system, and is responsible for the development and delivery of England's rare diseases action plans.

The devolved administrations have active rare disease research communities across both clinical and non-clinical disciplines which work collaboratively at a UK-wide level. The Central Portfolio Management System (CPMS) is an online database used for the management of all study records within the NIHR Clinical Research Network (CRN) Portfolio. Data for studies run by the Northern Ireland Clinical Research Network and the Northern Ireland Cancer Trials Network are uploaded to the CPMS database. Scottish recruitment data is uploaded to CPMS for NIHR CRN portfolio studies, which includes Scottish led or Scottish only studies that have an eligible funder or have been accepted via the extended review process. Data for eligible studies involving Wales are also included in the CPMS database. The NIHR CRN Portfolio search therefore included all eligible studies involving the devolved administrations (results detailed in Section 3.6.2 above). The below case studies provide details of completed, current or planned rare disease research in the devolved administrations. These studies provide insights into diagnosis, treatment and management of rare diseases, help to inform and shape service provision and create opportunities for the patient population in Scotland to participate in studies.

4.4.1 Scotland

The case study below details a piece of research funded by the Euan MacDonald Centre for Motor Neuron Disease Research, a charitable network based at the University of Edinburgh.

Case study: Acceptability of Wearable Sensors in Motor Neuron Disease

Motor neuron disease (MND) progression is traditionally evaluated with the revised amyotrophic lateral sclerosis (ALS) Functional Rating Scale, which is a questionnaire-based assessment with limited sensitivity to detect change. Therefore, there is an urgent need for more objective, detailed and sensitive measures of physical function to monitor individuals clinically and evaluate the impact of trial interventions.

The study aimed to explore if wearable devices, specifically the ActiGraph accelerometer, would be an acceptable method of measuring movement. Devices like these may be a useful alternative to questionnaire-based measures as they can be more sensitive to detecting smaller changes in motor function.

Ten people with MND participated, and wore an ActiGraph accelerometer on their right wrist and ankle for one day every fortnight across the twelve-week study. This study also assessed the acceptability of these devices; all participants were asked to complete questionnaires on their experience with the devices.

All participants reported a positive experience overall and enjoyed the opportunity to try a new device, remaining supportive of using devices to monitor health. One individual reported that the devices affected their sleep, and one person reported that they struggled to put on and take off the devices themselves and had to rely on a caregiver.

4.4.2 Northern Ireland

The case study below provides an example of research taking place in Northern Ireland that is already providing insights into treatment and management of rare diseases, helping to inform and shape service provision and creating opportunities for the NI patient population to participate in studies.

Case study: Needs of informal caregivers of people with a rare disease: a rapid review of the literature

Many people living with a rare disease are cared for by a family member. Due to a frequent lack of individual rare disease knowledge from healthcare professionals, the patient and their informal caregiver are frequently obliged to become 'experts' in their specific condition. This puts a huge strain on family life and results in caregivers juggling multiple roles in addition to unique caring roles including as advocate, case manager and medical navigator.

A rapid review of literature reporting on the unmet needs of informal caregivers for people living with a rare disease was conducted. Thirty-five papers were included in the final review and data extracted.

This rapid review presents several unmet needs identified by informal caregivers of persons with a rare disease. The related literature was organised thematically: caregiver burden, support through the diagnosis process, social needs, financial needs, psychological needs, information and communication needs and acknowledgement from healthcare professionals. This review provides evidence that increased meaningful support is required for caregivers, and led to a successful bid in the MRC Public Health Intervention Development funding opportunity to co-develop a 'Rare Disease Carer Support Tool in Northern Ireland'. This tool will support psychosocial needs of unpaid carers, and promote effective engagement with caregivers embedded in the project from initial conception, through to design and delivery. A carer was included as a formal co-applicant on the funding bid.

Active engagement should be encouraged from this cohort in future research and awareness raised of the support available to improve the quality of life for families living with a rare disease. The unmet needs identified through this review will benefit people living with a rare disease, caregivers, healthcare professionals and policy makers.

4.4.3 Wales

Welsh Government, through Health and Care Research Wales, funds the Wales Gene Park, an infrastructure support group hosted by Cardiff University's School of Medicine. The Wales Gene Park supports and promotes genetic and genomic research across Wales, including working closely with the All Wales Medical Genomics Service and Genomics Partnership Wales to develop and implement comprehensive, accurate and rapid diagnosis of rare genetic diseases by next generation sequencing.

The Sêr Cymru programme (led by the Welsh Government Office for Science) and Health and Care Research Wales (HCRW) both support both clinical and non-clinical fellowship awards. In addition, HCRW supports a specialty lead in Rare Diseases who provides strong UK-level engagement for Wales in clinical research portfolio monitoring and research delivery.

An important investment that was commissioned by Welsh Health Specialised Services Committee and funded by Welsh Government, and is beyond the timeframe used for this report, is the Wales Syndrome Without a Name (SWAN) clinic. This was first of its kind in the UK, and opened in October 2022 to offer hope to children and adults with syndromes so rare they don't have a name. It also helps to provide the basis for quality improvement and original research opportunities that can be used across other rare disease health settings.

Case study: New syndrome identification and translation into diagnostic tests

During the funding period highlighted in this report, new genomic methods for genetic diagnosis have been developed by researchers from Wales and implemented in the diagnosis of patients with Familial Adenomatous Polyposis Syndromes and Tuberous Sclerosis Complex (TSC).

This work involved working closely with the All Wales Medical Genomics Service and Wales Gene Park, and was supported by the Genomics Partnership Wales. The collaboration enabled patient recruitment, sample banking and analysis that contributed to improvements in the diagnosis of both of these conditions.

For Familial Adenomatous Polyposis Syndromes, this included the detection of patient mutations missed by initial diagnostic service screening which were recovered by genomic testing in a research capacity. The impact on these patients included more appropriate surveillance of disease progression and reduction of risk of cancer for those patients and their at-risk relatives. This work was funded through a HCRW Health Research Fellowship and a Precision Medicine Fellowship jointly supported by the Sêr Cymru programme and HCRW.

Extensive collaboration with industry in this area has also supported activities including a partnership with Cellesce Limited, a small to medium-sized enterprise with expertise in bioengineering and bioprocessing. This led to the development of 3D patient-derived organoid models for polyposis syndromes and resulted in income generation in 2018-2020 as well as generating novel IP.

In TSC, a recent study has resulted in many new TSC diagnoses for individuals where NHS diagnostic testing previously failed to identify a pathogenic variant. The identification of recurrent pathogenic variants in these individuals have also been incorporated into diagnostic screening by the All Wales Medical Genomics Service diagnostic service.

4.5 Rare disease registries

Each UK nation has a population-based congenital anomaly and rare disease registration system: England, NCARDRS; Scotland, CARDRISS; Wales, CARIS; Northern Ireland, NIRADCAR. These four national registries operate in close collaboration with one another. There are also several disease specific research or clinical registers that are owned and managed by clinicians or patient support organisations (such as the National Registry of Rare Kidney Diseases described in the case study box below). All these registries play a vital role in rare disease research, particularly in relation to data-driven epidemiological research and the identification of potential clinical research participants.

NCARDRS (National Congenital Anomaly and Rare Disease Registration Service) was established in 2015 and collects data on over 1400 different congenital anomalies and rare diseases across England, including data from newborn screening.

CARIS (Congenital Anomaly Register and Information Service) was established in 1998 as a register for congenital anomalies in Wales and always included some rare diseases, including those detected from the newborn Bloodspot Screening Program. Since 2013, CARIS expanded to include childhood rare diseases and, from 2020, rare diseases recorded in people over the age of 18 years.

CARDRISS (Congenital Conditions and Rare Diseases Registration & Information Service for Scotland) was commissioned in 2018 to establish a national congenital and rare disease register for Scotland. CARDRISS currently collects information on major structural or chromosomal conditions, or

recognised syndromes, diagnosed antenatally or in infants, in line with European Surveillance of Congenital Anomalies guidelines. No other rare diseases are currently included.

At the time of writing, the NIRADCAR (Northern Ireland Rare Diseases & Congenital Anomalies Registry) was under development, with information available for a small number of rare diseases.

National rare disease registries have significant potential to support UK-wide population health surveillance, health service delivery, and data-driven research. National rare disease registries strive to improve the identification of rare diseases in national datasets, and drive real-world, data-driven research at scale. Accurate and accessible real-world rare disease data is critically important for rare disease research; there is great appetite among rare disease researchers to work with, and get support from, national rare disease registries.

All national rare disease registries focus on accurately coding and identifying rare diseases (see case study box below). To effectively support patient care and development of new treatments, it is crucial that data systems are interoperable, and that data can be easily and securely shared. We are working to ensure that rare disease registries are considered as part of the work to implement the commitments in the Genome UK 2021 to 2022 implementation plan, which aims to ensure that the UK's existing genomic data sets are interoperable with each other. Interoperability both within and between datasets will facilitate the linkage of rare disease registries to a diverse range of data, including intensive care, genetics, molecular pathology, imaging, laboratory biochemistry, mortality, hospital episode statistics, patient reported experience measure (PREMS) and patient reported outcome measures (PROMS).

National rare disease registries are a valuable resource that should be capitalised on for rare disease service provision and support. For example, NCARDRS has been working in partnership with academics, clinicians and patient groups to collect high-quality data on rare diseases at a population level, resulting in the publication of research papers to improve understanding of rare diseases. Additionally, in England's 2023 Rare Diseases Action Plan, a commitment was made to increase data-sharing for patient benefit to improve the "findability" of people living with rare diseases using NCARDRS, by improving the quality, coverage, completeness and transparency of national rare disease registration data. With the availability of sufficient funding there is great potential for increasing the use of national rare disease registers for research.

Case study: Kidney Research UK

National Registry of Rare Kidney Diseases (RaDaR)

Rare kidney diseases, such as steroid resistant nephrotic syndrome (SRNS), are devastating diseases with massive morbidity. The National Registry of Rare Kidney Diseases (RaDaR) provides an essential resource for researchers seeking to understand rare kidney diseases, fulfilling a unique role in the rare disease research space, bringing together patients and researchers. By the end of June 2023, there were 30 Rare Disease Groups, covering 92 conditions/sub-conditions, with 33,065 UK patients recruited into RaDaR across the registries. The registry is financially supported by Kidney Research UK, who funded the initial grant with Kidney Care UK, and have continued to provide an annual grant, as well as having provided strategic management of the registry during the first few years. RaDaR has been credited in 29 publications since 2018.

The registry also forms the core repository of the clinical dataset for NURTuRE (National Unified Renal Translational research Enterprise), the first national kidney biobank with two initial cohorts for chronic kidney disease (CKD) and idiopathic nephrotic syndrome (INS) covering England, Scotland and Wales. This biobank acts as a key resource for the kidney disease research community, supporting innovative approaches to change the lives of patients, funded through a unique partnership between industry and Kidney Research UK.

Case study: NIRADCAR

Accurately coded data increases diagnostic yield and accelerates access to appropriate therapies

Scoping studies undertaken to support the development of NIRADCAR (Northern Ireland Rare Diseases & Congenital Anomalies Registry) highlighted digital and data challenges for rare diseases.

Focus groups and reviews of records confirmed no consensus for recording rare disease diagnoses across Northern Ireland healthcare records. For example, individual clinicians, associated healthcare professionals, biomedical and clinical scientists often recorded the same rare disease diagnosis by a range of different names. This was not unexpected considering there are over 8,000 rare diseases and the international classification of rare diseases (ICD-10) that is in routine use includes less than 500 rare conditions, only approximately 240 of which have a specific ICD-10 code. Using text-based searches is problematic considering different spelling and abbreviations – as an example, 19 different variants of 'spinal muscular atrophy' were identified. Norther Ireland are identifying bespoke training needs to help standardise recording of rare disease diagnoses and associated clinical coding.

Collaborative research by Queen's University Belfast, Belfast Health and Social Care Trust, and the Northern Ireland rare disease patient advisory group, demonstrated how improving digital infrastructure with more accurate, consistent coding, and extensive phenotyping of a small number of rare diseases, accelerated the diagnosis and treatment of patients. Standardising diagnoses in healthcare records will facilitate more effective implementation of emerging tools that support people living and working with rare disease(s).

4.6 Rare Disease Collaborative Networks (RDCNs)

Rare disease collaborative networks (RDCNs) are an important part of the NHS architecture initiated by NHS England and NHS Improvement to improve care and support for people living with a rare disease. RDCNs are made up of groups of rare disease service providers who have an interest in developing understanding of a particular rare disease. Providers who establish an RDCN are committed to working together to progress research, increase knowledge and improve patient experience.

The establishment of an RDCN is not accompanied by funding; it is expected that RDCNs should include providers that are already research-active in a particular rare disease. RDCNs help to bring together leading experts working in a particular rare disease area. To date, 18 RDCNs have been established across a range of specialties and disease groups, and in providers from a wide spread of regions across the UK, including in the devolved administrations.

RDCNs work with the Highly Specialised Commissioning team in NHS England to provide the evidence base for future potential commissioning decisions. RDCNs demonstrate a route for direct impact of translational and clinical research on the services provided to people living with a rare disease.

5 Discussion

5.1 The volume and diversity of rare disease research across the UK

This report collates, for the first time, an extensive picture of UK-wide rare disease research funding over a 5-year period. We report on the development of a search protocol, based on Orphanet rare disease names, which provides a novel tool to comprehensively identify rare disease research. Here we present a quantitative analysis of rare disease research funded by government, industry and charities between 2016-2021. We also present further narrative detailing rare disease research funded by other organisations, and additional examples of rare disease research funded in Wales, Scotland and Northern Ireland. Although different approaches were taken by different funders to gathering information to include in this report, together it provides the most comprehensive overview of the rare disease research landscape in the UK to date.

The information presented here demonstrates the breadth and depth of rare disease research across the UK. There is substantial research investment, and many research studies, with relevance to rare diseases, the diversity and volume of which is considerable. There were 2351 awards identified in the AMRC rare disease research portfolio; 698 awards identified in the NIHR Programmes and MRC rare disease research portfolio; and 254 industry research and development (R&D) projects on rare diseases in the UK. It is important to note that awards and projects can vary greatly in magnitude, so these numbers do not necessarily reflect the total amount of research funded. The awards accounted for 7% of the total research spend for NIHR Programmes and MRC, and 5% of the total research spend for AMRC member charities, within the five-year timeframe. There were also 1639 and 1686 rare disease related studies supported by NIHR infrastructure schemes and the NIHR Clinical Research Network respectively. The NIHR Programmes and MRC rare disease research portfolio, combined with the AMRC rare disease research portfolio, equates to over £1.2 billion of research funding. This is in addition to the rare disease research funding invested through NIHR infrastructure, industry and additional funders across the four nations of the UK. This is significant not only for the rare disease community, but also for the broader advancement of fundamental scientific understanding of the aetiology and pathophysiology of human disease.

5.2 The predominant foci of rare disease research funding

This project found that there are a small number of rare diseases for which there is a large amount of research; a moderate number of rare diseases for which there is a limited amount of research; and a very large number of rare diseases for which no research was identified within the report timeframe. In the NIHR Programmes and MRC, and AMRC, rare disease research portfolios respectively, there were 287 and 298 rare diseases associated with 1-3 awards. Whereas there were only 75 and 131 rare diseases associated with 4 or more awards in these two portfolios respectively.

The presence of a large amount of research on cystic fibrosis could be explained both by its relatively high prevalence and due to the underlying aetiology being understood, and therefore treatments being developed. There was also a large preponderance of neurological research. The trends seen in this project were reflective of the trends seen in the UK Health Research Analysis 2018, where neurological awards were the fourth largest category, after general health relevance, cancer and neoplasms, and infection (noting that the latter two categories were excluded in the analysis phase of this project). These findings could be demonstrative of the UK's strength and specialities in neurological research. However, within the neurological category, there are several rare diseases, ranging from rare to ultra-rare. The data show that motor neurone disease research tends to dominate the research within this category, meaning that there are likely many rarer neurological conditions that do not receive the large volume of research focus the analysis implies. Following neurological rare diseases, the data suggest that there are then several groups of rare diseases for which there are similar levels of research taking place.

The focus of industry efforts in the UK across earlier stages of R&D, is likely reflective of the UK's strong science base and globally competitive Phase I clinical trial ecosystem[7]. The difference in the number of projects between early phase clinical trials and late phase clinical trials, is likely due to Phase II studies being sufficient in generating the evidence needed to progress to license, resulting in fewer Phase III clinical trials being conducted, be that in the UK or globally. This trend could also be due to rare disease technologies being shown to be ineffective in early trials.

In 2021, the International Rare Diseases Research Consortium (IRDiRC) published State of Play Report (2019-2021). This report included a chapter summarising the international rare disease research landscape, using data on research projects and clinical trials that was sourced from the Orphanet database, the IRDiRC-Orphanet Rare disease Research Landscape Analysis Platform, and the World Health Organisation (WHO) International Clinical Trials Registry Platform Database of Clinical Trials. Whilst the State of Play report would have included information submitted by the UK Orphanet national team, the data gathered was likely less exhaustive than the data presented in this project. The State of Play report did not include analysis of research on rare cancers. Similarly, to the trends seen in this project, the State of Play report found that rare neurological disorders was the medical domain with the greatest amount of research associated with it, and Amyotrophic Lateral Sclerosis (ALS), Duchenne Muscular Dystrophy, Huntington Disease and Cystic Fibrosis were the rare diseases with the greatest number of research projects on them. The State of Play report also found that globally, over half of the rare disease research projects performed were basic research, and a quarter were pre-clinical studies. Most of the clinical trials identified by the State of Play report were in early development phases (phases II and III), with rare neurological disorders being the disease grouping with the greatest number of clinical trials associated with it.

[7] The Association of the British Pharmaceutical Industry, 2022. *Rescuing patient access to industry clinical trials in the UK.* Available online here: https://www.abpi.org.uk/publications/rescuing-the-uk-industry-clinical-trials/

In 2022, the European Commission published a report on European Union (EU)-funded research on rare diseases. This report detailed the EU funding programmes that have supported research into rare diseases, and emphasised the value of interdisciplinary, multinational collaboration in this field. This report emphasised the volume of research taking place across Europe into rare neoplastic and rare infectious diseases, and also found that a significant percentage of EU rare disease research funding was into rare neurological diseases.

5.3 Comparison of government, industry and charity rare disease research portfolios

From the data presented here it can be seen that there are several similarities between the government, industry and charity rare disease research funding portfolios. For example, motor neuron disease and cystic fibrosis are both among the rare diseases with the greatest number of awards or projects associated with them across all three of these rare disease research portfolios.

The total investment from government and charity in rare disease research over this timeframe was similar (NIHR Programmes and MRC rare disease research portfolio was almost £627 million, AMRC rare disease research portfolio was over £580 million). However, the total number of awards was higher, and the average value of awards was lower, in the AMRC rare disease research portfolio compared to the NIHR Programmes and MRC rare disease research portfolio. This demonstrates the strengths across different funders to deliver both breadth and depth of research funding.

The AMRC data represent a range of organisations that are funding rare disease research, from charities that focused on a specific rare disease (often with relatively small research spend), to multinational charities with a broad focus. These data also highlight the importance of co-funding between government, industry, charities and other organisations, with 15% of awards in the AMRC rare disease research portfolio being co-funded with another organisation. The benefits of inter-sector collaboration on research are further highlighted by the significant proportion of studies supported by NIHR infrastructure schemes that are funded by other organisations, including charities and industry which fund over 20% and almost 50% of NIHR CRN supported studies respectively. As well as partnerships between research funders on specific research projects, there are several broader strategic patient and public involvement and engagement (PPIE) partnerships that take place, which would not have been captured in this report.

5.4 Equity and geographical spread of rare disease research funding

Across the government, industry and charity rare disease research portfolios, most of the studies identified were led by, or contracted to, research organisations in London and the southeast. However, research organisations leading rare disease research were identified across all regions of England, as well as Scotland, Northern Ireland and Wales. This is reflective of the broader trends of geographical distribution of research that are seen across UKRI Research Councils collectively, as well as overall NIHR Programme data and AMRC members' charitable expenditure in 2022. This is reflective of the broader trends of geographical distribution of research that are seen across UKRI Research Councils collectively, as well as overall NIHR Programme data and AMRC members' charitable expenditure in 2022. This could be due to the locations of specialist centres for rare diseases, to which participants from across the UK might travel to. Therefore, whilst the results show the locations where research is taking place, these data do not show the geographical data for where research participants live. Collating these participant-focused data was beyond the scope of this project. Nevertheless, the regional disparities that could arise from these trends must be considered. This is important to ensure that people across the UK have equitable access to the benefits of research participation, and that research participants are a representative sample of the UK population.

This project found that there were many rare diseases for which no research was identified. The IRDiRC State of Play Report (2019-2021) also emphasised the large number of rare diseases for which no research or clinical trials were identified globally. It is estimated that approximately 400 rare diseases account for over 90% of the prevalence of all rare diseases[8]. Therefore, it would be interesting to understand whether the rare diseases that were identified in this project as being the most researched were also those with the highest UK-based prevalence.

Whilst the data presented here gives a UK-wide picture, it must be noted that research and the life sciences industry is global. Each country has its strengths in research, and it would not be possible for all rare diseases to be researched in each country. The absence of research on a particular disease in the UK does not necessarily mean that it is not being researched elsewhere. Research conducted throughout the world can bring benefits to people living with rare conditions irrespective of where they live. International collaboration is an underpinning theme of the UK Rare Diseases Framework, and we recognise the importance of international collaboration for rare disease research. Due to the nature of rare disease patient cohorts, clinical trials in this area are often multicentre and rely on recruiting patients from multiple countries. Centres of expertise are often spread across the world. Consideration of the UK-wide rare disease research funding portfolio in the context of international research on rare disease is important, but collecting international data was beyond the scope of this project.

5.5 Mapping of the NIHR Programmes and MRC rare disease research portfolio to the UK Rare Diseases Framework

As part of the analysis, the NIHR programmes and MRC rare disease research portfolio was mapped against the four priorities of the UK Rare Diseases Framework, with basic science as an additional category. It was found that most awards in the portfolio mapped to priority 4 (improving access to specialist care, treatment and drugs) or basic science research. Priority 1 (helping patients get a final diagnosis faster) was the category with the third highest number of awards mapped to it, whereas there were fewer awards mapped to priority 2 (increased awareness among healthcare professionals) and priority 3 (coordination of care). This was reflective of the trends seen when the data were analysed by HRCS Research Activity Codes (Figure 5), where 'aetiology' and 'evaluation of treatments and therapeutic interventions' were the two categories that had the greatest number of awards associated with them.

The general funding focuses of MRC and NIHR focus on basic science research and clinical research respectively. Therefore, it is important to consider that although the MRC and NIHR have different remits, this mapping exercise used a joint portfolio. As expected, it was found that most of the awards mapped to basic science were funded by MRC, whereas most of the awards mapped to the coordination of care priority were funded by NIHR programmes. It is relevant to note that no specific funding calls from either of these funders to specifically address the priorities of the Framework; most of the research funding data presented here was commissioned prior to publication of the UK Rare Diseases Framework.

There were limitations associated with this mapping exercise. For example, interpretation of the definitions was subjective, and the mapping was not apportioned when assigned to more than one category. Additionally, there are types of rare disease research which would not have readily fallen under any of the categories defined, such as descriptions of new gene-disease associations, or

[8] *Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database | European Journal of Human Genetics (nature.com)*

establishment of patient cohorts. Despite the need for cautious interpretation of these results, this remains a useful exercise to understand potential gaps in the research funding landscape, where evidence generation could inform future policy making decisions.

5.6 Limitations of the approach taken in this project

The results presented here reflect the limitations of the search protocol and each funder's best assessment of what to include. The input datasets used for government, industry and charity were all different to one another, so there are differences in the detail of searches performed and the outputs generated. Additionally, the search was limited by the award information in the input data. If there was insufficient information known about an award to apply the search criteria, it could not be included in this project. Factors such as a lack of consistency in terminology used, and spelling or abbreviation variations of rare disease names could have resulted in awards not being included. Therefore, in some cases the results presented here may underrepresent the rare disease research taking place. In other cases, there are conditions included in Orphanet, which are not universally regarded as rare, and so could be considered to over represent the amount of rare disease research funded.

This project does not include information on the global rare disease research landscape. Additionally, the analysis phase of this project did not include research related to rare cancers or rare infectious diseases; there is a significant amount of research that takes place both nationally and internationally on these conditions. Furthermore, there are categories of research that would not have been identified using the search protocol. For example, fundamental scientific research, including genomic research, that doesn't specifically mention rare diseases. It was also not possible to capture disease agnostic diagnostic and technological developments, such as genomic sequencing techniques, in this report. However, this research underpins many advancements that further the understanding, diagnosis or treatment of rare diseases.

This project represents a major step forward in being able to define, identify and classify rare disease research. However, several practical difficulties were encountered during the search phase of this project. The tools to understand the large and disparate portfolio of rare disease research are needed, but don't yet exist in a satisfactory form. For example, future iterations of similar work would greatly benefit from a comprehensive list of all known rare diseases, including associated naming and spelling variations. This would be aided by a universal definition and identification or coding system for rare disease research. The Orphanet coding and grouping system had the advantage of being relevant to rare diseases, but wasn't specifically designed to be used for the purpose of this project, and so had some associated caveats. For example, the mapping of awards to Orphanet groupings was inexact, and efforts to automate the search phase as far as possible using Orphanet meant that studies which ought to be included in the portfolio could have been missed. Additionally, some studies which ought not to be included based on the definitions used in this project are also likely to be included in the dataset.

An example of a tool that exists for portfolio analysis in a different disease area is the Common Scientific Outline that is used by the International Cancer Research Partnership, whereby all awards on their database are coded using a common language. The Common Scientific Outline is a classification system organised into six broad areas of scientific interest in cancer research and is complemented by a standard cancer type coding scheme. Together, these tools enable uncomplicated, comparable and consistent analysis of cancer research funding portfolios across research organisations. Improved identification and classification of rare disease research would be gratefully beneficial for increased understanding, and ease of analysis of, the rare disease research

funding landscape. Without this, there are several barriers to updating or repeating this piece of work regularly.

The timeframes used in this report represent a limited snapshot of rare disease research funding. Defining a timeframe provided a practical approach for data analysis and enabled comparison of an equivalent timeframe across different research funders and sectors. The Covid-19 pandemic occurred towards the end of this timeframe and could have impacted the status of awards. Analysing the impact of Covid-19 on the research funding portfolio was beyond the scope of this project. Additionally, the results presented here do not include the considerable funding into rare disease research that has taken place prior to, and following, this five-year period. For example, 2023 has seen some significant rare disease research investments, including the £14 million UK Rare Disease Research Platform, co-funded by MRC and NIHR, from July 2023 and the £40 million Rare Disease Translational Challenge launched by LifeArc in July 2023. Early findings from this landscape project were considered during the design and scoping phase of the UK Rare Disease Research Platform funding call. Together, these are significant investments that aim to overcome some of the most common challenges in the diagnosis, management and treatment of rare diseases, through building on the rich research base described in this report. They will enable greater connections between patients, and academic, clinical and industry experts across the country.

5.7 Opportunities for future work

5.7.1 Rare neoplastic diseases and rare infectious diseases

As described in Section 2.1.1 above, for policy-based reasons, rare cancers and rare infectious diseases were not included in the detailed analysis phase of this project. These groups of diseases are treated as distinct policy areas within the Department of Health and Social Care. Additionally, these groups of diseases attract a large amount of research funding, that would dominate the dataset. However, the NIHR Programmes and MRC dataset including these awards has been published alongside this report as Dataset 2 (see Section 2.4 above), to facilitate further analysis by interested parties.

To enable automated removal of these two groups of diseases from the NIHR programmes and MRC rare disease research portfolio, all awards allocated to the rare neoplastic Orphanet grouping were taken out of the dataset as a single group. This meant that many rare conditions that cause an inherited predisposition to cancer were likely not included in the onward analysis, as they were contained within the rare neoplastic Orphanet grouping. As part of England's Rare Diseases Action Plans, the Department of Health and Social Care remains committed to better understand the needs of those living with rare genetic conditions that cause an inherited predisposition to cancer. We hope to return to specifically analyse these data in the future.

5.7.2 Engagement on future directions for the rare disease research landscape

This report is the starting point for the discussion about gaps, priorities and levers for change in rare disease research. The findings presented in this report will be used to support further engagement work on future directions for the rare disease research landscape. The DHSC team with responsibility for the UK Rare Diseases Framework and England's Action Plans intends to work with the rare disease community (including people living with rare conditions, their families and carers; charities; researchers; health care professionals; research funders and health service commissioners) to discuss the data presented in this report, and capture feedback on gaps and priorities. Further discussions will aim to include a good spread of geographical representation, to hear from voices across the UK. We will present these findings to a broad spectrum of research funders, to allow consideration of whether action is needed to address gaps and priorities, and if so, what levers may

be drawn on to do so. For example, discussions could be held around the openness and applicability of funding calls to rare disease research.

Consideration may also be given to whether more should be done to incentivise research specifically on priorities 2 & 3 of the UK Rare Diseases Framework (increasing awareness of rare diseases among healthcare professionals, and better coordination of care respectively). Or, whether actions could be taken to address these two priorities in the design of research more broadly. Research that takes a more generic approach, such as improving care coordination and improving awareness of rare diseases among health care professionals, has the potential to benefit all people living with rare conditions. Funding more non-disease specific research could enable more people living with rare conditions to benefit from the significant investment in rare disease research across the UK.

The Academy of Medical Sciences report on clinical trials for rare and ultra-rare diseases detailed some of the significant challenges to research participation for people living with rare conditions, such as facing a significant physical, mental and emotional burden. Additionally, the challenges associated with accessing, identifying and recruiting participants for rare disease clinical trials were acknowledged in the report's recommendations. Initiatives such as the NIHR BioResource[9] (see Section 3.6.1.1 above), NIHR's Be Part of Research platform, and efforts led by rare disease patient organisations help to facilitate opportunities for people living with rare conditions to participate in research. The report also recommends the use of innovative clinical trial design as an effective way for a greater number of individuals to benefit from investment into rare disease research. This theme is being taken forward with significant investment in the UK Rare Disease Research Platform through the "Changing clinical practice in rare diseases through innovative trial designs" research node.

It could also be of interest to further understanding of the upcoming rare disease research and treatment pipeline by using the data underlying this report in horizon scanning work. Use of rare disease research portfolios for foresight thinking by service commissioners and medicine regulators could aid the development of patient pathway planning and medicines access pathways.

6 Conclusion

This is the first time that a comprehensive picture of the rare disease research landscape across the UK has been collated. The volume and diversity of rare disease research and development taking place across the UK that it demonstrates is highly significant. This ongoing dedication of the rare disease research community, from research funding to clinical delivery, will result in the continual improvement of the lives of those living with rare diseases. However, this would not be possible without the involvement of the rare disease community across all stages of research. The contribution to research by people living with rare diseases, those who care for them, and patient support organisations is essential to translate scientific and clinical advancements into real-world benefits.

The significant rare disease research investments announced following this timeframe, such as the UK Rare Disease Research Platform, co-funded by MRC and NIHR, and the LifeArc Rare Disease Translational Challenge, will impact on the future rare disease research landscape. The data presented in this report could contribute to the shaping of these, and future, research funding opportunities. Further engagement work on future directions for the rare disease research

[9] *NIHR Bioresource 2023. Rare diseases BioResource. Available online here: https://bioresource.nihr.ac.uk/centres-programmes/rare-diseases-bioresource/*

landscape will centre on discussions about gaps, priorities and levers for change in rare disease research. It is hoped that this work will help to promote stronger networks and collaboration across the rare disease research community, to ensure that those living with a rare disease derive maximum benefit from research.

Annexes

1 Detailed methods for MRC and NIHR portfolio search

To perform the detailed search of the entire NIHR and MRC portfolios, a bespoke search method was developed to identify research funding relevant to rare diseases. Neither NIHR nor MRC had a pre-existing internal search field to identify rare disease research. Development of this algorithm involved curating a complete list of search terms that were used to identify rare disease relevant awards. The full search methodology and algorithm script has been published alongside this report on NIHR OpenData and detailed below. The algorithm was developed and run by the Project Group, following input from both the Steering and Expert Groups on the search strategy.

Based upon the data sources and timeframe detailed below, all awards from the NIHR Programmes and MRC portfolios, including NIHR career development awards, were first combined into a joint-funder list. A set of terms (described in Annex 1.1 below), including individual rare disease names and associated terms such as 'rare genetic variant' or 'syndrome without a name', were then used to search within this list to identify all awards that met the search criteria, which were therefore identified as being research on rare diseases, as per the definition used in this project. The identified awards were then extracted to create an initial dataset that was validated by representatives from each funder to create the final dataset.

Data on the programmes part of the NIHR portfolio and data on the infrastructure part of the NIHR portfolio is held in different ways. This necessitated a different approach to searching, analysing and presenting results from NIHR programmes and NIHR infrastructure awards. NIHR infrastructure awards were searched in parallel to create the NIHR infrastructure rare disease portfolio. Within the infrastructure portfolio, studies supported by NIHR infrastructure schemes were distinguished from studies supported by the NIHR Clinical Research Network (CRN), as these data are held differently.

1.1 Search terms

Two lists of search terms were developed and combined for use in the search, to identify awards mentioning individual rare disease names (section 2.3.1.1) and awards mentioning 'rare disease' more broadly (section 2.3.1.2). Where available, the titles, abstracts, aims, objectives, keywords and summaries of each award were searched for matches to the terms in the below two lists. Further detail on the input fields is provided in Annex 1.2 below.

1.1.1 Individual rare disease names

- This list of search terms was used to identify research on specific rare diseases, which may or may not also identify the disease as 'rare'.
- Orphanet, which is a global network that provides a reference source for information on rare diseases, was used to derive the list of individual rare diseases that were searched for by the algorithm.
    - Orphanet uses the European Union Regulation on Orphan Medicinal Products (1999) to define a rare disease as a disease that affects no more than 1 in 2000 people in the European population. The UK contributes data to Orphanet. Therefore, this prevalence-based definition was used as the standard definition of a rare disease, to enable use of a single, standardised dataset. This definition includes diseases of all causes; diseases of childhood or adult onset; ultra-rare diseases; and syndromes without a name (SWANs). For the purposes of this project, all diseases that appeared on the Orphanet database were considered rare. This approach led to

some apparent anomalies, such as the inclusion of preeclampsia as a rare disease, as it is listed in the Orphanet database. However, using this standard approach enabled consistency and reproducibility.

- Orphanet performs biannual updates of its list of rare disease names via alignment to several external rare disease data sources[10]. The version of the aligned list of rare diseases that was used in this search was downloaded from Orphanet on 01 April 2022. The list included Orphanet disorders, disorder groups and disorder subtypes, and synonyms thereof.
- Several extensions to the Orphanet derived list were made to account for issues such as alternative UK and US spellings; minor grammatical differences in disease names (e.g., hyphenation, apostrophe use); or the removal of acronyms from names. Examples of terms added in this list included 'thalassemia' to account for the fact that the Orphanet list states 'alpha-thalassemia' only; and 'Cushing's syndrome' to account for the fact that the Orphanet list states 'Cushing disease' only. However, it was not feasible to cover all possible synonyms or naming variations. Instead, we aimed to use a consistent and reproducible approach. Modifications made are detailed in the full protocol and associated annexes published on NIHR OpenData.
- Additionally, 3 manually identified search terms were added when the Project or Expert Groups identified known gaps in the results[11], in some cases due to differences between the search terms used and names commonly used for diseases in the UK. Manual addition of search terms was limited as much as possible, so that the core basis for the search remained as the Orphanet list of individual disease names.
- In total, 23,797 search terms were used, to identify 9,640 disease entities (comprising 6,455 Orphanet disorders, 2,134 disorder groups and 1,048 disorder subtypes, as well as the 3 manually added terms[11]). The complete list of search terms is provided in the full protocol and associated annexes published on NIHR OpenData.

1.1.2 Search terms for rare diseases per se

- This list of search terms was used to identify research relevant to rare diseases, that may or may not mention any individual rare disease names in the award description. For example:
  - research into groups of rare diseases
  - research into rare genetic variants
  - research into syndromes without a name, or orphan drugs
  - research infrastructure that supports multiple rare diseases
- This list was curated by the Project Group, with input from the Expert Group, based upon prior knowledge and experience of research funding. The full list of 66 search terms that were used to identify rare diseases *per se* is provided in full protocol and associated annexes published on NIHR OpenData.

[10] *The rare disease data sources Orphanet performs biannual updates against are the International Classification of Diseases (ICD); the Online Mendelian Inheritance in Man (OMIM) database; the Unified Medical Language System (UMLS); the Medical Subject Headings (MeSH); the Medical Dictionary for Regulatory Activities (MedDRA); and the Genetic and Rare Diseases (GARD) Information Centre. Further information is available on the Orphanet website: Alignments – Orphadata.*

[11] *Three entries were inserted, for epidermolysis bullosa, spinal muscular atrophy and Charcot-Marie-Tooth.*

1.2 Data sources

The MRC portfolio that was searched included all awards listed in MRC's Siebel and Large Investments System (LIS) databases. This included research project and programme awards, strategic awards, partnerships, fellowships[12], as well as research programmes running in MRC Institutes and Units. The MRC portfolio did not include PhD studentships as these positions are typically devolved to doctoral training programme awards that are administered in detail by the host research organisations.

The NIHR portfolio that was searched included all awards listed in NIHR Programmes and Infrastructure databases, as detailed in Section 1.3.2 above. The NIHR Programmes database included career training awards including NIHR Fellowships, NIHR Professorships, Health Education England (HEE)/NIHR Integrated Academic Training Programme and the Clinician Scientist Award. There may be some other NIHR supported research related to rare diseases carried out as part of specialty training posts in the NIHR Integrated Academic Training Programme, which is not accounted for by these data. As was the case for MRC, pre-doctoral level career training awards, including PhD studentships, were not included. The NIHR portfolio did not include the Cochrane Review Groups which were funded by the NIHR Evidence Synthesis Programme, or NIHR Global Health Research Programmes, as these funding schemes were beyond the scope of this project.

1.3 Input and output fields

For MRC and NIHR programme awards, the data fields that were extracted from the databases and inputted into the search were:

- Funding body
- Funder award reference
- Funding programme
- Title
- Abstract
- Aims and objectives *(applicable to MRC awards only)*
- Keywords *(applicable to MRC awards only)*
- Lay summary
- Lead research organisation
- Award start and end dates
- Total award amount
- Health Research Classification System codes: health category and research activity code (RAC)

For NIHR Clinical Research Network (CRN) support awards, the data fields that were extracted from the databases and inputted into the search were:

- CRN ID
- Title
- Research Summary
- Inclusion Criteria
- Actual Open to Recruitment Date

[12] MRC fellowships include clinical research training fellowships (CRTF), clinician scientist fellowship (CSF), senior clinical fellowship (SCF), career development award (CDA), senior non-clinical fellowship (SNCF) as well as jointly funded clinical research training fellowship awards.

- Actual or Planned Close to Recruitment Date
- Study Recruitment Status
- Study Funders
- Managing Specialty
- Study Route
- Lead Administration
- Short Name / Acronym
- Lead local CRN (LCRN)

For studies supported by NIHR infrastructure schemes, 'title' was the only the data field that was extracted from the database and inputted into the search.

The output of the search included the above data fields, plus an additional field to show the search term(s) that were matched to the award.

1.4 Timeframe

The selected timeframe for the MRC-NIHR portfolio was awards that were awarded or active during the fixed five-year timeframe of 1 April 2016 until 1 April 2021. All awards active during this period were eligible for inclusion.

1.5 Validation of search outputs

After the search had been run, the search outputs were validated by members of the Project Group to exclude any awards where a rare disease was not the primary focus of the research. All research that included participants living with a rare disease, samples from people living with a rare disease or had direct relevance to a rare disease, was included in the final dataset.

During this validation, based on prior knowledge of portfolios, representatives from NIHR and MRC highlighted awards which were not identified by the search but were relevant for inclusion in the rare disease research portfolio. There were 96 awards identified in this manner that were manually reviewed by the Expert Group to confirm inclusion. Of these 96 awards, 56 were confirmed for inclusion. It is worth noting that this is a small percentage of the total numbers detailed in Figure 1. Additionally, careful manual review of the datasets prior to analysis reduced the likelihood of further omissions, however, the limitations of the approach taken are discussed further in 5.6 above.

For the NIHR infrastructure database, award title was the only input field for the search. Therefore, where a NIHR infrastructure award was matched only to a term from the list of 'search terms for rare diseases *per se*' (list 1.1.2 above), and not to an individual rare disease name (list 1.1.1 above), these studies were reviewed manually to confirm inclusion. In total 52 awards were reviewed manually and confirmed for inclusion.

1.6 Use of Orphanet groupings to remove rare neoplastic diseases and rare infectious diseases

In addition to a list of rare disease names, Orphanet provides an allocation (described as a 'linearisation') of these rare disease names into one of 30 groupings based on medical specialities. These groupings are defined in different ways and vary in size. Each individual rare disease name search term used in the protocol was linked to a rare disease name in Orphanet, which was in turn classified against an Orphanet grouping. Therefore, if an award was identified by more than one search term, it was possible for it to be mapped to more than one Orphanet grouping (see Annex 6.2).

Orphanet groupings were used to identify and remove awards related solely to rare neoplastic diseases or rare infectious diseases from the dataset. In the final dataset, the rare neoplastic and rare infectious Orphanet groupings accounted for 221 and 373 awards respectively, with 4 awards that were mapped to both groupings. After removal of these awards, there were 698 awards in total in the portfolio.

An exception was made if an award was mapped to the rare neoplastic or rare infectious Orphanet grouping in addition to another Orphanet grouping, in which case the award was included in the portfolio. There were 18 awards which were mapped to rare neoplastic disease and at least one other grouping, and 11 awards mapped to rare infectious and at least one other grouping, that were included in the portfolio. Therefore, the analysed portfolio still included some research awards which focussed on rare neoplastic and rare infectious disease.

1.7 Analysis of MRC and NIHR portfolio search

1.7.1 Breakdown of the NIHR programmes and MRC rare disease research portfolio

The search outputs were combined into a single Microsoft Excel spreadsheet. All subsequent descriptive analysis was undertaken using standard tools available within Microsoft Excel.

Career development awards were identified using the 'funding programme' data field (see Annex 1.3 above). For MRC awards, career development awards were defined as those tagged as 'fellowship', and for NIHR awards, career development awards were defined as those tagged as 'career development'.

1.7.1.1 Health Research Classification System (HRCS)

All research awards funded by MRC and NIHR are classified using the Health Research Classification System (HRCS). This provides a common language for analysing cross-funder research portfolios and enables meaningful comparisons, both between and within different funders and timeframes. Use of the HRCS involves the assignment of both 'health category' and 'research activity' to each award. This captures a summary of the focus and type of research taking place within the lifetime of an award.

1.7.1.1.1 Health categories

There are 21 health categories which encompass all diseases, conditions and areas of health. Research awards may span a range of categories, and multiple categories can be applied to each award (five maximum). Categories capture the area of health or disease being studied. For example, studies of normal hepatic function and studies of liver cirrhosis will both be classified in the 'Oral and Gastrointestinal' category.

For each individual award, the health categories assigned are given a percentage value. If an award is assigned to a single category, this will be 100%. If an award is assigned to multiple categories, they will be equally apportioned (for example, two categories would be apportioned 50%, and three categories would be apportioned 33.3% each). Apportionment can be unequally assigned in circumstances where different emphases of research aims are clearly stated in the research objectives, however unequal apportionments are avoided if possible.

1.7.1.1.2 Research activity

There are eight overarching groups of Research Activity Codes (RAC), that consist of 48 distinct codes, which encompass all aspects of health-related research activity ranging from basic to applied research. If research awards span more than one code, a maximum of two codes can be applied to

each award (or a maximum of four codes for a large programme of research). As with health categories, research activity codes are apportioned, with unequal apportionments avoided if possible.

1.7.2 Geographical distribution of awards within the NIHR programmes and MRC rare disease research portfolio

The NIHR programmes and MRC rare disease research portfolio included the postcode data of the lead or contracted research organisation. Using postcode data from Ordnance Survey (OS), a spatial lookup was performed to generate the English regions and devolved administrations in which the lead or contracted research organisations are located. The number of awards and total award value by English region/devolved nation were aggregated to show the number and value of awards per region and devolved nation in the period 2016 to 2021.

1.7.3 Mapping of awards within the NIHR programmes and MRC rare disease research portfolio to priorities of the UK Rare Diseases Framework

As part of the analysis, we aimed to map NIHR Programmes and MRC rare disease research portfolio against the priorities of the UK Rare Diseases Framework. To get a broader picture for this analysis, we included an extra year of funded research programmes, so the period ran from April 2016 until April 2022. For this analysis, members of the Expert Group were asked to assign each award listed in the extended NIHR programmes and MRC rare disease research portfolio to one of the following six categories:

- UK Rare Diseases Framework Priority 1: faster diagnosis
- UK Rare Diseases Framework Priority 2: increased awareness among healthcare professionals
- UK Rare Diseases Framework Priority 3: coordination of care
- UK Rare Diseases Framework Priority 4: improved access to specialist care, treatment and drugs
- Basic science research
- No priority

Eight members of the Expert Group were each asked to map a portion of the 787 funded programmes. Experts were provided with detailed instructions and definitions of the above categories (Annex 5). Experts were asked to select at least one of the six categories for each award, therefore, if relevant, some awards were assigned to more than one category. If awards were assigned to more than one category, awards were considered to address all assigned categories in an equal manner (these data were not apportioned). This exercise was completed based upon the input fields detailed above. Experts were asked to provide comments on any ambiguity when assigning awards. This feedback was reviewed by a single expert per priority to confirm assignment. Any additional discrepancies identified were resolved by the Project Group to ensure a consistent approach wherever possible. Once the mapping was complete, a summary of the portfolio mapped against each priority was written by the Project Group and reviewed by members from the Expert Group.

1.7.4 Analysis of the NIHR Infrastructure rare disease portfolios

Google Sheets were created for the search outputs of the NIHR Infrastructure schemes and the NIHR Clinical Research Network (CRN). All subsequent descriptive analysis was undertaken using standard tools available within Google Sheets. For the NIHR Infrastructure scheme data, the total number of awards were analysed, categorised by type of infrastructure. For the NIHR Clinical Research Network

(CRN) supported studies, Funder Type, Lead Administration, Lead Local Clinical Research Network and Managing Specialty were analysed.

2 Detailed methods used by other funders

2.1 Method used by the Association of The British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA)

The ABPI and BIA commissioned Clarivate™ to characterise the number of projects at each stage of research and development (R&D) and the top 30 rare disease conditions focused on in those projects between 2016 and 2021.

Data was pulled from the Cortellis Competitive Intelligence database on 29 May 2023 using the following criteria:

- Phase Start Date between April 1, 2016 and April 1, 2021
- Phase = Discovery, Preclinical, Clinical Trials (Phase I, II, III)
- Country = UK
- Only Indications related to Rare Diseases were included (matching to Orphanet)
- Academia-only projects were excluded (Academia - Industry collaborations were included)
- Total number of projects = 530

2.2 Method used by the Association of Medical Research Charities (AMRC)

For this project, the AMRC used award data reported annually by each full member charity on research funded, to identify all active awards between 1 January 2016 - 31 December 2020, and generate an AMRC award portfolio.

The following amendments were made to the search protocol developed by the Project Group (see Annex 1 above) to capture the full breadth of charity funded research:

- The analysis of rare disease awards within the AMRC award portfolio was carried out twice, with and without the DHSC exclusions of 'rare neoplastic' and 'rare infectious' disease, to better showcase the breadth of rare disease research funded and supported by AMRC members.
- The exclusion of 'rare infectious' and 'rare neoplastic' diseases was carried out during the search phase of the protocol, using the 'linearised' Orphanet groupings (Annex D in the RDRL report) mapped to the search terms to remove all search terms within these disease categories. This excluded 1842 search terms from the list of Individual Search Terms (Annex B.5 in the RDRL report)
- Additional search terms were used to capture 'missing' rare disease awards, identified through examining awards funded by self-defined rare disease charities (Annex 4). The awards identified through this list of additional search terms were manually curated to remove awards that were not rare disease relevant. This process added 42 new search terms and 300 rare disease awards to the AMRC rare disease research portfolio with awards mapped solely to the 'rare infectious' and 'rare neoplastic' Orphanet groupings not included.
- The analysis of rare disease awards by Orphanet disease name was carried out using all rare disease awards identified by award abstract. To account for multiple search terms, the award counts for each search term were added together for each Orphanet disease name. As there can be overlap in awards assigned to each search term, the number of awards assigned to diseases with multiple search terms may be an overestimate.

3 Governance groups membership

3.1 Project group

All members of the Project Group (listed below) also sat on the Expert Group and Steering Group.

Name	Organisation
Kath Bainbridge [chair]	DHSC
Lauren Watson	DHSC
Emily Staricoff	DHSC
Rosie Fox	DHSC
Clive Nicholls	MRC
Richard Evans	MRC
Adam Lockwood	NIHR
David Morgan	NIHR
Dawn Biram	NIHR
Dawn-Marie Burgess	NIHR
Howard Simons	NIHR
Suzy Hammerson	NIHR
William Rosenberg	NIHR

3.2 Expert group

All members of the Project Group (listed in Annex 3.1 above) also sat on the Expert Group, in addition to those listed below.

Name	Organisation
Kath Bainbridge [chair]	DHSC
William Rosenberg	University College London
Amy Jayne McKnight	Queen's University Belfast
Andrew Fry	Cardiff University
Catherine Bird	North Cumbria Integrated Care NHS Foundation Trust
David Jayne	University of Cambridge
Diana Baralle	University of Southampton
Gemma Chandratillake	Cambridge University Hospitals NHS Foundation Trust
Gillian Rea	Belfast Health and Social Care Trust
Holly Walton	University College London
Kate Tatton-Brown	NHS England
Palak Trivedi	University of Birmingham
Peter Lanyon	Nottingham University Hospitals NHS Trust
Robert Semple	University of Edinburgh
Sarah Kennedy	NHS Tayside
Shehla Mohammed	Guy's and St Thomas' NHS Foundation Trust
Stephen Morris	University of Cambridge
Tom Kenny	Rare Disease Research Partners
Victoria Hedley	Newcastle University

3.3 Steering Group

All members of the Project Group (listed in Annex 3.1 above) also sat on the Steering Group, in addition to those listed below.

Name	Organisation
Patrick Chinnery [chair]	MRC
Alison Pope	NHS England
Amy Hunter	Genetic Alliance UK
Ana Lisa Taylor Tavares	Genomics England
Ayesha Ali	NHS England
Catriona Manville	The Association of Medical Research Charities
Daniel O'Connor	Medicines and Healthcare products Regulatory Agency (MHRA)
Emily Crowe	National Institute for Health and Care Excellence (NICE)
Jennifer Harris	The Association of the British Pharmaceutical Industry (ABPI)
Kinga Malottki	The Bioindustry Association (BIA)
Mike Batley	DHSC Research Programmes
Paula Kirby	LifeArc
Rosie Lindup	The Bioindustry Association (BIA)
Sarion Bowers	Wellcome Sanger Institute
Julie McCarroll	Health and Social Care, Research and Development Division, Northern Ireland
Anthony Houston	Northern Ireland Executive
Brown, Helena	Northern Ireland Executive
McGrady, Finola	Northern Ireland Executive
Scott Morgan	Northern Ireland Executive
Martina Rodie	Office for Rare Conditions Glasgow
Alan Burns	Scottish Government
Mark Evans	Scottish Government
Sarah Ogilvie	Scottish Government
Scott Thomas	Scottish Government
Thomas Cranston	Scottish Government
Carys Thomas	Welsh Government
Delyth Morgan	Welsh Government
Kevin Francis	Welsh Government
Liza Evans	Welsh Government
Pat Vernon	Welsh Government

4 Additional search terms used by the AMRC

Disease	Search Phrase
Ataxia-Telangiectasia	A-T
Ataxia-Telangiectasia	ATM
Ataxia (Friedreich Ataxia)	FRDA
Ataxia (Spinocerebellar ataxias)	SCA
Ataxia (Spinocerebellar ataxias)	SCA2
Ataxia (Spinocerebellar ataxias)	SCA11
Dentatorubro-Pallidoluysian Atrophy	DRPLA

Cystic Fibrosis	CF
Cystic Fibrosis	CFTR
Duchenne	DMD
Muscular Dystrophy	muscular dystrophies
Muscular Dystrophy	FSHD
Epidermolysis Bullosa	EB
Epidermolysis Bullosa	EBS
Epidermolysis Bullosa	RDEB
Multiple System Atrophy	MSA
Motor Neuron diseases	motor neuron diseases
Motor Neuron disease	motor neurone disease
Motor Neuron disease	motor neurone disease
Amyotrophic Lateral Sclerosis/Motor Neuron disease	ALS/MND
Amyotrophic Lateral Sclerosis/Motor Neuron disease	MND/ALS
Amyotrophic Lateral Sclerosis	ALS-FUS
Amyotrophic Lateral Sclerosis	FUS-ALS
Frontotemporal dementia/ Amyotrophic Lateral Sclerosis	FTD/ALS
Frontotemporal dementia/ Amyotrophic Lateral Sclerosis	ALS/FTD
Frontotemporal dementia/ Amyotrophic Lateral Sclerosis	ALS-FTD
Frontotemporal dementia	FTD
Motor Neuron disease	MND
Amyotrophic Lateral Sclerosis	ALS
Niemann-Pick	NPC
Niemann-Pick	NPC1
Niemann-Pick	Niemann Pick
Niemann-Pick	NPCD
Progressive Supranuclear Palsy (PSP)	PSP/CBD
Progressive Supranuclear Palsy (PSP)	PSP
Spinal Muscular Atrophy	SMA
Systemic Sclerosis	SSc
Systemic Sclerosis subtype	SSc-ILD
Systemic Sclerosis subtype	dcSSc
Tuberous Sclerosis	TSC2
Tuberous Sclerosis	TSC
Tuberous Sclerosis	TSC1

5 Framework definitions

Framework Priority	**Priority Description**
Priority 1: Faster Diagnosis	Research is clearly focussed on improving the rate or process of detection, screening or diagnosis of rare diseases or on understanding the diagnostic pathway. Including but not limited to research on new diagnostic tests, identification of new genetic variants which cause rare diseases, development of new diagnostic technologies.
Priority 2: Increased awareness among	Social research into levels of awareness of rare diseases, how to improve awareness of rare diseases, evaluation of effectiveness of rare disease

healthcare professionals	educational resources, or research designed to communicate to healthcare professionals and improve knowledge of rare diseases.
Priority 3: Coordination of care	Social or economic research into the needs of rare disease patients for coordinated care; how care for people living with rare diseases could be better coordinated within a health or social care setting or how technology or innovation could improve coordination of care for people living with rare diseases. Includes research into coordination of care across geography, medical specialties and wider public services.
Priority 4: Access to specialist care, treatment and drugs	Research focused on the discovery and development of therapeutic interventions for rare diseases, and testing in preclinical, clinical, community or applied settings. Research into improving access to specialist care and treatments.
Basic science research	Any basic science research where rare disease is the primary focus, including the development of in vitro and in vivo models of rare diseases, and research into understanding the cause and development of rare diseases.
No priority	It will not be possible to map every award funded by NIHR or MRC to the priorities of the UK Rare Diseases Framework, or basic science research. This exercise aims to capture the awards which *do* have a clear link to one/more of the Framework priorities, rather than attempt to fit every award into a category. Please use 'no priority' for any awards which do not clearly map to any of Priorities 1-4, or basic science research.

6 Additional data

6.1 Full Research Activity Code (RAC) breakdown

Table 10 below shows a detailed breakdown of awards within the NIHR programmes and MRC rare disease research portfolio by the full list of 48 Research Activity Codes. A summary of these data is presented in Section 3.3 above.

Research Activity	Apportioned Number of Awards (n)	Apportioned Value of Awards (£)
1. Underpinning research		
1.1 Normal biological development and functioning	48	£72,932,112
1.2 Psychological and socioeconomic process	1	£354,034
1.3 Chemical and physical sciences	1	£3,041,425
1.4 Methodologies and measurements	2	£623,775
1.5 Resources and infrastructure	1	£1,806,011
2. Aetiology		
2.1 Biological and endogenous factors	198	£226,578,229
2.2 Factors relating to physical environment	8	£5,836,069
2.3 Psychological, social and economic factors	1	£3,898,533
2.4 Surveillance and distribution	3	£3,452,328
2.5 Research design and methodologies (aetiology)	7	£3,815,219
2.6 Resources and infrastructure (aetiology)	3	£4,494,737
3. Prevention of disease and conditions		
3.1 Primary prevention interventions to modify behaviours or promote well-being	4	£2,644,213

3.2 Interventions to alter physical and biological environmental risks	2	£1,155,475
3.3 Nutrition and chemoprevention	1	£402,369
3.4 Vaccines	2	£3,209,379
3.5 Resources and infrastructure (prevention)	1	£293,442
4. Detection screening and diagnosis		
4.1 Discovery and preclinical testing of markers and technologies	43	£35,887,754
4.2 Evaluation of markers and technologies	42	£26,184,633
4.3 Influences and impact	4	£1,488,174
4.4 Population screening	4	£3,067,408
4.5 Resources and infrastructure (detection)	3	£2,166,505
5. Development of treatments and therapeutic interventions		
5.1 Pharmaceuticals	36	£36,858,439
5.2 Cellular and gene therapies	47	£33,349,231
5.3 Medical devices	3	£2,723,099
5.4 Surgery	1	£702,336
5.5 Radiotherapy and other non-invasive therapies	0	£139,907
5.6 Psychological and behavioural	1	£150,067
5.7 Physical	2	£781,413
5.9 Resources and infrastructure (treatment development)	1	£2,708,976
6. Evaluation of treatments and therapeutic interventions		
6.1 Pharmaceuticals	103	£55,099,400
6.2 Cellular and gene therapies	19	£29,173,033
6.3 Medical devices	9	£5,368,137
6.4 Surgery	10	£7,843,096
6.5 Radiotherapy and other non-invasive therapies	3	£2,861,359
6.6 Psychological and behavioural	5	£3,305,058
6.7 Physical	13	£3,966,989
6.8 Complementary	1	£297,380
6.9 Resources and infrastructure (treatment evaluation)	2	£402,372
7. Management of diseases and conditions		
7.1 Individual care needs	22	£13,470,475
7.2 End of life care	2	£187,199
7.3 Management and decision making	11	£10,046,662
7.4 Resources and infrastructure (disease management)	3	£1,708,693
8. Health and social care services research		
8.1 Organisation and delivery of services	7	£3,878,490
8.2 Health and welfare economics	2	£359,030
8.4 Research design and methodologies	6	£1,524,866
8.5 Resources and infrastructure (health services)	1	£179,710
Total	**685**	**£620,417,242**

Table 10: The full breakdown of the number and value of awards in the NIHR Programmes and MRC rare disease research portfolio active between April 2016 and March 2021 by HRCS Research Activity Code (RAC) for the rare disease research portfolio, where HRCS coding has been applied (n=685 awards). A small proportion (n=13) awards in the combined portfolio are uncoded (n=3 awaiting coding, n=10 uncodeable) and are not included in the above chart.

6.2 Orphanet groupings and the NIHR programmes and MRC rare disease research portfolio

Orphanet groupings, which categorise rare diseases by medical specialities and are described in Section 2.1.1 above, were used to identify and remove awards assigned to the rare infectious and rare neoplastic groupings from the analysis of the NIHR programmes and MRC rare disease research portfolio. There are 30 Orphanet groupings in total, and the number of diseases within each grouping varies significantly, as shown in Table 11. Due to this fundamental difference in how the Orphanet groupings are defined, it was not possible to provide meaningful comparisons between Orphanet groupings in this project. To enable a fair comparison between Orphanet groupings, the number of awards associated with each grouping would need to be normalised against the number of diseases in the grouping, however, this was beyond the scope of this project.

Within the NIHR programmes and MRC rare disease research portfolio, awards were associated with 21 out of the 30 Orphanet groupings. Table 11 shows the list of 30 Orphanet groupings, the number of rare diseases included in each of these groupings, and the number of awards in the NIHR programmes and MRC rare disease research portfolio that were associated with each grouping. The two groupings that contained awards that were removed from the portfolio prior to analysis are shaded in grey. In the NIHR programmes and MRC rare disease research portfolio 79 awards (out to 698 total awards) were not associated with an Orphanet grouping, due to not all search terms in the 'rare diseases *per* se' list (see Annex 1.1.2 above) being associated with an Orphanet grouping.

Orphanet grouping	Number of diseases in grouping	Number of awards associated with grouping
Rare developmental defect during embryogenesis	2290	60
Rare neurologic disease	1176	219
Rare neoplastic disease	555	16
Rare inborn errors of metabolism	517	20
Rare skin disease	430	22
Rare bone disease	392	10
Rare ophthalmic disorder	251	45
Rare endocrine disease	229	23
Rare hematologic disease	219	46
Rare systemic or rheumatologic disease	184	70
Rare immune disease	178	13
Rare infectious disease	178	11
Rare renal disease	130	15
Rare gastroenterologic disease	94	11
Rare respiratory disease	79	92
Rare hepatic disease	75	17
Rare cardiac disease	53	7
Rare otorhinolaryngologic disease	49	0
Rare disorder due to toxic effects	25	0
Rare odontologic disease	24	0
Rare circulatory system disease	19	23
Rare gynaecologic or obstetric disease	12	28
Rare urogenital disease	12	4

Rare infertility	9	0
Rare abdominal surgical disease	7	0
Rare maxillo-facial surgical disease	7	0
Rare surgical thoracic disease	6	0
Rare genetic disease	4	5
Rare disorder potentially indicated for transplant or complication after transplantation	2	0
Rare surgical cardiac disease	1	0

Table 11: The list of Orphanet groupings, showing the number of rare diseases in each grouping, and the number of awards in the NIHR programmes and MRC rare disease research portfolio that were associated with each grouping. Includes awards active between April 2016 and March 2021 and which have been mapped to one or more Orphanet Groupings using the individual rare disease search terms mentioned in the award details (n=619).

6.3 NIHR Infrastructure Local Clinical Research Network study recruitment data

Figure 22 shows the number of research studies supported by each NIHR Local Clinical Research Network (LCRN), which were open or active between 1 April 2016 – 1 April 2021, and recruited participants. The number of participants recruited to these studies is shown in Figure 10.

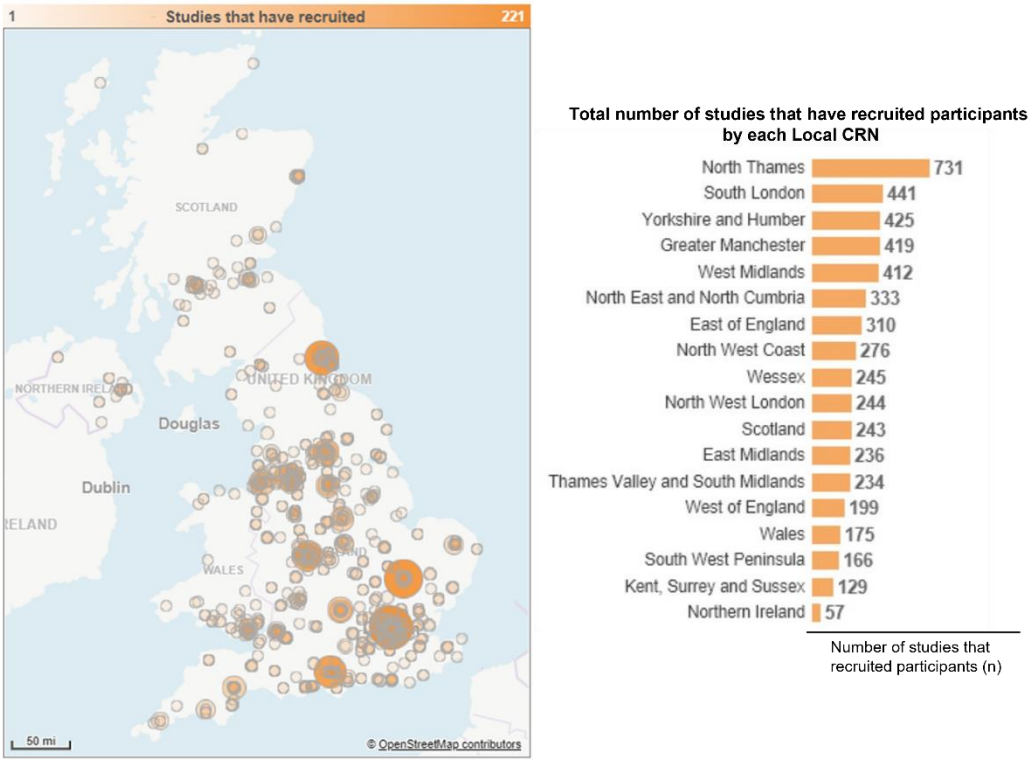


Figure 22: Total numbers of NIHR CRN supported rare disease studies that were open or active between 1 April 2016 – 1 April 2021 and recruited participants. The map (left) shows the number of studies that recruited participants by research site (each circle represents a single research site), with the colour intensity and the size of the circle indicating number of recruiting studies. The darker the colour intensity (see scale bar at the top of the map), and the larger the circle size, the greater the number of studies that recruited participants at that site. The bar chart (right) shows the total number of studies that recruited participants by each Local CRN region (each LCRN is a network of several research site).