FULL TITLE: CO-ORDINATED CARE OF RARE DISEASES

SHORT TITLE: CONCORD

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STUDY SUMMARY

Full title	CONCORD: CO-ordiNated Care Of Rare Diseases
Health condition(s) or problem(s) studied	Rare diseases
Study type	Mixed methods study comprising a scoping study, a survey and discrete choice experiment, qualitative research to develop a taxonomy of co-ordinated care for rare diseases, and a cost analysis
Participants	• Focus groups to discuss findings of the scoping review and to help with the design of the survey and Discrete Choice Experiment (DCE) = two groups of 6-8 patients and carers affected by rare diseases (one face-to-face, one virtual), one face-to-face group of 6-8 professionals. • Interviews by telephone or Skype with 15-20 patients and carers affected by rare diseases, to help with the design of the survey and DCE. • Pilot survey and DCE questionnaire with 30 patients, carers and professionals (6 think-aloud interviews, 24 providing written or verbal feedback). • 1500 respondents for survey and discrete choice experiment (at least 300 patients affected by rare diseases, 300 carers, 300 professionals). • Up to 30 national and local stakeholders interviews for development of taxonomy (national leads on specialist health care commissioning, national patient groups and charities, local providers of coordinated care (health care, social care, voluntary sector); local commissioners of coordinated care). • Focus groups for development of taxonomy: 4 focus groups with 6-8 patients and carers affected by rare diseases in each. • Workshops for development of taxonomy: up to 5 workshops involving up to 20 attendees each ((1) adult patients (aged 18+) and carers of adult patients, (2) carers of younger patients (aged under 18 years), (3) care providers (health, social services, voluntary sector) treating adults with rare conditions; (4) care providers (health, social services bridging health and social care, voluntary sector) treating children with rare conditions, and (5) commissioners of co-ordinated care provision, including NHS England and local authorities).
Study Duration/length	30 months
Start Date	1 June 2018
End of Study definition and anticipated date	30 November 2020
Key Study milestones	• Project set-up (including ethical approval): Study months -5 to 8 (January 2018 to January 2019) • Scoping review: Study months 1 to 10 (June 2018 to March 2019) • Survey and discrete choice experiment: Study months 1 to 18 (June 2018 to November 2019) • Development of taxonomy: Study months 8 to 24 (January 2019 to May 2020)

	• Cost analysis: Study months 19 to 27 (December 2019 to August 2020) • Final Report: Study months 28 to 30 (September 2020 to November 2020)
Funder	NIHR Health Services and Delivery Research programme (HS&DR Project: 16/116/82)
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KEY WORDS

Rare diseases
Care co-ordination
Mixed methods
Scoping study
Survey
Discrete choice experiment
Taxonomy
Cost analysis

LIST OF ABBREVIATIONS

BME	Black and Minority Ethnic (groups)
BWC	Birmingham Women's and Children's NHS Foundation Trust
Co-I	Co-Investigator
DCE	Discrete Choice Experiment
GOSH	Great Ormond Street Hospital for Children NHS Foundation Trust
IP	Intellectual Property
NHSE	NHS England
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PPIAG	Patient and Public Involvement Advisory Group
REC	Research Ethics Committee
RQ	Research Question
REC	Research Ethics committee
SSC	Study Steering Committee
SWAN	Syndrome's Without A Name

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1 INTRODUCTION

1.1 Brief overview

The aims of this study are to use quantitative and qualitative research methods to investigate whether and how care services for people with rare diseases are co-ordinated in the UK and how patients and their families affected by rare diseases and health care professionals who treat rare diseases would like them to be co-ordinated.

The objectives are:
1. To identify what characterises "co-ordinated care", the components of co-ordinated care, and in what ways and why co-ordinated care for people with rare diseases might be similar or different to co-ordinated care for people with other conditions.
2. To understand whether and how care of people with rare diseases is co-ordinated in the UK according to these characteristics.
3. To analyse preferences for different models of co-ordinated care by patients and families, and health care professionals.
4. To develop a taxonomy of different models describing how care for people with rare diseases could be co-ordinated.
5. To calculate the costs of the models of co-ordinated care identified in the taxonomy.
6. To work in partnership with patients and families throughout the project and to disseminate findings widely.

The associated research questions are:
RQ1: What are the specific components which characterise "co-ordinated care" and in what ways and why may co-ordinated care for people with rare diseases be similar or different to co-ordinated care for people with other conditions?
RQ2: Is care for people with rare diseases in the UK co-ordinated, and if so, how?
RQ3: What are the preferences of patients and families and professionals in relation to how care for rare diseases should be co-ordinated?
RQ4: What are the different ways in which care for people with rare diseases might be co-ordinated
RQ5: How much do these options cost?

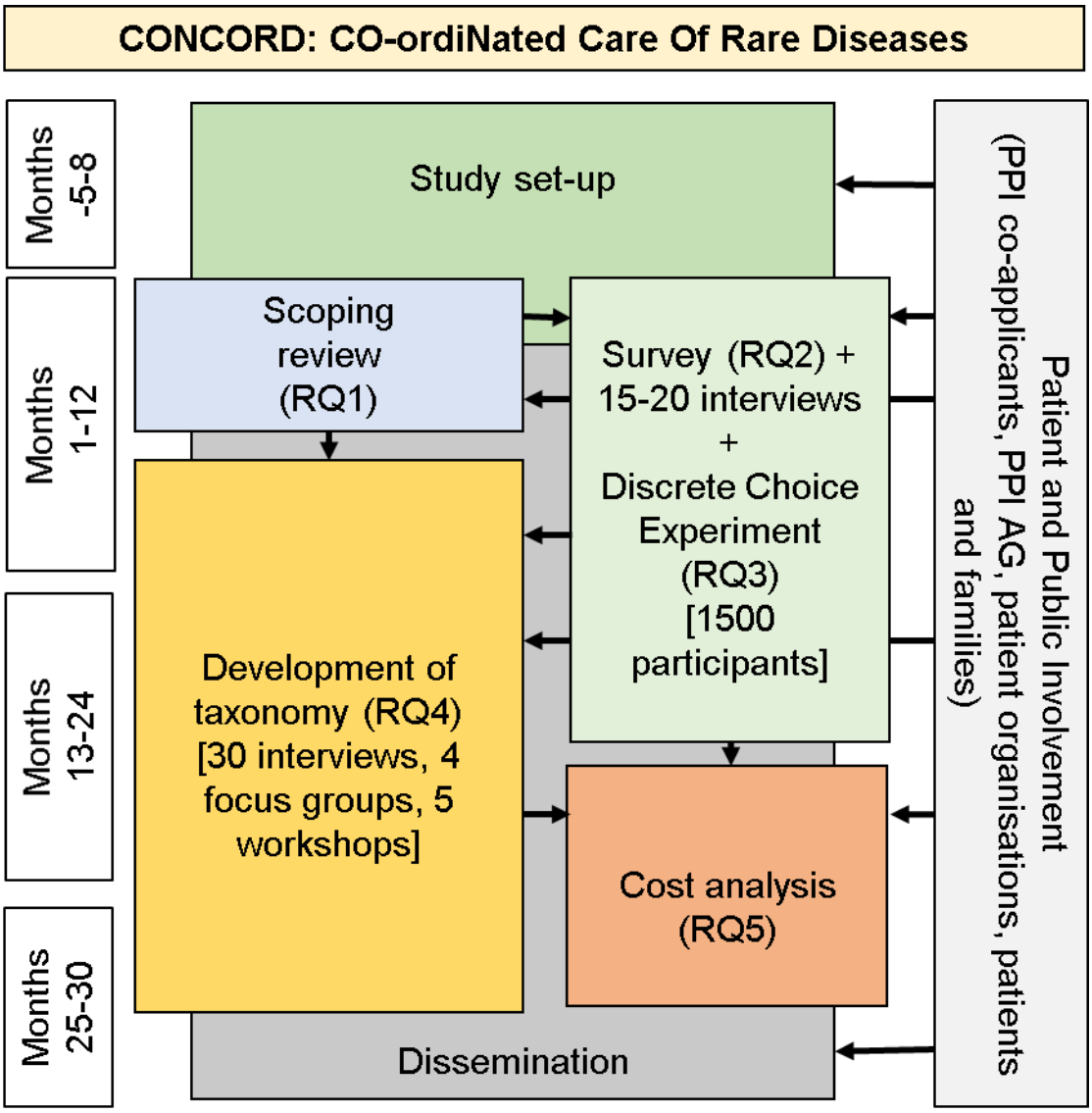
1.2 Summary of methods

For RQ1 we will undertake a scoping review to identify the components of co-ordinated care, focusing on care co-ordination across organisational boundaries and interventions employed to support and improve this. For RQ2 and RQ3 we will create a questionnaire-based survey of current experiences and costs, incorporating a discrete choice experiment of preferences. RQ4 will involve interviews, focus groups and workshops with a range of stakeholders to develop a taxonomy of co-ordinated care for rare diseases. RQ5 will calculate the costs incurred in setting up and running these services. We will hold a dissemination event to present study findings and discuss how these might be applied more widely.

1.3 Main benefits of this research

The proposed research will improve our understanding about how co-ordinated care could be optimised according to both the preferences and needs of patients and families affected by rare diseases, and the experiences of care professional working in the area. We will provide evidence about how care is currently co-ordinated, and the variations that exist in co-ordinated care provision. Finally, we will investigate the costs and benefits of models of care that would better serve the needs of patients and families affected by rare diseases. This will inform how care co-ordination might be centred around the needs and preferences of patients and families affected by rare diseases.

1.4 Study flow chart



2 BACKGROUND AND RATIONALE

2.1 What is the problem being addressed?

There are over 8,000 rare diseases.[1] Each disease affects fewer than 5 in 10,000 of the population,[1] but combined they affect over 3.5 million people in the UK. The problem addressed by this study is the variation in how care is co-ordinated for people with rare diseases in the UK, depending on where they live and the disease they are affected by. This variation often manifests itself according to whether or not patients have access to a specialist clinical centre and/or a named care co-ordinator.

A systematic review conducted in 2007 proposes the following working definition of care co-ordination[2]: "the deliberate organisation of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of health care services."

Rare diseases are often serious, chronic and complex in nature, affecting multiple systems of the body. As a result, patients often have multiple professionals involved in their care. Depending on the disease

and where they live, patients may receive treatment at specialist clinical centres, which bring together various professionals so patients can see them all in a single visit. For many people it is usual to have to visit different hospitals several times for management, which can be inconvenient, costly and stressful. Also, for most people with rare diseases some care is received nearer to home by the local hospital or GP. This can cause problems because co-ordination between the different professionals is sometimes not very good and some patients may have gaps in their care as they do not see the right professionals. Some people have access to named care co-ordinators to help with this, but many do not.

2.2 Why is the research important?

This study will identify lessons that will support improved co-ordination of care for people with rare diseases. There is a health need for this research to understand in which ways care co-ordination makes the treatment that people with rare diseases receive more effective, cost-effective, accessible and convenient.[3] A 2016 survey by Rare Disease UK in over 1200 patients and carers affected by rare diseases found that information on test and procedure results and treatment is not shared effectively between services, meaning that patients may receive sub-optimal treatment.[4] It also found that patients and families frequently have to attend multiple clinics and travel significant distances to them: "Our survey found that 1 in 3 respondents have to attend three or more different clinics, with a further 12% attending more than five different clinics for their condition. 23% of respondents indicated that they attend clinics at least monthly, 32% at least every 6-8 weeks, 55% at least quarterly, and 92% at least once a year. For the average rare disease patient this means attending no less than three clinics, at least, during every quarter."[4] In addition, not only do patients have to frequently visit multiple clinics, nearly half the survey respondents reported that they travelled over an hour to get to their furthest clinic, and 11% had to travel for more than 3 hours.[4] The survey also found that 81% of patients do not have a care co-ordinator or advisor, and a further 8% are unsure whether or not they do. It also found that 40% of respondents do not know if there is a specialist centre for their condition, and of the patients who are aware there is a specialist centre for their condition, only 66% use it.[4]

The need for this research has also been expressed by the UK governments. In 2013 the four Departments of Health of the UK (Department of Health, Northern Ireland Executive, Scottish Government, National Assembly for Wales) published the UK Strategy for Rare Diseases,[3] which said it was essential to co-ordinate care for people with rare diseases. It also stated that more needed to be done to improve co-ordination, and that in particular research was needed on how care for people with rare diseases should be co-ordinated. In the progress report from the All Party Parliamentary Group on Rare, Genetic and Undiagnosed Conditions (February 2017) it was noted "patient care continues to be poorly co-ordinated".[5]

The UK Governments have shown a sustained interested in co-ordination of care for rare diseases in the UK, as evidenced by the 51 commitments made in the Strategy for Rare Diseases[3] (8 of which relate to co-ordination of care) and the stated ambition to implement the strategy by 2020.

This study will provide new research findings, which will fill the existing gaps around how care is currently co-ordinated for people with different rare diseases, and propose evidence-based recommendations for how it ought to be co-ordinated in the future.

2.3 How does the existing literature support this study?

Two pieces of evidence from the existing literature motivate this study. First, the survey by Rare Disease UK in 2016 painted a clear picture of the heavy burden placed on patients and families dealing with rare diseases which could be ameliorated by better co-ordination.[4] Second, research by Genetic Alliance UK identified the hidden costs of rare diseases in the UK.[6] The aims of this second study

were to examine how services are co-ordinated for patients with rare diseases, what is known about the impact of the lack of coordinated care, what costs and outcomes are important to patients and families, and how might these best be collected. The study included interviews with patients, families and patient organisations. The main conclusions were: coordinated care is important for rare disease patients, yet remains a challenge; the full costs and benefits of different models of care for rare disease patients are unknown; patients and families face significant hidden costs (financial and psychosocial) associated with the way care is managed; and existing research and data sets are limited.

Evidence about how best to co-ordinate care is sparse. A 2013 report by Rare Disease UK[7] provided anecdotal evidence of the benefits of having a named care co-ordinator and concluded there was strong case for investment in care co-ordinator posts. In the only research we could find, Van Groenendael et al. analysed a national service for an ultra-rare disease and compared outcomes and costs of the service to standard care.[8] They found that organised, multidisciplinary "one-stop" clinics achieve better outcomes at similar costs compared with standard care. We searched the directory of ongoing research projects on the orphan.net portal for rare diseases (last search 25/05/2018)[9] and found none evaluating co-ordinated care for rare diseases.

3 AIMS AND OBJECTIVES

3.1 Aims

The aims of this study are to use quantitative and qualitative research methods to investigate whether and how care services for people with rare diseases are co-ordinated in the UK and how patients and their families affected by rare diseases and health care professionals who treat rare diseases would like them to be co-ordinated.

3.2 Objectives

1. To identify what characterises "co-ordinated care", the components of co-ordinated care, and in what ways and why co-ordinated care for people with rare diseases might be similar or different to co-ordinated care for people with other conditions.
2. To understand whether and how care of people with rare diseases is co-ordinated in the UK according to these characteristics.
3. To analyse preferences for different models of co-ordinated care by patients and families, and health care professionals.
4. To develop a taxonomy of different models describing how care for people with rare diseases could be co-ordinated.
5. To calculate the costs of the models of co-ordinated care identified in the taxonomy.
6. To work in partnership with patients and families throughout the project and to disseminate findings widely.

4 STUDY DESIGN

4.1 Overall design and conceptual framework

There is no single agreed definition of co-ordinated care. However, a previous systematic review[10] proposed that a useful way of thinking about co-ordination of care is to consider two categories of integration (in terms of information or responsibility):

1. Between components of the care system, including: between team members, between care teams, between personal and professional caregivers, and between organisations

2. Over time, including: between episodes of care, across the lifespan, and across the trajectory of the condition

An analysis of theoretical frameworks for studying co-ordination of care[11] identified 14 key concepts addressed by such frameworks: 'external factors', 'structure', 'tasks characteristics', 'cultural factors', 'knowledge and technology', 'need for coordination', 'administrative operational processes', 'exchange of information', 'goals', 'roles', 'quality of relationship', 'patient outcome', 'team outcome', and '(inter)organizational outcome'; and notes that the 'Multilevel Framework'[12] and the 'Relational coordination framework'[13] cover these concepts most comprehensively. Burden of Treatment Theory may also provide a helpful theoretical framework for co-ordination of care for people affected by rare diseases.[14] This theory suggests that redesigning health care services so that they are better co-ordinated and more patient-centred means that they are more able to account for the complexity of patient needs and patient preferences, implying that patients could be better equipped to handle their health problems.[14]

We are undertaking a mixed-methods study to consider the above two categories of integration around the needs and preferences of patients and families and care providers affected by rare diseases. The methods used include a scoping study, a survey, a discrete choice experiment, qualitative research to develop a taxonomy of co-ordinated care for rare diseases, and a cost analysis. We will use a partnership approach throughout the research process, working closely with patients and families affected by rare diseases in particular to co-produce the research. The components of the study designed to answer the research questions listed above are as follows:

Scoping review (RQ1): This will identify what characterises care as "co-ordinated" and what the elements of co-ordinated care are, acknowledging these might vary between population groups and contexts. We will rapidly review published papers and documentary evidence, focusing on co-ordination across organisational boundaries and interventions employed to enhance this. The review will consider in what ways and why co-ordinated care for people with rare diseases may be similar (and in what ways and why may it be different) to care for other conditions, and will explore what can be learned from existing or emerging evidence in these other contexts to understand what co-ordinated care could or should comprise for people with rare diseases. The review will be theory-driven.[15]

Survey (RQ2) and Discrete Choice Experiment (RQ3): We will run a survey to understand how care of people with rare diseases is co-ordinated in the UK, what the costs and benefits to patients, families and professionals are, and what outcomes are important to these stakeholders. This will incorporate a DCE to examine preferences for co-ordinated care, relative importance of attributes of co-ordinated care, and how preferences vary between stakeholders. The target sample size is 1500, accessed via patient organisations and care providers with no restrictions on diseases. The questionnaire will be informed by interviews and focus groups, examined by the Patient and Public Involvement (PPI) Advisory Group (PPIAG; see section 9), and will be piloted. In the questionnaire we will also ask respondents if they would be willing to participate in a future study to evaluate different models of co-ordinated care (see RQ6 below).

Development of taxonomy (RQ4): Based on the above we will develop a taxonomy of how care for people with rare diseases may be co-ordinated. This will be informed in part by the scoping study and by the survey, which will provide data on how care is currently co-ordinated. We will also conduct interviews with national and local commissioners and providers, and run focus groups with patients/carers to derive the taxonomy. We will discuss the taxonomy at workshops with stakeholders and amend it according to feedback received.

Cost analysis (RQ5): Using the options identified in the taxonomy (RQ4) we will undertake preliminary cost analyses of the identified models of co-ordinated care, including estimating how much they cost to set up and to run.

We wish to investigate experiences of co-ordinated care for both children and adults with rare diseases, and from a range of ethnic groups. For adults aged 18+ we will investigate their experiences directly as part of the qualitative work underpinning the scoping review (RQ1), the survey and DCE (RQs 2 and 3), and the development of the taxonomy (RQ4). Experiences of children aged less than 18 years will be captured by their parents/carers in each of these parts of the study. Patients and families from Black and Minority Ethnic groups will be invited to participate throughout the study via the Breaking Down Barriers project (http://breaking-down-barriers.org.uk/).

There are numerous interdependencies between the different components of the planned study (see study flow chart in section 1.4): The scoping review (RQ1) will provide the theoretical underpinnings for the taxonomy of co-ordinated care (RQ4), help to inform the content of the survey and DCE (RQs 2 and 3) and describe what is known about the costs of co-ordinated care (RQ5). The interviews in RQs 2 and 3 will inform the scoping review (RQ1). The survey and DCE will help to identify different models of care co-ordination, which will be used to create the taxonomy. They will also provide data that can be used in the cost analysis of the different co-ordination models. The cost analysis itself will be heavily informed by the taxonomy, which will delineate the options to be costed. There will be extensive patient and public involvement (via the PPI co-applicants, the PPIAG, patient organisations and patients and families) throughout (section 9).

In summary, the key features of the proposed study design are:

- Partnership approach involving working with a range of stakeholders at each stage
- Mixture of qualitative and quantitative research methods
- Clear dependencies and linkages between the different elements of the research

4.2 Setting/context

This study is concerned with how people with rare diseases of any kind are cared for across a range of organisational settings in the UK, including the NHS, social care and the third sector. Our primary focus is NHS care, but we are also interested in providers who are gatekeepers to social care provision and third-sector care, as significant elements of co-ordination specifically relate to the integration between health and social care, and health and third-sector care. The study will include a range of geographical settings, as we are interested in understanding variation in the type of co-ordination, which may vary by geographical area, depending on access to specialist centres and care-co-ordinators. No limitations will be set on the range of rare diseases, as we wish to identify as many different models of co-ordination as possible, and include as broad a range of experiences and preferences with regards to care co-ordination as possible, accounting for both categories of integration referred to above (between components of the health system and over time).

Given this broad setting there are a large number of stakeholder groups who will be involved in the study including:

- Patients and families, including parents and carers of children under 18 years of age with rare diseases
- Patient organisations, charities and other third sector organisations
- Patients for whom there is no dedicated support group
- Clinical experts from range of rare diseases caring for both adults and children
- NHS commissioners in England, Health boards in Scotland
- NHS providers across primary, secondary and tertiary care at service and governance levels

- Social care commissioners and providers at service and governance levels who provide the bridge between health and social care
- Policy-makers (e.g., Rare Diseases Advisory Group at NHSE, Welsh Rare Diseases Implementation Group)

4.3 Scoping review (RQ1)

4.3.1 Objective

The objective is to identify what characterises "co-ordinated care", what the components of co-ordinated care are, and in what ways and why co-ordinated care for people with rare diseases may differ from co-ordinated care for people with other conditions. This will help us to understand what aspects of co-ordinated care could or should be provided in order for it to be more effective, cost-effective, accessible and convenient for people with rare diseases. It will also improve understanding of what may be 'particular' or 'special' about effective co-ordinated care for people with rare diseases.

During the 'hidden costs of rare diseases in the UK' project conducted by Genetic Alliance UK in 2016[6] the researchers thoroughly and systematically searched for reviews of co-ordinated care for people affected by rare diseases and found no studies. Hence, we will undertake a broader, rapid review here, including evidence on co-ordination for 'non-rare' chronic diseases, on the basis that there may be learning from this wider literature, particularly with regards to co-ordination across organisational boundaries. This review will focus on components of co-ordinated care that are appropriate for people with rare diseases.

Unlike systematic reviews and meta-analyses, scoping studies "aim to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available, and can be undertaken as stand-alone projects in their own right, especially where an area is complex or has not been reviewed comprehensively before."[16] In this study we will examine the extent, range and nature of research around co-ordinated care for chronic diseases and will follow the five stages of the methodological framework for conducting scoping studies proposed by Arksey and O'Malley [17] and subsequently developed further.[18]-[19] This will build on the team's substantial experience of conducting rapid scoping reviews.[20]-[21]

4.3.2 Stage 1: Identifying the research question:

The scoping review will address the following questions: what does "co-ordinated care" mean? What are the elements of co-ordinated care? How is co-ordinated care for people with rare diseases different to co-ordinated care for people with other conditions? These issues will also be discussed via the in-depth interviews with patients and carers living with a rare disease for RQs 2 and 3 (see below).

4.3.3 Stage 2: Identifying relevant studies

We will conduct a review of reviews of the evidence on different aspects of care co-ordination in general (not just for rare diseases). This will aim to identify factors that have been shown to be important to co-ordinated care from a substantial evidence base (e.g. a systematic review conducted in 2007 reported 4370 papers and 75 systematic reviews studying care co-ordination [2]).

We will adopt a search strategy that involves searching for evidence from a range of different sources. This will be informed by discussions with the PPIAG and other stakeholders but is likely to include the following:

- Electronic databases (e.g., MEDLINE, Scopus, CINAHL Plus, Web of Science, ProQuest Social Science, and ProQuest Nursing and Allied Health).
- Hand-searching of key journals (e.g., BMJ Quality and Safety, Orphanet Journal of Rare Diseases, Journal of Health Services Research and Policy, Implementation Science)

- Existing networks, relevant organisations and conferences (e.g., HSRUK)
- Reference lists of retrieved studies

We will limit the search to studies published after 2006 (the comprehensive 2007 review[2] included papers published up to 2006) to capture relevant major policy changes and to ensure that the outputs reflect the current health care context. Unless stakeholders are aware of important papers in languages other than English, foreign language material will be excluded because of the cost and time involved in translating material.

4.3.4 Stage 3: Study selection

Study selection criteria will be developed iteratively, based on increasing familiarity with the literature, but are likely to include the type of study, whether or not it focuses on co-ordination of care in some form and focuses on patients with chronic diseases or long-term conditions. Two researchers will screen the identified studies in three phases (title, abstract and full text). Articles published in peer-reviewed journals, as well as grey literature such as commentaries and think pieces will be included.

4.3.5 Stage 4: Charting the data

We will extract data obtained from the identified research reviews included in our scoping review. For each study we will record the following:

- Authors, year of publication, study location
- Details of programme
- Study population
- Aims of study
- Methodology
- Outcome measures
- Important results
- Process of each intervention so that its outcome can be contextualised

4.3.6 Stage 5: Collating, summarising and reporting the results

We will present an overview of all materials reviewed. This will include tables mapping the characteristics of the included studies, and thematic analysis of their results. Given our central research question is concerned with co-ordinated care we will organise the data thematically according to characteristics of the co-ordination programme.

4.3.7 Stage 6. Focus groups

We will present our draft overview to 3 focus groups; 2 will include 6-8 patients aged 18+ years of age and carers of children aged under 18 years of age and adults with rare diseases and carers of adults with rare diseases (one face-to-face, one virtual); and 1 group of 6-8 professionals. The aim of all 3 groups is to validate our findings and to develop our analysis and interpretation of findings, including in what potential ways and why issues for co-ordinated care of people with rare diseases are similar or different to those in other contexts.

The main outputs from this research will be a series of mid-range theories[22] (theories that are sufficiently abstract to be generalised, while still sufficiently grounded in evidence to be tested in practice) of what “co-ordinated care” means including a summary of in what ways and why co-ordinated care is similar or different to co-ordinated care for other conditions. This will also provide an analysis of how co-ordinated care makes a difference in different contexts, e.g., depending on the number and nature of transitions involved in a person’s condition. Early findings from this review will be used to inform the development the survey in RQ2; this study will also be useful for framing the construction of the taxonomy of co-ordinated care in RQ4.

4.4 Survey (RQ2) and Discrete Choice experiment (RQ3)

4.4.1 Objectives

The objectives of the survey and DCE are to understand whether and how care of people with rare diseases is co-ordinated in the UK, and to analyse preferences for different models of co-ordinated care by patients and carers, and health professionals (i.e., what type of co-ordination people prefer). We will run a large survey to understand how care of people with rare diseases is co-ordinated in the UK, what the costs and benefits to patients, families and professionals are, and what aspects of co-ordination are most important to these different stakeholders. The questionnaire will incorporate a DCE to examine the relative importance of attributes of co-ordinated care, and how preferences vary between stakeholders. It will be informed by a series of in-depth interviews with patients and carers.

4.4.2 Interviews with patients and carers living with a rare disease

We will undertake 15-20 semi-structured qualitative interviews with patients and carers. The main purpose of the interviews is to identify the important costs (both financial and non-financial) associated with living with rare conditions. Specifically, 8-10 interviews will be conducted with adults with a rare disease, and 8-10 interviews will be conducted with parents and carers of children or adults with a rare disease in order to ensure the survey design captures the burden associated with the care needs of people living with a rare disease. We will also ask the interviewees about their experiences of different models of care co-ordination to inform the taxonomy that follows (RQ4). We will conduct the interviews by telephone or Skype. Interviews will be audio-recorded, transcribed and analysed thematically.

4.4.3 Survey sampling

Survey participants will comprise three groups: patients affected by a rare disease; carers and professionals. Patients surveyed directly will include adults aged 18+ years of age with a rare disease. Carers will include parents and carers of children aged under 18 years of age with rare diseases, and carers of adults with a rare disease. Health professionals will include doctors, nurses and allied health professionals involved in the care of people for rare diseases. The overall target sample size is 1500, with no restrictions on diseases included, patient demographic factors or geographical location within the UK.

We have a minimum target of 300 responses for each of our three main study groups (i.e., 300 patients, 300 carers, 300 professionals). There are several issues that have informed these figures. First, sample size calculations for DCEs are rarely undertaken because they are not at all straightforward, and depend on several factors such as question format, the complexity of the choice tasks, the desired precision of the results, the degree of heterogeneity in the target population, the availability of respondents, and the need to conduct subgroup analyses. As a result, sample sizes for DCEs are often not reported, and where they are they are usually based on simple “rules of thumb”[23]; according to these rules a sample size of 300 is commonly recommended.[24] This value was used here to justify the sample sizes of our three main groups, giving us confidence that analyses undertaken separately on these three groups will be adequately powered. Second, in terms of the survey component, sample size calculations for surveys are possible based on population size, desired confidence level and maximum acceptable margin of error. Assuming a population size of upwards of 20 000 (predicted sample size remains close to constant for populations larger than 20 000), a margin of error of 3% and a confidence level of 95% the required sample size is 1014 (https://www.surveymonkey.com/mp/sample-size-calculator/; accessed 05/11/2017); this number is comfortably exceeded with our proposed sample size. Third, our target figure of 1500 partly stemmed from another survey using a similar research design in the UK; that study - a 2016 survey by Rare Disease UK[4] – achieved a sample size of 1213 and provided useful research, including analyses by sub-groups. Therefore our target sample is realistic and will provide useful results.

For the DCE we will not analyse these pre-defined sub-groups separately unless they achieve a minimum sample size of 100, as recommended in previous studies.[23] For the non-DCE parts of the survey the focus of the analysis will be descriptive, and we will only present data for disease and other sub-groups where the sub-group size is more than five, which is consistent with NHS Digital rules on dealing with small numbers (http://content.digital.nhs.uk/media/1592/HES-analysis-guide/pdf/HES_Analysis_Guide_Jan_2014.pdf).

The main route to access patients and families affected by rare diseases will be determined in discussion with the PPIAG with whom we will explore the right methods for recruiting participants, especially hard-to-reach patients and families affected by rare diseases. Participants will be accessed via patient and provider organisations. We have excellent links with these organisations via Genetic Alliance UK networks, allowing us to access a large number of potential respondents. As well as through registered supporters of Rare Disease UK (which has over 2,000 registered supporters including academics, clinicians, industry, individual members and patient organisations [25]) and Genetic Alliance UK (which is a national alliance of organisations with a membership of over 190 charities supporting patients and families affected by genetic disorders),[26] we will also access participants via the Syndromes Without A Name (SWAN) UK organisation, which is a support network for families of children and young adults with undiagnosed genetic conditions in the UK run by Genetic Alliance UK. Patients and families from Black and Minority Ethnic groups will be invited to participate via the Breaking Down Barriers project.

While people affected by rare diseases may have links with a patient organisation or charity there will be patients and families who do not. It may be that some patients and families prefer not to be at all active in those groups, but they are still on their mailing lists and so will find out about our project and be asked to participate in it. Some patients and families would like to be part of a patient group but are not able to be because one does not exist. These families might join umbrella organisations such as Rare Diseases UK, who will be publicising our project and so will be reached that way. Many families use social media platforms such as RareConnect (https://www.rareconnect.org/en), which is a free online platform with disease-specific communities and general discussion groups. We will publicise our project, and the survey and DCE in particular, via these routes. For people affected by rare diseases who are not part of a patient group or networks described above we will alert them about the project via two major care providers and regional genetics service, using provider websites, mailing lists, and online and physical notice boards. Participants will be recruited via Birmingham Women's and Children's NHS Foundation Trust and Great Ormond Street Hospital for Children NHS Foundation Trust and the North East Thames Regional Genetics Service.

We will collect data in the survey on demographic and clinical features of responding patients and attempt to confirm whether or not these features represent those of the patient population with that rare disease. The best single source of these data is Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), which has a searchable database of diseases containing some epidemiological data and a clinical description of the condition. These data will be limited for some diseases, and so we will supplement this with searches of published studies and websites for patient organisations to identify population characteristics wherever possible.

The main route to access health professionals will be via the organisations linked with Genetic Alliance UK networks as above, the British Society of Genetic Medicine and its constituent organisations and Special Interest Groups,[27] the Primary Care Genetics Society,[28] the NIHR Clinical Research Network: Genetics,[29] and our study sites (Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH), Birmingham Women's and Children's NHS Foundation Trust (BWC) and the North East Thames Regional Genetics Services).

4.4.4 Data collection

The questionnaire will be developed in the following stages, replicating an approach we have used successfully in previous studies:[30]

1. The research team will discuss the potential content and design of the questionnaire with the PPIAG.
2. The researchers will produce a first draft of the questionnaire accounting for the recommendations of the PPIAG, and informed by the outputs of the scoping review and in-depth interviews and focus groups. This will then be reviewed by the PPIAG and amended accordingly.
3. The questionnaire will be reviewed by the Plain English Campaign to ensure it is easy to understand.
4. The questionnaire will be piloted in 30 respondents (6 think-aloud interviews, 24 providing written or verbal feedback by telephone or Skype) and amended according to feedback received.
5. The questionnaire will be passed to a survey company to generate online and hard-copy versions of the questionnaire ready for circulation.

The questionnaire will be made available on-line via a dedicated website. We expect that most respondents will complete the questionnaire electronically, upon receiving an emailed invitation to do so via their organisation. The email will include a weblink to the online questionnaire. If preferred, the questionnaire can be mailed to participants and completed in hard copy before being returned using a pre-paid envelope. Some participants may prefer to complete the questionnaire over the telephone or via Skype (e.g. those with vision problems) and that will be accommodated by the research team.

As noted the content of the questionnaire will be informed by the in-depth interviews and finalised in discussion with the PPIAG. At this stage we expect the questionnaire is, among other things, likely to cover the following issues:

- Whether the respondent is a patient, carer or professional;
- Socio-demographic characteristics of the respondent (e.g., age, gender, ethnic group, nationality, socioeconomic status);
- Region of residence/working;
- Disease/disease area of clinical expertise and body systems affected;
- Co-morbidities and behavioural problems;
- Type of organisation (health professionals only);
- Whether a diagnosis has been obtained and if so year of diagnosis (patients and carers only);
- Number of contacts with the NHS, social care and third sector in a given time period;
- Average travel distance and travel time for contacts (patients and carers only);
- Out-of-pocket expenses incurred when receiving care (patients and carers only);
- Whether or not the patient has a named care co-ordinator and if so their profession/speciality (patients and carers only);
- How well informed the respondent feels about their condition (patients and carers only);
- Services available for transition from children's to adults' services;
- Whether or not the respondent is aware of a specialist centre for their condition (patients and families only);
- Which specialists respondents see, regardless of whether or not they attend a specialist centre;
- Range of specialists available in specialist centres; and,
- Links between specialist and local providers;

The survey will mainly include close-ended categorical, ordinal and interval questions. We will also include open-ended questions allowing free-text responses where appropriate to allow respondents the opportunity to provide more expansive responses.

We will also ask respondents whether or not they would be willing to participate in a future evaluation of the costs and benefits of different models of co-ordinated care (RQ6), and what aspects of care services and delivery are important when evaluating the impact of co-ordination.

The DCE will form one part of the questionnaire. This will elicit preferences for the way in which care is co-ordinated for the 3 groups of respondents. The process for designing the DCE will be consistent with the questionnaire design process described above (input and review by the PPIAG, review by the Plain English Campaign, piloting). Additionally, the DCE will include the following design stages:

a. When producing the first draft of the questionnaire we will identify key attributes of the potential costs and benefits of co-ordinated care to be considered for inclusion in the DCE. A long list of attributes will be drawn from the scoping review, will describe the extent of co-ordination and could potentially include: the number of contacts with the NHS, social care and third sector; travel distances; out-of-pocket expenses incurred when receiving care; loss of annual leave from employment or annual income; links between specialist and local providers; and whether or not the patient has a named care co-ordinator; and NHS and third-sector costs of providing services. Based on previous studies we have run, the DCE will include a maximum of seven attributes, as having more attributes than this can make the DCE difficult for participants to understand and complete. Attributes will be selected so that there is minimal overlap between them; any residual overlap will be accounted for in the multivariate regression analyses (see below).
b. The preferred list of up to seven attributes to be included in the DCE will be informed by the scoping review and in-depth interviews and focus groups. This preferred list of attributes will be reviewed by the PPIAG as above.
c. We will assign levels to these attributes based on feasible ranges derived from reviews of documentary evidence and feedback from the PPIAG and the in-depth interviews.
d. We will design the DCE questionnaire using a pairwise choice framework and will compile a set of pairwise scenarios that describe the feasible combinations of levels and attributes of different models of co-ordinated care. Respondents will complete 8-12 choice questions. Using a pairwise choice framework, in each choice question respondents will be asked to choose one of two models presented to them which are differentiated by their attributes. We will include an opt-out option within the pairwise choice framework, allowing respondents to pick neither of the offered choices. The experimental design will include main effects only. The number of pairwise choices will be reduced to a manageable number for participants to answer based on a fractional design applied using the –dcreate– command in Stata,[31] which creates efficient designs for DCEs. Based on previous evidence and our own experience about the maximum number of choice questions respondents are able to answer, we will reduce the total number of feasible pairwise choice questions to 16-24, and that these will be split into 2 blocks of 8-12 (i.e., each participant will complete 8-12 choice questions. Half the respondents in each of the 3 sub-groups will be assigned to receive each block. Hence, overall, there will be 6 versions of the DCE questionnaire (2 versions for patients, 2 for carers, 2 for health professionals).
e. To complete the DCE we will also ask respondents to providing a simple ranking of the attributes according to importance.

4.4.5 Data analysis

For the non-DCE parts of the survey the analysis will be descriptive. Results of the categorical, ordinal and interval questions will be reported as frequencies and percentages, or means and medians with corresponding measures of spread (e.g., confidence intervals (CIs) or interquartile ranges (IQRs)), as

appropriate. Analyses will be based on completed responses to each question. Interpretation of all results will acknowledge possible biases arising from the nature of the sampling, e.g., we cannot be certain all those intended to receive the questionnaire did, and due to the nature of the online distribution we cannot make any conclusions about rates and characteristics of non-responses to the questionnaire. Questionnaire responses and missing data will be summarised by group (patients, carers, health professionals). We will also examine differences between other sub-groups of respondents, e.g., by disease, geographical location or demographic factors. Comparisons between groups will be presented as absolute differences (e.g., difference in means, difference in proportions) with associated measures of spread. Qualitative responses to the survey will be analysed thematically, examining patterns within the data, focusing in particular on preferences for co-ordinated care, the reasons for these preferences, and the costs and benefits associated with different models of co-ordinated care. As noted above, we will present data for disease and other sub-groups where the sub-group size is more than 5, which is consistent with NHS Digital rules on dealing with small numbers.

The DCE part of the questionnaire will allow us to estimate the preferences for co-ordinated care held among the participant groups and the weighting of the relative value attached to attributes determining these preferences. It will also provide an indication of respondents' willingness to trade between attributes. We will analyse preference data using either conditional logit or mixed logit regression analysis, as recommended in international guidelines.[24] The results will indicate which attributes significantly affect preferences, and which attributes are most and least important to respondents, conditional on the other attributes included in the analysis. Data will be analysed for all respondents jointly and separately by group, as above. We will deal with sample heterogeneity using covariate adjustment in regression analyses. As noted above, for the DCE we will run analyses by sub-groups separately where the sub-group size is at least 100. The final set of attributes will be determined after the preparatory phase described above, but the 'cost attribute' in our DCE is likely to be NHS and third-sector costs of providing services. We will use this to calculate marginal rates of substitution (MRS) with respect to costs. The MRS allows direct assessment of how much of one attribute participants are willing to trade for one unit of another attribute and therefore enables a comparison of different attributes on a common scale. To calculate the MRS involves dividing the coefficient for each attribute by the coefficient for the 'cost attribute'. Calculating MRS values using the 'NHS and third-sector costs of providing services' attribute as the denominator, gives a measure of the 'willingness to pay' for each attribute, e.g., providing a measure of how much respondents are on average willing to pay for a named care co-ordinator. We will also use the regression results to calculate the predicted probability that different combinations of the attribute levels (i.e., different models of care co-ordination) would be selected. This will allow us to rank different models of co-ordinated care in terms of their order of preference by the participants,[32] and to explore how this ranking varies by group.

The ranking exercise included at the end of the DCE will be used to show the relative importance of the different attributes; it is an imperfect measure as it does not account for the attribute levels. We will ask respondents to rank the attributes included in the DCE in order of importance to them. We will present the results graphically as 100% stacked bar charts showing the proportion of respondents who ranked each attribute first, second, third, fourth, etc.. We will present these data for all respondents combined and also for the three sub-group (patients, carers, health professionals). We will measure inter-rater agreement using kappa statistics. We will put this after the DCE in the questionnaire so it does not influence the DCE responses (e.g., by encouraging non-trading).

4.5 Development of taxonomy of different models of co-ordinated care (RQ4)

4.5.1 Objective

The objective of this element is to develop a classification of different models describing how care for people with rare diseases could be co-ordinated. It will build on the findings from the scoping review and survey. Based on what we know already about the care that people with rare diseases receive this may include treatment at specialist clinical centres, which bring together various professionals so patients can see them all in a single visit. An alternative or complementary model may involve having a named care co-ordinator to organise care between different organisations. The research to meet this objective will involve qualitative research and will also be informed in part by the survey, which will provide data on how care is currently co-ordinated. Different models of co-ordination may be feasible for different groups of rare diseases and we will identify where this is so in the analysis.

4.5.2 Sampling

We will conduct interviews and run focus groups with stakeholders to derive the draft taxonomy. The sampling framework will be designed to capture experience with different models of care co-ordination. We will then discuss the draft taxonomy at workshops with stakeholders and amend it according to feedback received. We will conduct 30 interviews with national and local stakeholders:

- National leads on specialist health care commissioning (up to five interviews)
- National patient groups and charities (up to five interviews)
- Local - providers of coordinated care: health care, social care, voluntary sector (up to 15 interviews)
- Local - commissioners of coordinated care (up to five interviews)

Sampling will be guided by experience with different types of model of care co-ordination. We will also conduct four focus groups conducted with 6-8 patients and carers each, with different demographic backgrounds

- Adults aged 18+ years of age with rare/ultra-rare conditions and their carers (two focus groups)
- Parents and carers of younger service users aged under 18 years with rare/ultra-rare conditions (two focus groups)

Participants affected by a range of different rare diseases will be invited to participate. We recognise it will not be possible to include participants affected by every rare disease so we will purposively sample participants experiencing different types of care co-ordination (including no co-ordination at all).

4.5.3 Data collection and analysis

The semi-structured interviews and focus groups will be conducted with a range of stakeholders, using topic guides that focus on key aspects of care co-ordination that is organised around needs and preferences of the individual. This will include; access, format, composition, frequency and location of specialist clinics; information sharing between specialist and local services; transition from child to adult services; implications of co-ordination (or lack thereof) on number of clinics attended and travel distances; and influential factors affecting the ability to provide co-ordinated care including the local and national context. Interviews and focus groups will be digitally recorded for professional transcription, and will only be conducted with written or recorded verbal informed consent. Data will be stored securely and anonymised (see section 11). Fieldwork notes will also be kept by the researchers.

Ongoing iterative and thematic analysis of all data will be undertaken concurrently, following established procedures. This will also account for outputs from the scoping review, survey and DCE. Initial analysis and category building from the interviews and focus groups will be led by the qualitative researchers; interpretation of findings will be contributed to by the whole research team, including

the PPIAG. Validity will be assessed in relation to Patton's four criteria of validity in qualitative research: verification, rival explanations, negative cases and triangulation.[33]

From the analysis of data from the interviews and focus groups we will produce a draft taxonomy which we will test in consensus-building workshops. We plan to run up to 5 workshops each of 2 hours duration and involving up to 20 attendees each. Each workshop will have a different focus and composition of attendees:

- Adult patients aged 18+ years of age and carers of adults with rare conditions;
- Carers of younger patients aged under 18 years with rare conditions;
- Care providers (health, social services, voluntary sector) treating adults with rare conditions;
- Care providers (health, social services, voluntary sector) treating children with rare conditions;
- Commissioners of co-ordinated care provision, including NHS England and local authorities

Each workshop will involve roundtable discussions with the different groups of stakeholders and will produce recommendations about the classification. Participants will be asked about the costs of each of the models under review to inform the cost analysis (RQ5). Discussions and suggestions will be captured in writing for later analysis, focusing on key recommendations and priorities. The outputs from the workshops will be accounted for in the final production of the taxonomy again led by the qualitative researchers but finalised in collaboration with the whole research team and PPIAG.

4.6 Cost analysis (RQ5)

4.6.1 Objective

The objective of this component of the project is to undertake preliminary cost analyses of the models of co-ordinated care identified in the taxonomy. This will include how much they cost to set up and implement, and how much they cost to run. The analysis is likely to include a range of different models, for example differentiated by the use of specialist centres and of named care co-ordinators. This analysis is not a formal analysis of the incremental costs of care co-ordination, as such an analysis is not possible at this stage without detailed evidence about the long-term impact of co-ordination on health outcomes and health care use. The focus in this analysis is on the 'intervention' costs associated with setting up and running different models of co-ordinated care.

4.6.2 Data collection and analysis

We will take both an NHS and a societal perspective to measure the set-up and running costs associated with different types of co-ordinated care for rare diseases. The time horizon will be one year (i.e., we will calculate costs incurred during a one-year period). Our analysis from an NHS perspective will model the typical number of contacts to see health professionals of different types over the period and account for differences in these costs depending on whether the contacts occur at a single specialist centre or multiple specialist providers, plus local providers. The analysis undertaken from a societal perspective will also account for costs borne by third sector providers and the travel costs and other out of pocket expenses borne by families. We will also account for variations in the model of care by diseases, to be identified in the development of the taxonomy. We will calculate the mean cost per patient and the total cost across the expected population (population size to be determined from epidemiological data).

As well as including running costs, the analysis will also estimate the set-up and implementation costs of new services within each model, for example, the one-off costs of staffing a specialist clinic or care co-ordinator network. This will include the costs of changes in physical infrastructure and training costs, which are both likely to incur up-front costs.

Data for this analysis will be based on deriving typical care pathways for each of the models of co-ordination identified. These will be based on data from the survey (RQ2), and the workshops for RQ4. Unit costs will be taken from published sources and applied to the derived care pathways. The output from this research will be a delineation of the care pathways associated with different models of care co-ordination, the likely costs of setting up and implementing these models, and the costs of running them over a one year period.

5 STUDY SCHEDULE

The study schedule is summarised in Table 1. It has been derived from the study design described above and includes planned recruitment and consent procedures for research participants in each component of the study.

Table 1. Planned recruitment and consent of research participants

RQ	Activity	Who/numbers	Recruitment channels	Recruitment and consent process	What do participants do?	Approx. time	Study months	Which ethics committee?	R&D approval needed?
1	Focus groups to scoping review	2 groups of 6-8 patients and carers affected by rare diseases, 1 group of 6-8 professionals	Genetic Alliance UK, SWAN UK and Rare Disease UK networks Breaking Down Barriers project	Participation in activity is advertised via recruitment channels with clearly defined eligibility criteria. Interested individuals approach study researcher and are asked to provide information about themselves with respect to the eligibility criteria. Potential professional participants additionally approached by study researchers via email or 'phone. Study researcher explains purpose of study verbally, and provides a PIS. Allows 48h to elapse then contacts potential participate again to ask for agreement to participate. Complete written consent form prior to taking part; verbal consent recorded for virtual focus group.	Read easy-to-read report on findings of scoping review in advance. 1 focus group with patients and carers to be face-to-face, 1 virtual; focus group with professionals to be face-to-face; 1 face-to-face meeting to be in London, 1 in Birmingham	2 hours (plus travel)	Dec 2018-Mar 2019	UCL EC	No (no NHS sites involved)

2,3	Interviews to help with the design of the survey and DCE	15-20 patients and carers affected by rare diseases	Genetic Alliance UK, SWAN UK and Rare Disease UK networks Breaking Down Barriers project	Participation in activity is advertised via recruitment channels with clearly defined eligibility criteria. Interested individuals approach study researcher and are asked to provide information about themselves with respect to the eligibility criteria. Study researcher explains purpose of study verbally, and provides a PIS. Allows 48h to elapse then contacts potential participate again to ask for agreement to participate. Complete written consent form prior to taking part; verbal consent recorded for phone or Skype interviews.	Take part in interview with researcher (phone or Skype).	1 hour	Sep 2018-Nov 2018	UCL EC	No (no NHS sites involved)
2,3	Pilot questionnaire for survey and DCE	30 patients and carers affected by rare diseases and professionals	Genetic Alliance UK, SWAN UK and Rare Disease UK networks Breaking Down Barriers project PPIAG members	Participation in activity is advertised via recruitment channels with clearly defined eligibility criteria. Interested individuals approach study researcher and are asked to provide information about themselves with respect to the eligibility criteria. Potential professional participants additionally approached by study researchers by email or phone.	6 think-aloud interviews where participants complete the draft questionnaire during an interview (phone or Skype). 24 participants will then be asked to complete the draft survey and provide written feedback to researcher (who will offer to discuss by phone or Skype if preferred).	40 minutes	Dec 2018-Mar 2019	UCL EC	No (no NHS sites involved)

				Study researcher explains purpose of study verbally, and provides a PIS. Allows 48h to elapse then contacts potential participate again to ask for agreement to participate. Complete written consent form prior to taking part; verbal consent recorded for phone or Skype interviews.					
2,3	Main survey and DCE	1500 (at least 300 patients affected by rare diseases, 300 carers, 300 professionals)	Genetic Alliance UK, SWAN UK and Rare Disease UK networks Breaking Down Barriers project Rare Connect NHS sites (GOSH, BWC, North East Thames Regional Genetics Services) British Society of Genetic Medicine (and its constituent organisations and Special Interest Groups), the Primary Care Genetics Society, and the NIHR Clinical Research	Weblink to survey and PIS sent by email via recruitment channels, with offer to also send hard copy by post or to complete verbally over the 'phone with researcher. For recruitment at NHS sites (GOSH, BWC North East Thames Regional Genetics Services), details about the study advertised via websites, mailing lists, and online and physical notice boards at each site, plus research co-ordinators at each site will identify potential participants and ask if they are willing to participate, forwarding details if so. Consent implied if complete/return survey.	Complete survey (online or hard copy or over the 'phone)	20 minutes	Mar-Aug 2019	NHS REC	Yes, for GOSH, BWC, North East Thames Regional Genetics Services

			Network: Genetics British Paediatric Surveillance Unit						
4	Interviews for development of taxonomy	Up to 30 national and local stakeholders (national leads on specialist health care commissioning, national patient groups and charities, local providers of coordinated care (health care, social care, voluntary sector); local commissioners of coordinated care)	Genetic Alliance UK, SWAN UK and Rare Disease UK networks NHS sites (GOSH, BWC, North East Thames Regional Genetics Services)	Participation in activity is advertised via recruitment channels with clearly defined eligibility criteria. Interested individuals approach study researcher and are asked to provide information about themselves with respect to the eligibility criteria. Potential participants additionally approached by study researchers via email or 'phone. Study researcher explains purpose of study verbally, and provides a PIS. Allows 48h to elapse then contacts potential participate again to ask for agreement to participate. Complete written consent form prior to taking part; verbal consent recorded for phone or Skype interviews.	Take part in interview with researcher (either by phone, skype or face to face, e.g., at participants home or place of work).	1 hour	Apr-Dec 2019	NHS REC	Yes, for GOSH, BWC, North East Thames Regional Genetics Services
4	Focus groups for development of taxonomy	4 focus groups with 6-8 patients and carers affected by rare diseases in each	Genetic Alliance UK, SWAN UK and Rare Disease UK networks	Participation in activity is advertised via recruitment channels with clearly defined eligibility criteria. Interested	Read briefing not on background to taxonomy.	3 hours (plus travel)	Apr-Dec 2019	NHS REC	Yes, for GOSH, BWC, North

			Breaking Down Barriers project NHS sites (GOSH, BWC, North East Thames Regional Genetics Service)	individuals approach study researcher and are asked to provide information about themselves with respect to the eligibility criteria. Potential participants also identified by research co-ordinators at NHS sites (GOSH, BWC) and asked if they are willing to participate, forwarding details to study researchers if so. Study researcher explains purpose of study verbally, and provides a PIS. Allows 48h to elapse then contacts potential participate again to ask for agreement to participate. Complete written consent form prior to taking part; verbal consent recorded for virtual focus groups.	2 focus group to be face-to-face, 2 virtual; 1 face-to-face meeting to be in London, 1 in Birmingham				East Thames Regional Genetics Services
4	Workshops for development of taxonomy	Up to 5 workshops involving up to 20 attendees each ((1) adult patients aged 18+ years of age and carers of adult patients, (2) carers of younger patients aged under 18 years, (3) care providers	Genetic Alliance UK, SWAN UK and Rare Disease UK networks Breaking Down Barriers project NHS sites (GOSH, BWC, North East Thames Regional	Participation in activity is advertised via recruitment channels with clearly defined eligibility criteria. Interested individuals approach study researcher and are asked to provide information about themselves with respect to the eligibility criteria.	Take part in workshops with researcher at a central location (could be different locations for different workshops). Read summary of workshop findings and send comments by email.	3 hours (plus travel)	Oct 2019-Mar 2020	NHS REC	Yes, for GOSH, BWC, North East Thames Regional Genetics Services

		(health, social services bridging health and social care, voluntary sector) treating adults; (4) care providers (health, social services, voluntary sector) treating younger people, and (5) commissioners of coordinated care provision, including NHS England and local authorities)	Genetics Service)	Potential participants also identified by research co-ordinators NHS sites (GOSH, BWC) and asked if they are willing to participate, forwarding details to study researchers if so. Potential professional participants additionally approached by study researchers via email or 'phone. Study researcher explains purpose of study verbally, and provides a PIS. Allows 48h to elapse then contacts potential participate again to ask for agreement to participate. Complete written consent form prior to taking part.					

6 ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

The characteristics of research participants in each activity are described in Table 1. People with a rare disease will comprise adults aged 18+ with no restrictions on rare diseases included, demographic factors or geographical location within the UK. Where possible we will ensure a mix of participants varying by:

- Whether or not the patent is receiving co-ordinated care (including access to a highly specialised service and/or specialist centre and access to a named care co-ordinator).
- Whether or not the patient has a diagnosis for their condition.
- Whether patients with a diagnosis have a rare or ultra-rare condition.
- Age range (aged 18-25 years and 26-59 years, 60+ years).
- Whether treatment is available or not for the rare disease.
- Ethnic group.

People with rare diseases include those with conditions that remain undiagnosed (i.e. they have a syndrome without a name). Carers will comprise parents and other carers of children aged under 18 years of age with a rare disease, and those of adults aged 18+ years.

Professionals will comprise doctors, nurses and allied health professionals involved in the care of people for rare diseases.

We will also include a range of other national and local stakeholders (national leads on specialist healthcare commissioning, national patient groups and charities, local providers of coordinated care (health care, social care, voluntary sector); local commissioners of coordinated care).

6.2 Exclusion Criteria

Children aged under 18 years will not be directly included in the study. Potential participants who are not able to understand English to the extent that they are unable to complete the requirements of the study will be excluded.

7 RECRUITMENT AND CONSENT

Recruitment channels for research participants and the consent process is summarised for each study activity in Table 1.

For all activities involving participation by patients affected by rare diseases and carers other than the main survey and DCE (which is described below) the recruitment and consent process will be as follows. First, the activity will be advertised via Genetic Alliance UK, SWAN UK and Rare Disease UK networks and the Breaking Down Barriers project, with clearly defined eligibility criteria. Interested individuals are invited to approach the study researcher by email or ‘phone and are asked to provide information about themselves with respect to the eligibility criteria (see section 11 for details about data storage). If these criteria are met the study researcher will contact the potential participant and explain the purpose of the study verbally by ‘phone, and provide a participant information sheet. If the potential participant is still interested and agreeable, the researcher allows at least 48 hours to elapse, then contacts the potential participant again to ask for his/her agreement to participate in the

activity. The potential participant is free to withdraw at any point: when first approached, again when asked for agreement 48 hours later, and at any point subsequently, up to and during the actual interview or focus group and may request for their data to be withdrawn after it has been collected prior to its anonymised publication. A consent form is completed prior to taking part in the activity; written consent will be obtained for face to face activities; consent will be obtained verbally and recorded for other activities.

For professionals the same process will be followed. In addition, potential professional participants may be approached initially by the study researchers via email or 'phone.

For the main survey and DCE the recruitment and consent process for all participants will be different. The final approved version of the questionnaire (postal or online) will include a cover letter and participant information sheet informing potential participants about the study, what participating will entail, how data will be managed and stored, and who they can contact if they have questions or encounter any issues. For patients and parents/carers, participants will be recruited by circulating an email to Genetic Alliance UK, SWAN UK and Rare Disease UK networks, the Breaking Down Barriers project, RareConnect and the British Paediatric Surveillance Unit, including a weblink to the online survey and the PIS. Professionals will additionally be contacted via email distribution lists for the British Society of Genetic Medicine (and its constituent organisations and Special Interest Groups), the Primary Care Genetics Society, and the NIHR Clinical Research Network: Genetics. In the email, participants may also request to receive a hard copy of the questionnaire and PIS by post, along with a pre-paid envelope to return the completed questionnaire. Some participants may prefer to complete the questionnaire over the telephone or via Skype (e.g. those with vision problems) and this will be undertaken by the research team, with the PIS being sent either by email or post and explained verbally over the telephone or via Skype. Consent to participate in the survey and DCE will be implied if the participant completes and returns the questionnaire; this will be made clear in the PIS. All study materials seen by participants will have prior approval from an NHS ethics committee.

In addition, participants in the survey and DCE may be recruited via NHS sites (GOSH, BWC, North East Thames Regional Genetics Service). Details about the study will be made available to potential participants via websites, mailing lists, and online and physical notice boards at each site, plus research co-ordinators at each site will identify potential participants about the survey verbally and via email. Further, for the interviews, focus groups and workshops to develop the taxonomy, research co-ordinators at both sites will identify potential participants according to the pre-defined eligibility criteria and ask if they are willing to speak to study researchers about the study. If they are willing, their details will be passed by the research co-ordinator to a study researcher who will then contact them to explain the purpose of the study verbally, and provide written information, then proceeding as above.

In terms of recruitment and consent documentation, participant information sheets will be developed by the research team in collaboration with PPIAG. Every PIS will clearly describe the purpose of the study activity, how long undertaking the activity is estimated to last, and state that any (personal or research) data will be stored securely and not used for any purpose beyond this analysis. They will also state that participation is entirely voluntary, that participants may withdraw at any time, and who they should contact if they have questions or encounter any issues. For the survey and DCE the materials will additionally state that completion of the survey implies consent to participate. For the online questionnaire, an opening page will provide equivalent information and consent details plus a link to the data policy on the study webpage; to begin the survey, participants will have to press a button stating "I understand - click here to take the survey", which equates to giving consent to participate.

8 ETHICAL ISSUES

8.1 Assessment and management of risk

The focus groups for the scoping study, the survey and DCE, and the interviews and consensus-building workshops for the development of the taxonomy may raise issues for our anticipated participant groups (patients, parents/carers, professionals). For patients and parents/carers affected by rare diseases, participation in these activities may potentially cause distress, as participants revisit previous experiences of care. For professionals, it is possible that the situations presented might cause distress in terms of raising personal concerns in relation to potential changes to their own services, or in terms of their own concerns in relation to quality of care for managing rare diseases. For the focus groups and consensus-building workshops this distress may be exacerbated by sharing views in a group setting. To address these concerns, the research team and the PPIAG will review the survey tools and interview, focus group and workshop topic guides to ensure that the questions and topics to be discussed are presented in a sensitive fashion. In addition, the Participant Information Sheets will make clear the (minimised) risk of distress, and make clear that participation is voluntary, and that participants may withdraw at any stage. Support will be offered to any patient or carer who seems distressed through appropriate channels, e.g., referral to a relevant support group.

In addition, patients and carers receiving care, and professionals engaged in commissioning, planning and/or delivering services for families affected by rare diseases may feel reluctant to raise criticisms of services provided in any of the above activities, as the research team may not be seen as suitably independent. The Participant Information Sheets will make clear the independence of the researchers involved in these activities, the importance of identifying challenges as well as successes, and that any information will be anonymised as much as possible.

Participants (patients, carers, health professionals) will be informed in the PIS about the limits of confidentiality when participating in the study. While the researchers may use quotes from participants in written reports, academic publications or conferences, participant's real names will not be used, and every effort will be made to protect the identity of participants. However, because some rare conditions only affect a very small number of people, or only a small number of health professionals treat some rare conditions, we will make it clear that it will not be possible to completely guarantee that an individual could not work out the identity of a participant. For that reason, participants will be given the opportunity to opt in or out of being quoted on a consent form.

8.2 Ethical approval

University (UCL) Ethics Committee approval will be obtained for the focus groups for the scoping study, the interviews to help with the design of the survey and DCE, and the pilot questionnaire for the survey and DCE (Table 1). NHS Research Ethics Committee approval will be obtained for the main survey and DCE, and the interviews, focus groups and workshops for the development of the taxonomy.

9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients and the public will be actively involved in the study in the following ways:

- Design of the research
- Management of the research (e.g. steering / advisory group)
- Developing participant information resources
- Undertaking / analysing the research (e.g. member of research team)

- Contributing to the reporting of the research
- Dissemination of research findings

Patient representatives have played a significant role throughout the planning of this study, and we will continue this approach throughout the study. The research team includes representatives from Genetic Alliance UK, a national patient organisation that is an alliance of over 200 individual organisations of patients and families affected by genetic conditions, and two PPI co-applicants. Amy Hunter is Director of Research at Genetic Alliance UK and has extensive experience managing research with significant PPI. Kerry Leeson-Beevers is a parent of a child affected by a rare disease and National Development Manager at Alström Syndrome UK. Lara Bloom is an adult affected by a rare disease and is the International Director of The Ehlers-Danlos Society. Both organisations are members of Genetic Alliance UK. Both PPI co-applicants have experience of different models of care for the diseases they represent. Previous work by Genetic Alliance UK that influenced this application include its 2016 survey of patients with rare diseases[4] and 2016 study of the costs of rare diseases borne by patients and families[6]. All PPI co-applicants met with the research team during application development and reviewed application drafts. Their contribution has in particular informed plans for recruiting patients to the study (in particular the feasibility of recruiting participants from patient and provider organisations), formation of the PPI Advisory Group and the Plain English summary.

The PPI co-applicants are part of the research team, and will take part in monthly research team meetings (face-to-face, by 'phone or Skype), as well as annual Study Steering Committee (SSC; see section 13) meetings (which will also have additional PPI representation), and stakeholder events. They will ensure patients' and families' priorities and needs remain the focus of the study, and will contribute to the design and management of the study, patient recruitment, data collection, interpretation of findings, and dissemination. They will run the project's PPIAG, which will involve managing and working with a group of 6-8 patients and carers, meeting twice a year for the duration of the project. The PPIAG will support the development of resources and participant information, patient recruitment, and dissemination of findings.

All meetings will be designed to optimise accessibility and engagement, e.g. ensuring hard copies of papers are available, and shared well in advance of the meeting. Appropriate training and support will be offered for all PPI co-applicants and PPIAG members, e.g., on how to effectively participate in meetings. We have budgeted for PPI activities at recommended rates.

Recommendations on effective involvement and payment of patients and members of the public will be followed.[34]-[37]

We will also seek input from the Young Person's Advisory Group (YPAG) at GOSH and parent and family groups at BWC, when appropriate and recommended to do so by our PPIAG.

10 FUNDING

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via the Local Clinical Research Network. The research costs for the study have been supported by the NIHR Health Services and Delivery Research programme (HS&DR Project: 16/116/82), funding amount £732,217, date of award 4 December 2017.

11 DATA HANDLING AND MANAGEMENT

11.1 Data transfer (handling, processing and storage)

11.1.1 Overall strategy

In the study, quantitative data (from the survey and DCE) and qualitative data (from the interviews, focus groups and workshops) will be collected from participants in accordance with the study schedule (section 5). The processes for handling, processing and storing these data are described below.

11.1.2 Quantitative data (survey and DCE)

Electronic data provided as part of the survey will be transferred securely using the Data Transfer Portal into the UCL Data Safe Haven (DSH; https://www.ucl.ac.uk/isd/itforslms/services/handling-sens-data/tech-soln). All electronic data will be stored, handled and analysed within the DSH. This is a secure electronic environment that has been certified to the ISO27001 information security standard and conforms to the NHS Information Governance Toolkit. It has a file transfer mechanism that enables information to be transferred securely.

Any paper-based quantitative data – such as completed hard copy surveys – will be stored in locked filing cabinets in security card protected office space at the UCL Department of Applied Health Research. These data will be transferred to electronic format and also stored and analysed within the DSH.

No data will be stored or transferred outside of the EU.

The Principal Investigator will act as the data controller of quantitative data for the study. He will process, store and dispose of all quantitative data in accordance with all applicable legal and regulatory requirements, including the General Data Protection Regulation (GDPR) and the new UK Data Protection Act 2018and any amendments thereto. Data will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the participants' consent.

11.1.3 Qualitative data (interviews, focus groups and workshops)

Interview data will be collected from participants in accordance with the consent forms, participant information sheets and sections 4 and 5 of this protocol. Interviews will be recorded on an encrypted, password-protected digital audio recorder to which only the researcher knows the password. Data collected by the qualitative researchers based at UCL and Genetic Alliance UK and will be anonymised and transferred into the DSH where it will be stored securely for analysis. The data will be cleared from the digital audio recording device when it has been transferred. Participant identifier codes will also be stored in the DSH and will be kept completely separate from study data. Interview data will be anonymised and organised by participant codes. Data will be shared between UCL and Genetic Alliance UK qualitative researchers using the DSH.

Digital audio recordings of interviews will be appropriately sent to Essential Secretary (http://www.essentialsecretary.co.uk/) for transcription. Digital audio recordings of interviews, anonymised interview transcripts, data for the documentary analysis will be stored for analysis on a secure computer network to which only named team members have access via password-protected computers at the UCL Department of Applied Health Research and Genetic Alliance UK. Only the research team will have access to participants' personal data (i.e. name and status). Any paper-based data – such as signed written consent forms – will be stored in locked filing cabinets in security card protected office space at the UCL Department of Applied Health Research.

Co-investigator Professor Naomi Fulop will act as the data controller of such data for the study. She will process, store and dispose of all qualitative data in accordance with all applicable legal and regulatory requirements, including the General Data Protection Regulation (GDPR) and the new UK Data Protection Act 2018 and any amendments thereto. Data will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent.

12 PEER REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCL. The Sponsor considers the procedure for obtaining funding from the NIHR Health Services and Delivery Research programme to be of sufficient rigour and independence to be considered an adequate peer review.

13 MONITORING AND AUDITING

The Principal Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality. They will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

The Principal Investigator will provide overall leadership of the project and project team, lead the survey and DCE, and manage the quantitative researcher. Naomi Fulop will lead the qualitative analyses, and manage the qualitative researcher. Amy Hunter will co-ordinate the PPI activities. The project manager will co-ordinate all other activities.

The research team will meet approximately monthly throughout the study to discuss the status of the project, support progress with data collection and analysis, and to ensure effective dissemination of findings and stakeholder engagement. These meetings will be chaired by the PI; administration will be provided by the project manager; teleconference and videoconference facilities will be used to optimise participation from research team members based outside of UCL. The research team meeting will take place in person once per year.

Sub-groups of the research team will be formed to lead on particular aspects of data collection and analysis. The subgroups will report on progress to the whole project team at the research team meetings. At these meetings findings from each sub-group will be discussed and interdependencies and mutual learning between each element of the project will be explored.

Project oversight will be provided by the SSC, which will be constituted and will operate according to Terms of Reference of the funder. In addition to members of the research team, the SSC will comprise an independent Chair and a wide range of stakeholders, including representatives of service users and carers, commissioners, and academics with expertise in qualitative and quantitative methods including discrete choice experiments.

14 TRAINING

The Principal Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

15 INTELLECTUAL PROPERTY

While the researchers possess substantial know-how relating to this research study, they do not hold IP in this area.

This research may generate new IP. Any such product will be dealt with appropriately with guidance from UCL Business (see below), and in partnership with the other parties involved in the study.

During the project we anticipate producing the following IP:

- Survey tools for understanding whether and how care of people with rare diseases is co-ordinated in the UK (RQ2) and for evaluating the preferences of stakeholders (RQ3).
- The taxonomy of different models describing how care for people with rare diseases may be coordinated (RQ4).
- Dissemination materials produced throughout the study.

These will be protected by copyright law, according to the Copyright, Designs and Patent Act 1988. Copyright law protects any work which is written and is original. We will use "(c) University College London" (followed by the year of creation) to make clear that UCL asserts its right to copyright protection in these works.

IP generated through this research will be managed by UCL Business, who will work closely with the project team to ensure that any valuable IP is protected by patent filing or copyright as outlined above. Our dissemination plan allows for free and open access publication of the intervention manuals and peer-reviewed journal articles. Should the interventions prove effective and cost effective we anticipate they will be adopted by NHS commissioners across the UK as new models for cancer service delivery.

The aim of the project is to generate knowledge for wider benefit. Nothing we will produce will necessarily generate income and it is likely that all our tools and outputs will be maximally accessible and free at the point of delivery.

As the IP from this research will relate to methodological approaches and lessons relating to how care for people affected by rare diseases should be organised, we do not anticipate regulatory hurdles associated with medical technologies (e.g. MHRA approval). Barriers to adoption will mainly take the form of stakeholders' lack of awareness of and engagement in the lessons derived from our research. To address this we will disseminate the findings as widely as possible (as described above).

16 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

17 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator

confirms that he will archive the study master file at University College London for 20 years from study end.

18 PUBLICATION AND DISSEMINATION POLICY

18.1 Dissemination

Key beneficiaries of this study are patient organisations, patients and families affected by rare diseases, commissioners and providers at local and national levels, and staff caring for people with rare diseases. We will develop a dissemination plan during the project set-up phase detailing dissemination objectives, intended audiences, timelines, resources and strategy (including partners and influencers, messaging, channels, coverage and frequency, and potential risks and sensitivities). This will be co-produced between the research team and the PPIAG and shared with the Study Steering Committee for comment. It will be updated regularly at research team and PPIAG meetings.

We will work with Genetic Alliance UK and Rare Disease UK to communicate study progress and findings extensively via newsletters and social media. Genetic Alliance UK will send out an e-update to all members (>200 patient groups) and to other stakeholders every three months. Both organisations are active on Facebook and Twitter.

The PPIAG will advise how best to disseminate the research to patient associations, patients and families, and will write user-friendly summaries for these groups. We will press-release findings to promote reporting of them in the media. We will develop a social media strategy including a Twitter account, project website, Pinterest board, Facebook group, and YouTube video blog, to disseminate progress and findings as widely as possible to the hugely diverse stakeholder groups. The project website will be updated frequently.

Research articles based on key findings will be published as open-access in high impact peer-reviewed journals. These will be distributed with an accessible summary to a stakeholder dissemination list, which will be created for this study. The research team will present findings at national and international academic and practitioner-led conferences, plus meetings primarily aimed at patients and families affected by rare diseases.

We will send study outputs to the UK Rare Disease Forum (responsible for monitoring implementation of the UK Strategy for Rare Diseases), NHS England's Rare Diseases Advisory Group (which makes recommendations to the UK governments on implementing the Strategy), the devolved administrations, the Royal Colleges, the Health Select Committee, The House of Commons and Lords Libraries (who produce briefing papers for MPs and Peers), and the Parliamentary Office for Science and Technology (POST). We will offer to meet with them to discuss actions they could take based on our findings. We will write summaries for commissioners and providers and disseminate them via the NHS Confederation.

We will hold an event at the start of the study to publicise it and generate national interest in it. We will hold a one day conference at the end of the study to disseminate findings. All events will be filmed and shared online.

We will also liaise with EURORDIS (Rare Diseases Europe) and the European Patient Forum to disseminate our findings throughout Europe.

18.2 Projected outputs:

Projected outputs from this study include:

- A scoping review of what "co-ordinated care" means, what the elements of co-ordinated care are, and in what ways and why may co-ordinated care for people with rare diseases be similar and/or different to co-ordinated care for people with other conditions.
- Results from the survey describing how care of people with rare diseases is co-ordinated in the UK, what the costs and benefits to patients, families and professionals are, and what outcomes are important to these stakeholders.
- Results from the DCE describing what types of co-ordination patients, families and professionals who experience rare diseases prefer.
- A taxonomy delineating different models of co-ordinated care.
- An illustration of the costs incurred in setting up and running these different models of care
- Creation of a network of stakeholders (researchers, patients and families affected by rare diseases, patient organisations and other third sector organisations, patients for whom there is no dedicated support group, clinical experts, NHS commissioners and providers, social care commissioners and providers, policy makers) who are willing and able to contribute to future research investigating co-ordinated care of rare diseases.

18.3 Funder requirements

We will follow the guidance stipulated by the NIHR when communicating our research:

- Notification of outputs and copies of any paper/article should be sent to the funder 28 days before they is due to be published.
- The NIHR's contribution should be acknowledged in full by including a funding statement.
- Research articles should be published in journals as open access that make the output available using the Creative Commons Attribution (CC BY) licence, and allow immediate deposit of the final published version in other repositories without restriction on re-use.
- The independent nature of the research and its intellectual property provenance should be emphasised by a disclaimer ("This article/paper/report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.").

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