PIRU POLICY INNOVATION RESEARCH UNIT

Diagnostic odyssey for rare diseases: exploration of potential indicators

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Executive summary

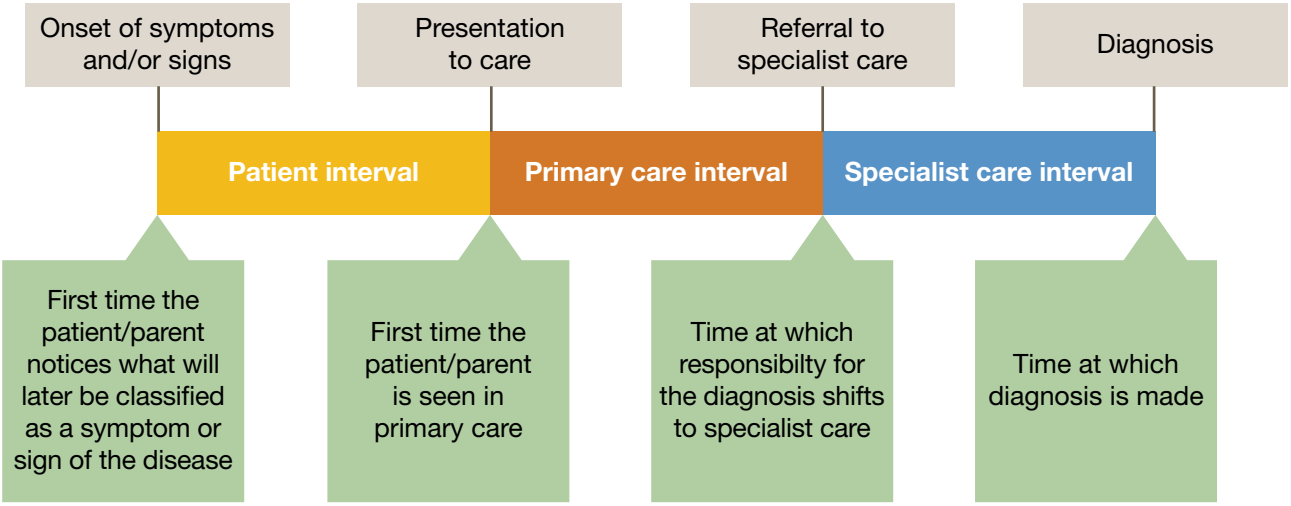
1. The medical journey travelled by patients with a rare disease (and their families) from initial disease recognition or onset of symptoms to a final diagnosis may involve serial referrals to several specialists and a plethora of, often invasive, tests. This odyssey can be prolonged and, as a result, have serious consequences for the health of patients.

2. Measuring diagnostic odysseys presents several methodological challenges:
   - the small numbers of people affected means there is only weak statistical power to detect changes in the length of odysseys;
   - the low incidence of each disease means that, except for specialist centres, collecting data on patients dispersed over a large number of providers is a logistical challenge;
   - there is no universally agreed definition of the start and end points of odysseys.

3. Our aim was to explore whether an accurate, robust and cost-effective method can be developed for the routine measurement of rare diseases diagnostic odysseys to enable the impact of interventions and policies, such as the 2013 UK Strategy for Rare Diseases, to be evaluated.

4. We carried out:
   - a review of 66 studies of 40 rare diseases to establish how the diagnostic odyssey has been investigated in the UK and elsewhere;
   - a review of databases that monitor the time to diagnosis in other conditions that can have prolonged diagnostic odysseys (cancers and diabetes);
   - a review of five categories of databases that offer opportunities to provide information about rare diseases diagnostic odysseys: generic hospital databases; primary care databases; rare diseases databases; specialist department databases; and the recently established National Congenital Anomaly & Rare Disease Registration Service;
   - interviews with 22 experts in the field of rare diseases.

5. The diagnostic odyssey comprises three periods of time: patient interval; primary care interval; and specialist care interval:



6. We recommend that:
    - monitoring of the odyssey should be retrospective in design and focus on a 'basket' of tracer diseases;
    - primary care data should form the foundation initially restricted to data from primary care research databases;
    - the foundation provided by primary care data should be enhanced and validated by the addition of data from three other sources: rare diseases databases; specialist department databases; and patient/parent surveys;
    - these proposals should be subject to widespread consultation among all those with an interest in and expert knowledge of the clinical, diagnostic and management of the conditions;
    - whatever course of action is subsequently decided upon will need to be rigorously tested in pilot studies of two or three rare diseases.

    The policy adopted will need to be reviewed in the light of two promising prospects: the availability of the General Practice Extraction Service and the National Congenital Anomaly & Rare Disease Registration Service. These may provide better options for monitoring the diagnostic odyssey than the short-term solutions being proposed.

1. Introduction

1.1 Background

The medical journey travelled by patients with a rare disease (and their families) from initial disease recognition or onset of symptoms to a final diagnosis may involve serial referrals to several specialists and a plethora of, often invasive, tests. This odyssey can be prolonged and, as a result, have serious consequences for the health of patients. A 2004 European survey of the time between identification of early symptoms and a final diagnosis for a subset of rare diseases (Crohn's disease, Cystic fibrosis, Duchenne muscular dystrophy, Ehlers-Danlos syndrome, Marfan syndrome, Prader Willi syndrome, Tuberous sclerosis, Fragile X syndrome) reported 25% of patients had to wait between 5 and 30 years [1]. During the odyssey people may receive sub-optimal care and support, which will also have adverse resource implications for the health service [2].

A rare disease is a life-threatening or chronically debilitating disease that affects five people or fewer in 10,000 and requires special, combined efforts to enable patients to be treated effectively. The total number of rare diseases is steadily increasing (current estimates suggest 5000 to 8000) because genetic research is beginning to explain disease patterns that were not understood before. Research suggests that one in 17 people may suffer from a rare disease at some point in their lifetime. In the UK, this means that more than 3 million people may have a rare disease. At least 80% of rare diseases have an identified genetic origin and 50% of new cases are in children. Measuring diagnostic odysseys presents several methodological challenges:

- the small numbers of people affected means there is only weak statistical power to detect changes in the length of odysseys;
- the low incidence of each disease means that, except for specialist centres, collecting data on patients dispersed over a large number of providers is a logistical challenge;
- there is no universally agreed definition of the start and end points of odysseys.

Several options have been proposed and adopted:

Starting point
Initial symptoms/concern raised by patient or parent
Presentation to primary care
Presentation to secondary care
End point
Clinical diagnosis
Laboratory results suggestive of diagnosis
Laboratory results confirm diagnosis
Condition-specific management started

Depending on the particular condition and each person's particular experiences with that condition, a diagnostic odyssey may be conceptualised as beginning when the affected person first became symptomatic or at each stage of the health service pathway necessary in order for a diagnosis to be possible.

The end of the diagnostic odyssey for conditions that have an easily accessible, highly specific laboratory test is often clearly defined. However for some conditions, early laboratory results may be suggestive – but not definitive – of a diagnosis of a rare disease. Other conditions can only be diagnosed clinically by an appropriately experienced clinician. For such conditions the point at which a differential diagnosis becomes a

confirmed diagnosis is unclear; it may therefore also be appropriate to consider a diagnostic odyssey to have ended once a specific management plan is commenced.

The 2013 UK Strategy for Rare Diseases [2] seeks to address, amongst other issues, the delay in diagnosis and, hence the delay in timely and appropriate intervention. In order to assess the effectiveness of the UK strategy for rare diseases and the associated actions, it would be helpful to explore whether a monitoring system might be established that provides some measure or indicator of any improvement in the diagnosis of rare diseases to shorten the duration of the diagnostic odyssey.

Consistent with the notion of 'rare' diseases used by the UK Strategy and the underlying concerns about prolonged diagnostic odysseys, this project does not consider several categories of rarely occurring diseases:

- cancers;
- acute conditions including infectious diseases;
- congenital anomalies;
- conditions which are screened for in neonates (in which there is no prolonged odyssey. Some neonates will be incorrectly diagnosed as suffering from a rare disease – false positives – and subsequently experience a diagnostic odyssey but these unfortunate instances are beyond the scope of this report).

While the focus is on past and current attempts to measure the odyssey for rare diseases, any lessons that can be learnt from similar challenges in other clinical areas (such as cancers) were explored.

1.2 Aim

To explore whether an accurate, robust and cost-effective method can be developed for the routine measurement of the rare diseases diagnostic odysseys to enable the impact of interventions and policies, such as the 2013 UK Strategy for Rare Diseases, to be evaluated.

1.3 Objectives

To carry out a literature review on rare diseases diagnostic odysseys to establish how it has been investigated in the UK and elsewhere.

To consider existing databases that monitor the time to diagnosis in other conditions (eg certain cancers).

To identify existing sources of data on rare diseases that might be used including GP-based records, hospital administrative data, and specialist clinical databases and registries of rare diseases. To assess the extent to which each database includes details about the duration of the pathway to diagnosis, the quality of the data, the availability of historic data, and the feasibility of linking data to other databases.

To develop a conceptual framework of the diagnostic odyssey for the purposes of monitoring.

To develop options for ways of monitoring the diagnostic odyssey for patients with rare diseases and assess against pre-determined criteria.

2. Methods

2.1 Systematic review

The aim was to identify and synthesise quantitative research into the diagnostic odyssey of long-term, non-communicable rare diseases, with a primary focus on how studies have defined, collected and analysed time to diagnosis. The inclusion criteria were:

- conducted in OECD countries;
- measured, evaluated or sought to understand time to diagnosis;
- investigated one or more non-communicable, chronic rare diseases;
- reported explicitly defined quantitative measures of time to diagnosis in a population of patients with a rare disease.

Included studies were not limited by language, type of publication or publication date. All quantitative study designs were eligible, with the exception of single case studies or very small case series, unless this represented the entire population for a given disease, as such designs would not assist the aim of this review. In contrast to the subsequent phases of this project, the systematic review did include rare diseases due to malignancies, congenital anomalies and conditions screened for during the neonatal period.

Medline, Embase and PsychINFO databases were searched using search strategies based on the following broad logic:

[rare disease] AND *[diagnostic odyssey]* AND *[quantitative study design]* AND *[OECD country]*

Full search strategies for each database are included in Appendix 1 along with the full review protocol. Institutional repositories of key organisations concerned with rare diseases were also searched, key experts were contacted, and the references of identified studies were screened. After removal of duplicate entries, 10% of retrieved articles were independently screened (by abstract followed by full text) by two members of the review team using EPPI-Reviewer software, with the remainder screened by a single reviewer.

Data were extracted by one reviewer and checked for accuracy by a second. Data extracted included: study design; rare disease(s) investigated; population sampled including method and sampling frame; definition and operationalization of time to diagnosis; data collection and analysis method; findings; conclusions; and methodological limitations identified by authors. Full details appear in Appendix 2.

A narrative synthesis was conducted. As the primary aim of the review was to synthesise the data collection methods rather than the actual results, no formal quality appraisal tool used. Instead, the quality of studies was appraised as part of the synthesis and discussion rather than a separate process.

In addition to an overall analysis, it was intended to consider two sub-groups: studies using routine data only; and studies measuring time to diagnosis as a continuous rather than categorical variable. However, there were only five studies that measured time to diagnosis so the latter analysis was not conducted.

2.2 Lessons that can be learnt from databases in other clinical areas

The challenge of achieving early diagnosis also exists for several common conditions, most notably some cancers and diabetes. Measurement of time to diagnosis in these areas is likely to provide lessons for rare diseases. We conducted a rapid review of the literature and sought the views of experts to identify significant research that has been carried out in cancer and in diabetes.

Medline and Embase were searched using synonyms for 'time to diagnosis' or 'diagnostic odyssey', and MeSH (Medical Subject Heading) terms for the United Kingdom, limited to studies published in English from 2008 onwards but not limited by disease. Search results were consecutively screened by title, abstract and full text by a single reviewer. Data were extracted on the definition of 'time to diagnosis', data collection method and data analysis method.

2.3 Review of databases with information on rare diseases in England

Data regarding the diagnostic pathway of patients with rare diseases is included in the large amount of information that is generated from daily clinical activity in the English NHS. Although not all these data are routinely available, useful data can be extracted for ad hoc research studies. There are two principal categories of database: generic and disease-specific.

Generic databases

Web searches and interviews with experts identified four sources of generic patient-level clinical data routinely collected in England (from all or large samples of the population): the Clinical Practice Research Datalink (CPRD, which includes the former General Practice Research Database, GPRD); the Health Improvement Network (THIN); the QResearch database; and Hospital Episode Statistics (HES). These were investigated to assess whether their data would allow a robust measure of the diagnostic odyssey for rare diseases. (Two other commercial databases were identified, DIN-Link [3] and UK IMS Disease Analyzer [4], but were not considered to be relevant).

The websites for the four databases were reviewed and some users were interviewed. In addition, research papers that relied on the databases were identified and reviewed to obtain detailed information about: the variables included in the databases (data dictionaries); data collection mechanisms; extent of national coverage; opportunities to link with other databases; and the completeness and accuracy of the data for measuring time to diagnosis.

Disease-specific databases

Several databases exist that collect data about patients with rare diseases. They are often referred to as registries. In January 2014 Orphanet published a list of such databases across Europe [5]. We reviewed the list and identified 74 (Appendix 3) that provide data on England. Some were then excluded for one of the following reasons:

- conditions where a diagnostic odyssey is unlikely to occur because of the natural history, such as obvious or life-threatening conditions presenting at birth;
- acute diseases and cancers, considering that delay in diagnosis for such conditions (which may well be rare in terms of prevalence) represent significantly different issues in terms of health services and policy research from those investigated in the present study;

- conditions that neonates are screened for, the gold-standard intervention to reduce time to diagnosis;
- regional coverage only, so could not provide data for a national indicator (though national networks of regional databases were included if they covered much of the country).

The websites of the 48 databases were reviewed to assess the information they included. This led to a shortlist of databases that would allow the time to diagnosis to be determined. We focus on the databases that exist in England (or the UK). Although some of these contribute to European databases, reviews of the latter would provide no additional information so no attention was paid to the wider European composite databases.

2.4 Key informant interviews

Interviews were conducted with a range of experts with an interest in the diagnosis and management of rare diseases in the UK, including patients and parents. Participants were purposively sampled, to maximise variation in perspectives, from the following groups: specialist clinicians who care for people with rare diseases; specialist laboratory staff; generalist clinicians who occasionally care for people with rare diseases; policymakers and commissioners; and patient organisation representatives. Participants were selected to cover a range of rare diseases and geographical locations across the UK (Appendix 4).

The majority of interviews were conducted in-person by one or two members of the research team. When preferred by the participant, or a face-to-face meeting was not possible, the interview was conducted by telephone or email.

Interviews were semi-structured, informed by a topic guide (Appendix 5) developed iteratively throughout the research, and lasted on average 30 minutes. Notes were taken and content analysis performed.

2.5 Develop a conceptual framework of diagnostic odyssey

The interview data and findings of the literature reviews were used to develop a conceptual framework. This informed both the criteria used to identify sources of data and the appraisal of existing databases. The conceptualisation of diagnostic odyssey that was developed was influenced by the Aarhus Statement which addresses definitions of milestones and intervals in cancer diagnosis odysseys [6].

2.6 Assess options for monitoring the diagnostic odyssey

The database options for monitoring the odyssey were assessed against the following criteria:

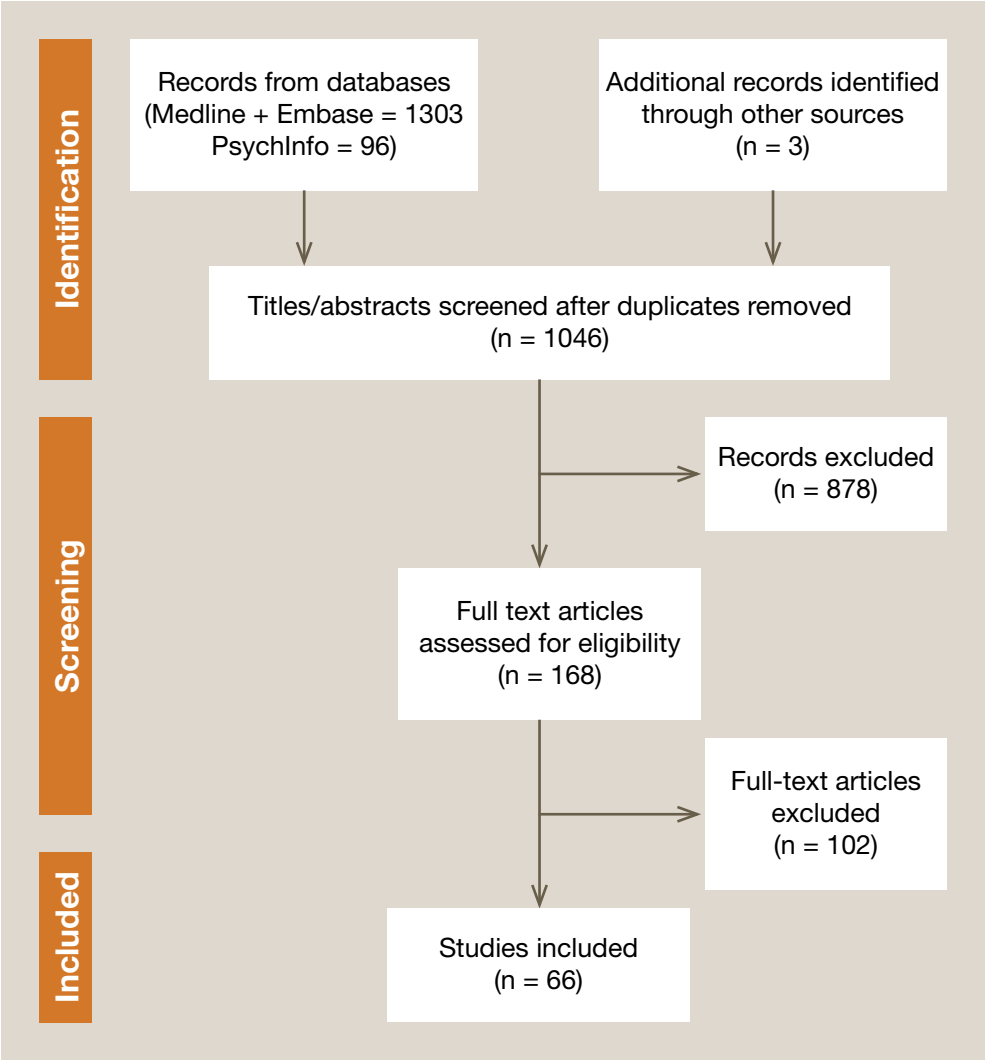
- *range of rare diseases included*;
- *information on diagnostic odyssey:* extent to which data are included;
- *representativeness of cases included:* extent of selection bias;
- *accuracy of case recruitment:* sensitivity (no false negatives) and specificity (no false positives);
- *data completeness:* extent to which missing data might bias findings;
- *validity of data:* on diagnostic odyssey;

- *credibility:* how meaningful the data are to patient/parents and clinicians;
- *timeliness:* how up-to-date the data are;
- *burden and cost of additional data collection:* additional time and expense to provide data on diagnostic odyssey.

3. How has the rare disease diagnostic odyssey been assessed?

3.1 Systematic review search results

Figure 1 PRISMA flow diagram showing screening and selection of studies



A total of 1046 unique abstracts were screened to give 66 included studies (Figure 1). The references that are cited in this section appear in Appendix 6. Studies were conducted in the UK[1-10], USA[11-25], Denmark[26, 27], Norway[28, 29], Austria[30], Germany[31-36], Greece[37, 38], Italy[34, 39-41], Spain[42, 43], New Zealand[44, 45], France[46-50], Canada[25, 48, 51-54], Israel[55], Sweden[56, 57], Switzerland[35], Australia[58, 59], Ireland[60, 61], Netherlands[62], Estonia[63] and three multi-country studies covering more than ten European studies[64-66].

The 66 Included studies covered 40 rare diseases or categories of rare disease. The majority of these diseases were only investigated in one or two studies, with the exception of cystic fibrosis (13 studies), Fabry disease (4 studies) and Fragile X (3 studies) as shown in Table 1.

Table 1 Frequency of rare diseases investigated by included studies

Disease	Number of studies
Cystic Fibrosis	13
Fabry Disease	4
Fragile X	3
Alpha1-antitrypsin deficiency, Bronchiectasis, Duchenne muscular dystrophy, Haemophilia, Infantile Spasms/West Syndrome, Niemann-Pick disease type C, Takayasu arteritis	2
Acquired Angioedema, Adult-onset Still's disease, Amytrophic lateral sclerosis, Batten Disease/neuronal ceroid lipofuscinosis, Cerebrotendinous xanthomatosis, Cervical Dystonia, Chylomicron retention disease/Anderson's disease, Clarkson's disease/ Idiopathic systemic capillary leak syndrome, Complex regional pain syndrome, Congenital Dyserythropoietic Anemia Type I, Congenital Hypothyroidism, Dopa-responsive dystonia, Dystonia or hemifacial spasm, Erythromyalgia, Familial amyloid polyneuropathy, Gastric Cancer, GM2 gangliosidosis, Hereditary angio-oedema, Hirschsprung's Disease, Homocysteinuria, Inborn errors of metabolism, Juvenile dermatomyositis, Long QT syndrome, Lymphangioleiomyomatosis, Marfan Syndrome, Myasthenia gravis, Myotonic dystrophy, Porphyria, Primary immunodeficiencies, Primary myoclonus-dystonia, Pyridoxine dependent seizures, Variant Creutzfeldt-Jakob Disease	1

3.2 Method of data collection

The most common data collection method was retrospective case record review, followed by data already held within disease-specific databases and information from patient/family by questionnaire or interview (Table 2).

Sample sizes ranged from 8[27] to 27,692[16], with a median of 98 patients. Studies that required clinicians to complete special questionnaires or perform direct consultations had smaller sample sizes, while those using disease-specific databases had the largest.

Table 2 Number of studies and mean sample size by data collection method
Studies using multiple data collection methods are recorded more than once.

Data collection method	Number of studies	Mean sample size
Retrospective case record review	34	187
Disease-specific database	15	2777
Patient/family: questionnaire or interview	11	211
Clinician: questionnaire	7	65
Specialist questionnaire	5	63
Surveillance unit	4	97
Facility database	3	1211
Generic database	2	1311

Existing routine data were used in 26 studies while the rest collected new data. Not surprisingly the former studies included more patients (mean sample sizes 1667 and 230 respectively). The majority of studies (n=43) collected data retrospectively.

3.3 Representativeness of patient populations

There are several potential challenges to ensuring that data on people with rare diseases are representative of the entire population of such people:

i. patients with mild symptoms may not present to a doctor[57, 63] and, conversely, those with severe symptoms may die before a diagnosis can be made[52];
ii. if diagnosis relies on clinician judgement (rather than an accurate diagnostic test), some patients may remain undiagnosed[8];
iii. if diagnosis depends on a diagnostic test that is not widely available, cases may be unrecognised;
iv. if inclusion of cases in a database depends on voluntary reporting by doctors rather than active case finding, recruitment is likely to be incomplete which may bias the information;
v. diagnosis may later be revised after the benefit of a longer period of observation[28, 56];
vi. databases held by pharmaceutical companies may be biased towards those who are eligible for treatment; those with co-morbidities that contraindicate the treatment or who are unable to access the treatment may be under represented[11];
vii. given that patients can only be included once they are diagnosed, databases will be biased towards those whose time to diagnosis is shorter[26];
viii. if diagnosis depends on a new test, its introduction will detect previously unrecognised cases that never contributed to the estimation of time to diagnosis. As a result, the time to diagnosis for patients with that condition may increase, suggesting a deterioration in the service rather than an improvement[51];
ix. where a sampling frame is limited to a particular specialty or department, patients managed primarily by other specialties may be missed. For example, patients with primary immune deficiency are normally managed by immunologists but some specific disease are managed in haematology or rheumatology[36].

3.4 Definition of start and end of time to diagnosis

The most common definition to mark the beginning of time to diagnosis was that of symptom onset, used in 49 studies (Table 3). Many studies gave little or no information about how symptom onset was operationalised for data collection – those that did are shown in Appendix 7. Specific symptoms were either defined in advance, particularly studies collecting data from large databases[32, 33], or were elicited through open questions to ascertain the start of symptoms or concerns.

Table 3 Frequency of choice of start of time to diagnosis

Definition of start of time to diagnosis	Number of studies
Birth	14
Symptom onset	49
Presentation – primary care	9
Presentation – secondary care	3
Presentation – tertiary care	4
Not specified	1

Fourteen studies used the patient's date of birth to mark the beginning of time to diagnosis for congenital or genetic conditions. A minority used the date of first presentation to primary care (or any health care worker) and a few used presentation to specialist care in order to focus specifically on health service delays to diagnosis.

Table 4 Frequency of choice of end of time to diagnosis

Definition of end of time to diagnosis	Number of studies
Definitive diagnosis	62
Probable diagnosis	3
Treatment/disease specific management started	4

Most (94%) studies used the date of definitive diagnosis to mark the end of time to diagnosis. One study specified that they considered the diagnostic odyssey to end only when that result had been communicated to the patient [34].

Three studies used the date of probable or presumptive diagnosis: one on congenital hypothyroidism was conducted in 1978 when laboratory tests were new and symptomatic diagnosis was common[53]; one on variant Creutzfeldt-Jakob Disease where a definitive diagnosis is only possible post-mortem[9]; and one on inborn errors of metabolism defined a diagnosis once 'clinical history, physical examination and initial laboratory investigations pointed to a condition and therapy and counselling were instituted' [54].

Of the four studies that used the commencement of disease-specific clinical management as a proxy for diagnosis, one of particular note used the date of referral to a specialist as a proxy for the diagnosis of complex regional pain syndrome[55], making the assumption either that a referral would not occur unless a diagnosis had been made, or that the specialist clinic would be guaranteed to make the 'correct' diagnosis immediately.

Notable limitations for defining the start and end points include:

i. the challenge of balancing the specificity of symptoms defined as heralding the onset of the disease and the danger of excluding or under-representing non-specific or non-classical symptoms;
ii. ascertaining symptom onset is likely to require patient-reported data which may be subject to recall bias if asked at or after the time of diagnosis[50];
iii. relying on health care professionals reporting may misrepresent patients' views[66] and precludes the ability to prompt for more subtle, earlier signs of disease [23];
iv. using presentation to a particular level of care as a starting point for time to diagnosis excludes those who have never entered that level of care, for example those using centres in a different geographical area[45], milder cases or those who were felt unsuitable or did not want specialist care[53];
v. studies using start of treatment as a proxy for date of diagnosis make the assumption that treatment starts soon after a diagnosis is made[25].

3.5 Types of analysis of time to diagnosis

The majority of studies (n=42) reported means or medians of time to diagnosis. One study noted a bimodal distribution of time to diagnosis: patients were either diagnosed quickly on presentation or experienced a prolonged delay (or were never diagnosed)[54]. Therefore parametric tests or summarising time to diagnosis using means or medians may fail to represent the actual odyssey that people experience.

4. What can be learnt from other clinical areas?

A search revealed potentially helpful attempts to assess the diagnostic odyssey in two other clinical areas – cancer and diabetes. Four different approaches have been used that might be considered for rare diseases.

4.1 One-off national service evaluation

Concern about delays in cancer diagnosis led to the establishment of a service evaluation, the National Audit of Cancer Diagnosis in Primary Care [7]. Conducted in 2009/10 in 1170 general practices in England, data on 18,879 patients who had a confirmed malignancy were collected from clinical records and hospital correspondence. Three intervals were identified within the diagnostic pathway: patient interval, that is time between the first symptom and the first consultation; primary care interval, the time between first presentation and date of referral (the number of consultations for relevant symptoms that they had with a GP before referral was also collected) and referral interval, defined as the time between referral and first specialist consultation.

4.2 General practice research databases

Another approach in cancer care involved use of the General Practice Research Database (GPRD) which includes data on about 10% of the population. Patient data were extracted to compare the length of the whole diagnostic interval (time between first presentation with symptoms attributable to cancer and cancer diagnosis) in two cohorts of patients, one diagnosed in 2001-2002 and the other in 2007-2008 to see if the time to diagnosis changed after the adoption of the 2005 NICE Referral Guidance for Suspected Cancer [9, 10]. This work suggests that data included in GPRD (now incorporated in the Clinical Practice Research Datalink, CPRD) may be accurate and detailed enough to attribute recorded symptoms to later diagnoses, using a set of putative symptoms derived from the literature or diagnostic guidelines.

4.3 Primary care information systems

The National Adult Diabetes Audit, the largest annual clinical audit in the world, collected primary care data from 2.47 million patients in 2011/12 [11]. Although the diagnostic pathway is not a focus of the audit, it illustrates how primary care data are potentially an effective option for studying this topic. Until concerns were raised about care.data, data were extracted by local primary care staff. The data required was specified by the Health & Social Care Information Centre (HSCIC) and extraction processes were produced to be run on the different information systems that general practices use to store health records [12]. In time it is hoped to extract data using the General Practice Extraction Service (GPES) which will offer greater flexibility and not require any work for local primary care staff [13].

4.4 National disease registries

The National Cancer Research Service collects data from the cancer registries in England. Data from the eight English registries are combined with similar data from the rest of the UK by the National Cancer Registration Service. It includes data on the date of referral from primary care and date of diagnosis so provides a model for determining the specialist care interval.

5. Conceptual framework for diagnostic odyssey

The definition of key time points in the Aarhus statement [6] was adapted to inform the proposed conceptual framework. A number of theoretical choices were made, influenced by the literature review and of the opinions of the experts interviewed.

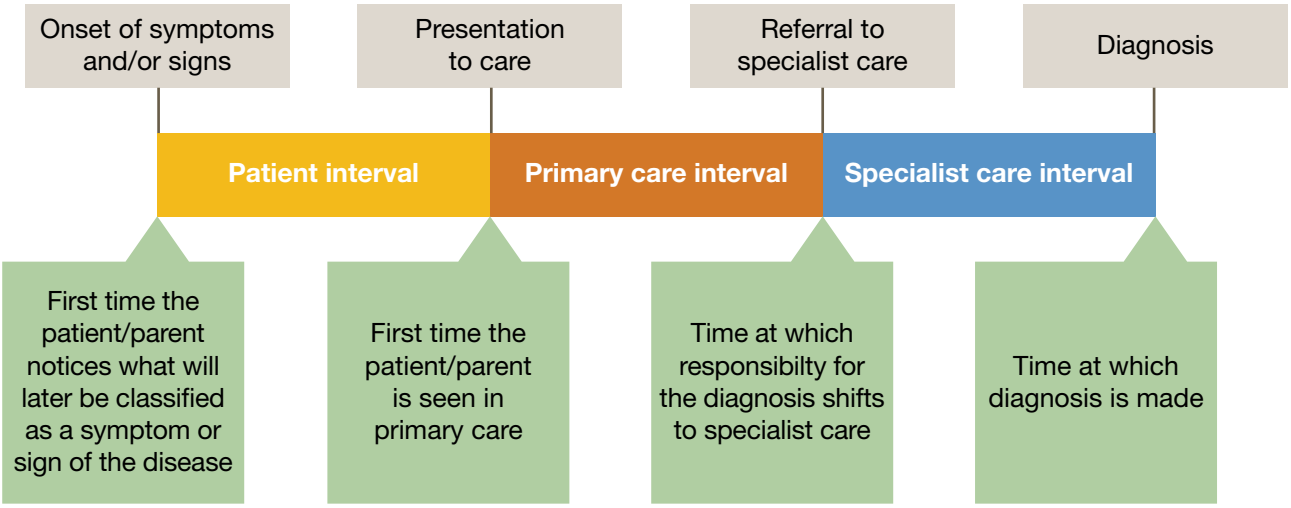
The framework recognises four time points (Figure 2):

- *date of onset of symptom/s:* defined as the first time the patient /parent notices what will later be classified as a symptom of the disease;
- *date of presentation to primary care:* time at which it would be feasible for a clinician to start investigating or referring to specialist care;
- *date of referral to specialist care:* time at which responsibility for the diagnosis shifts to specialist (secondary or tertiary) care. When there is direct presentation to emergency or to secondary care, such an interval would be zero;
- *date of diagnosis:* time when the final diagnosis is given to the patient.

The four time points allow three intervals to be calculated:

- *patient interval:* between the time of onset of symptoms and the presentation to primary care; includes the waiting time for an appointment;
- *primary care interval:* between the first presentation to primary care and referral to specialist (usually secondary) care;
- *specialist care interval:* time between the first referral and diagnosis; includes waiting time for an appointment. May involve further referrals from 'general specialist' such as general paediatrician to specialist in tertiary care.

Figure 2 Conceptual framework



6. What can existing databases contribute?

Five categories of databases were identified that offer opportunities of providing information about rare diseases diagnostic odysseys: generic hospital databases; primary care databases; rare diseases databases; specialist department databases; and the recently established National Congenital Anomaly & Rare Disease Registration Service.

6.1 Generic hospital databases

Hospital Episode Statistics (HES) collects data about all episodes of hospital care being provided by NHS hospitals in England (with similar systems in the other parts of the UK) [14]. In theory, once a person had been diagnosed with a rare disease, their previous outpatient consultations and inpatient episodes could be identified. Thus, a picture of their odyssey from date of referral to specialist care could be constructed. In addition, patients could be linked to other databases (see below) to complete the odyssey.

In practice, shortcomings in data completeness, accuracy of the diagnostic data, and difficulties in linkage (partly due to failure to always use patients' NHS numbers) severely limit the capability of HES. As a result, the information on rare diseases odysseys would be incomplete and may be misleading if systematic biases exist in the data collection (eg more complete data for those patients with shorter odysseys). In practice, no examples of using HES to inform the odyssey were found.

6.2 Primary care information systems

Primary care is theoretically the best setting to collect data about the diagnostic odyssey in rare diseases, given that virtually all information about the patient's clinical pathway is supposed to be either generated by primary care or transmitted to it by other care providers. GP information systems should contain data which would be accurate enough to measure the diagnostic odyssey of rare diseases.

General practices use one of several information systems to manage their clinical records. There are four main providers: INPS, EMIS, Microtest and TPP. Until late 2012 a fifth provider existed (CSC, iSoft system) but has since been withdrawn from the market [15]. Data from these systems are increasingly being used to create aggregated databases either for research purposes or for service functions (management, reimbursement, clinical audit).

Research

The three main databases constructed for research from GP systems are the CPRD, THIN, and QResearch.

(i) Clinical Practice Research Datalink (CPRD)

This routinely collects data from general practices in the UK using INPS Vision software from self-selected practices that have volunteered to participate. It is funded by the National Institute of Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) and covers about 10% of the population [4, 16]. In March 2011 it contained records from over 12 million patients and by December 2013, there were over 13 million patients, of which approximately 5.5 million were active. The CPRD aims to link data from what was previously known as the General Practice Research Database (GPRD) with HES and other patient databases. Such linkage is reported to be currently available for about 60% of the participating practices. Many research studies have used GPRD data (either before or after its incorporation in the CPRD): 1159 publications in 1988-2013 [8].

One example of a study of a rare disease was the determination of the prevalence of Huntington disease in UK [17]. Another example of use of these data for a rare disease is a study being carried out at IMS Health, in collaboration with Novartis Pharmaceuticals, where the clinical pathway of patients with tuberous sclerosis is being constructed from GP data linked to HES data [18]. Time to diagnosis in these patients is not a specific focus but data that has been extracted, cleaned and consolidated would allow this kind of measurement to be made.

(ii) The Health Innovation Network (THIN)

Data collected by general practices using the INPS Vision software is also available through this database. It was developed from GPRD but, since 2002, it has been independent and run commercially by CSD Medical Research UK (formerly known as EPIC). Many general practices using INPS Vision provide data to both databases. THIN covers 587 practices and contains data on 12.3 million patients, 3.6 million of which are active. It is commonly used in research: 477 research papers published in 2004-2014 relied on data extracted from THIN [19].

(iii) QResearch

This is a database that collects data from general practices using the EMIS information system [20]. It is jointly owned by the University of Nottingham and EMIS. It currently gathers data from 950 general practices (about 12% of all practices), including health records from over 13 million patients. The number of practices participating has increased significantly since 2006. Around 200 research papers have been reported on the QResearch website since 1998. Data from QResearch has been extensively used to derive risk prediction algorithms for a number of conditions.

Two issues were identified as specifically associated with the use of data from these research databases. First, there is concern about the representativeness of the data. Although this has been thoroughly assessed and is generally considered to be acceptable [21], it has not been established in the case of rare diseases. Because of their rarity, a partial coverage of English patient records together with the low prevalence of cases may substantially affect the statistical power and the generalisability of the measurements made. Second, there are concerns about the truncation of data. Since these databases are restricted to a small sample of general practices, patients moving in and out of practices will truncate the data and provide incomplete information. The impact of this as regards measuring a diagnostic odyssey needs to be assessed.

Service use

To overcome concerns about the representativeness of data from self-selected practices participating in research databases, increasingly there are opportunities to extract data from all practices. There are two principal approaches to obtaining patient-level data: local extraction and central extraction.

(i) Local extraction

This requires the cooperation and involvement of staff in each and every general practice who have to interrogate their local information system. This is the approach used to obtain data centrally for the Quality & Outcomes Framework for which practices have a strong financial incentive to participate. There are two recent examples of use of this approach in cancer and adult diabetes.

The NACDPC recruited general practices and asked them to extract data on cancer patients from their information system. It had to be reported in a standard way by

entering the data into a spreadsheet. This approach gave good results in terms of participation and validity, where representativeness of data was found to be satisfactory when compared with cancer registry data.

The National Adult Diabetes Audit used a strategy designed centrally but with an application for each of the brands of software in use locally. In other words, the terms used to identify patients with diabetes and those used to identify the data that were being requested were translated into the different languages that local systems use. Each participating practice ran a number of instructions prepared by the NDA for their system and obtained the data that needed to be returned. Most (88%) of general practices in England participated in 2011-2012 and the quality of data collected was reported to be excellent [22]. The method depended on local staff downloading the extraction software, running it and transmitting the output to the Health & Social Care Information Centre (HSCIC).

(ii) Central extraction

To overcome additional work for local general practice staff and to ensure 100% coverage, the General Practice Extraction Service (GPES) was conceived. It is to be hosted by HSCIC and is intended to provide data from all the main general practice information systems. Once up and running, the GPES will provide access to a much larger proportion of English patients' primary care records than existing databases. Currently technical challenges and political concerns about patient confidentiality are impeding progress to establish the GPES. Thus the level of accuracy of the data it would provide or its consistency is not known. No published use of this extraction system has been identified from web and database searches. Although extremely promising for the future, the GPES cannot yet be considered as a viable option to measure the diagnostic odyssey in rare diseases.

Three issues were identified as specifically associated with the use of data from these service databases. First, there are transcription issues. Currently, information generated in secondary care, such as a diagnosis made by a specialist, needs to be manually transcribed into primary care records. This may or may not happen and, if it does, there is a danger of errors being introduced. Letters reporting a diagnosis may simply be attached as document files to the patient record, or written in an open text comment, but not properly coded as such. This means that querying a primary care database for patients with a specific diagnosis may miss cases and that a more complicated and possibly iterative process could be needed.

Second, there are coding issues. The Read Codes used in primary care clinical information systems is unlikely to be specific enough to allow the correct identification of some (many) rare diseases. In addition, the lack of a code for a rare disease will lead to inconsistent coding, with the same condition being coded differently in different patients.

Finally, there are limitations in the reporting of symptoms before a diagnosis is made. The probability that the first symptoms of a rare disease are timely and accurately reported at presentation depends on their severity, the specificity of available codes and on clinician judgement. This means that the same symptoms may or may not be reported by different clinicians for different patients. This risk is likely to be higher with more unspecific and less severe symptoms.

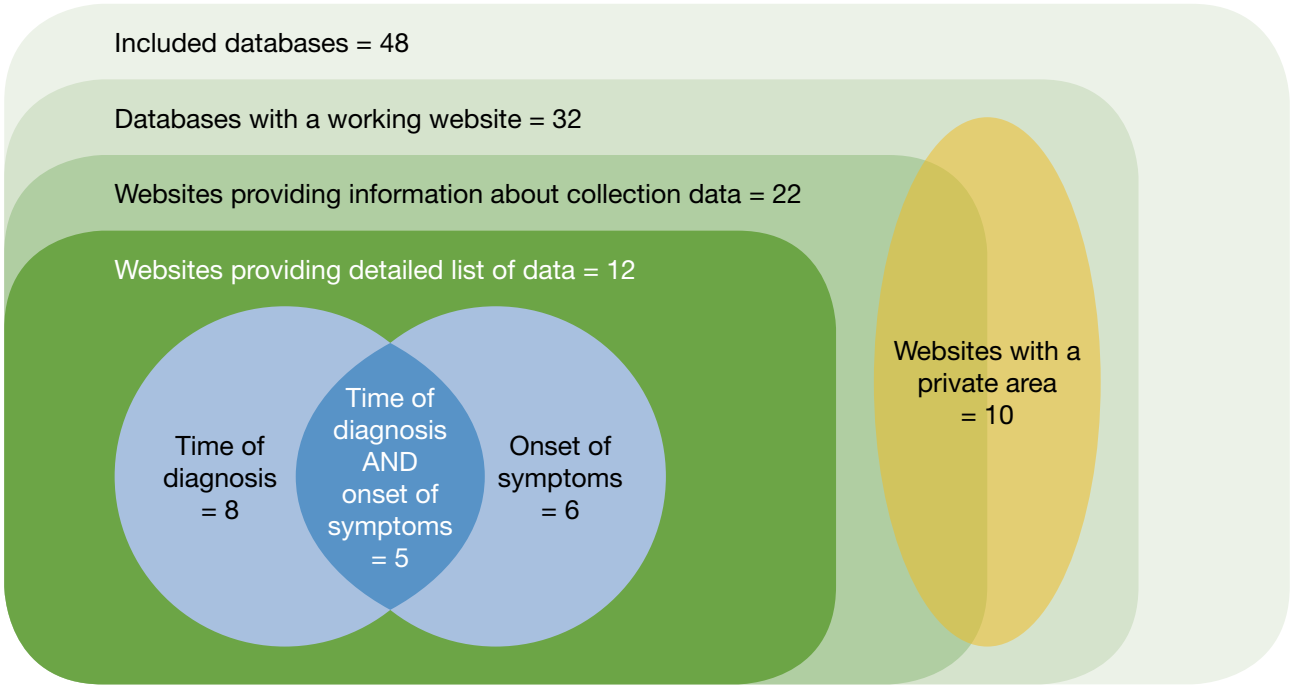
6.3 Rare disease databases

Orphanet identifies 74 unique rare disease databases in England. However, 26 did not meet the inclusion criteria of this review and were excluded: 12 were regional rather than national in coverage (mostly congenital anomaly registers which were included as part of the British Isles Network of Congenital Anomaly Registers); nine were conditions obvious at birth or already targeted by screening; and five were cancer or acute diseases.

Of the 48 databases meeting the inclusion criteria, 32 had an active, functioning website (Figure 3). Of those, 22 provided some information on the data variables collected including 12 that provided details. The details were either contained in a data dictionary or in a protocol for the database. As regards the diagnostic odyssey, five collected both the time of onset of symptoms and the time of diagnosis. It is possible that a larger number of databases collect such data but either the data dictionary was not available online, or access was restricted to those registered or contributing data.

In those databases that collect data about time of onset of symptoms and time of diagnosis, the definitions used to identify such events were generally vague. Thus the validity of these data should be appraised before being accepted and used.

Figure 3 Summary of databases collecting data about rare diseases in England



6.4 Specialist department databases

Some specialist departments (such as clinical genetics laboratories or centres for investigating and treating rare metabolic conditions) have created their own databases. While some may include information on the diagnostic odyssey, they are inevitably limited in scope to the experiences of a single specialist centre. Despite this limitation, such specialist databases could assist in identifying patients with a rare disease.

The National Pulmonary Hypertension Audit, managed by HSCIC, is an example of how specialist department databases can be used to collect patient-level data on a rare condition [23]. All eight centres designated for the care of patients with pulmonary hypertension in the UK participate, collecting data on patient demographics, diagnosis, clinical management and survival. The audit does not collect data on time to diagnosis but its functioning mechanism could be replicated for other conditions, where a limited set of centres for specialist care exists.

Although a disease that is diagnosed by means of a genetic test is not synonymous with it being a rare disease, a large number of the latter involve genetic testing as part of their diagnostic odyssey. Databases run by different genetic laboratories are unlikely to record information about onset of symptoms but as they always include a patient's NHS number, linkage to other databases could prove fruitful. In addition, specialist department data will have high validity and accurate coding. There are 32 laboratories in the UK Genetic Testing Network so establishing a national data collection system appears feasible, although a detailed assessment would need to be carried out.

6.5 National Congenital Anomaly & Rare Disease Registration Service (NCARDRS)

Public Health England is currently creating a single comprehensive national congenital anomaly and rare disease registration service. Their vision is influenced by their experience of creating and managing the National Cancer Registration Service (NCRS). As the NCARDRS is currently at an early stage of development it is not yet clear what its structure and contents will be. The aim is that all rare diseases identified in the internationally recognised Orphanet rare disease classification system will be included. The service will provide data for patients, their families, clinicians, public health and research to improve monitoring of the frequency, nature, cause and outcomes of congenital anomalies and rare diseases [24].

The Registration Service will encompass the existing British Isles Network of Congenital Anomaly Registers (BINOCAR), which covers about half the population, with plans to extend it to the whole country by the end of 2015. BINOCAR currently collects data on 89 conditions, 60 of which are listed as rare diseases. Given that the majority of these conditions are diagnosed prenatally or immediately after birth, this initiative will not meet concerns about prolonged diagnostic odysseys. Nonetheless the wider vision of the NCARDRS, which plans to use rare diseases databases and seeks to identify affected people from other sources, may have something to contribute to measuring diagnostic odysseys.

7. Options for monitoring the rare disease odyssey

There are three existing sources of data that could provide data on the diagnostic odyssey – general practice information systems, GP research databases, specialist department databases – and two potential sources that either are being planned – NCARDRS – or could be established – patient/parent surveys. We consider the strengths and limitations of each as well as the developmental opportunities that exist to enhance them.

7.1 Primary care information systems

Local general practice information systems contain clinical data on all registered members of the population. Diagnoses are identified by Read codes.

Strengths

- general practice clinical records contain detailed data about all episodes of primary and secondary care received by each patient which could identify the key points in the diagnostic odyssey;
- systems cover all patients registered in the UK; people with rare diseases are likely to be registered;
- may be possible to identify first presentation of what later turn out to be relevant symptoms/signs.

Limitations

- the Read codes, by which symptoms and diagnoses are coded, may not be detailed enough to identify all rare diseases;
- the time of onset of symptoms may not have been recorded;
- data extraction awaits the successful implementation of GPES;
- practices would have to be individually enrolled, though could be part of overall agreement for all national clinical audits;
- information governance issues (care.data) need to be addressed;
- key items of data may not be in the GP's electronic record but in letters and documents from specialist care, accessible only by free text scanning of attached documents.

Development opportunities

- lack of detail in Read codes could be addressed if diagnoses were validated from other sources (by linkage to HES, rare disease databases, and specialist department databases); or national monitoring could be restricted to a 'basket' of rare diseases for which Read coding is adequate;
- time of onset of symptoms could be estimated by GPs but compliance by GPs and accuracy (hindsight bias) uncertain;
- GP participation rates are likely to increase if a financial Incentive (as with the QOF) is deployed;
- as and when GP Extraction Service becomes available, there will be no extra workload on practice staff (though the level of participation by practices may be less than 100%);
- estimates of cost could be obtained from a review of the costs associated with NDA and with NACDPC. Similarly, lessons could be learnt about information governance issues.

7.2 Primary care research databases

These databases (CPRD, QResearch and THIN) provide higher quality data than GP data information systems in general but are restricted to samples of self-selected practices that may not be representative.

Strengths
- data have been checked, cleaned and shown to be meet certain quality standards;
- strong cooperation with the participating practices would facilitate any additional data requirements.

Limitations
- the Read codes, by which symptoms and diagnoses are coded, may not be detailed enough to identify all rare diseases;
- the time of onset of symptoms may not have been recorded by those entering data;
- data truncation may affect the validity of measured time to diagnosis;
- each database covers a limited proportion of UK population: CPRD (the largest) has about 5.5 million patients, about 10% of the population. This will limit the statistical power of diagnostic odyssey measurements, particularly for diseases of very low prevalence.

Development opportunities
- lack of detail in Read codes could be addressed if diagnoses were validated from other sources (by existing linkage to HES or new linkages to rare disease databases and specialist department databases); or national monitoring could be restricted to a 'basket' of rare diseases for which Read coding is adequate;
- time of onset of symptoms could be estimated by GPs though accuracy (hindsight bias) uncertain;
- combining data from the three major databases (CPRD, THIN and Qresearch) would increase statistical power.

7.3 Rare disease databases

A small number of rare diseases have a specific national database (register) that includes patient level data.

Strengths
- data have been checked, cleaned and shown to be meet certain quality standards.
- use of multiple sources to identify all cases should ensure high sensitivity and specificity for cases included;
- database custodians are likely to be well motivated to make data available for monitoring diagnostic odyssey;
- likely to have high credibility with patients/parents and clinicians;
- some databases have strong patient/parent involvement and sense of ownership.

Limitations
- only five such databases that include data on time of onset of symptoms/signs and time of diagnosis have been identified, but more may exist;
- the representativeness and completeness (sensitivity) of cases included is unknown but likely to vary between databases.

Development opportunities
- many other existing rare disease databases may be able to expand their datasets to include information on the odyssey at minimal extra burden or cost.

7.4 Specialist department databases

Many specialist facilities (hospital departments, clinical genetic laboratories) maintain their own databases, holding administrative and clinical information at patient-level. As they directly support the clinical management of patients, the data are detailed, complete and up-to-date.

Strengths

- high volume of patients with a range of rare diseases;
- appropriate for the rarest conditions and conditions managed in one or a small number of facilities;
- quality and completeness of data likely to be high;
- likely to be amenable to addition of additional data variables on odyssey;
- likely to have high credibility with patients/parents and clinicians;
- database custodians are likely to be well motivated to make data available for monitoring diagnostic odyssey.

Limitations

- not so useful for conditions that are managed at different levels of care, or in multiple facilities in a given catchment area;
- lack of standardisation of data collected between specialist facilities could limit opportunities for aggregating data to gain national information;
- limited in scope by geography (unless a national centre) and disease type – those not treated or tested for in specialised facilities will not be included;
- unlikely to collect data on early phases of diagnostic odyssey;
- lack of clear catchment population may lead to some patients being excluded. This may underestimate length of odyssey as those missed likely to experience longer journey;
- datasets collected may have altered over time limiting longitudinal monitoring;
- facilities that maintain the best databases may also be those that minimise the length of the odyssey, this biasing the results.

Development opportunities

- specialist facility databases which currently do not include data on the odyssey could add variables on time to diagnosis;
- the UK Genetic Testing Network provides an opportunity to create national information through sharing data from specialist facilities.

7.5 Patient/parent survey

Rather than relying on clinical records, an alternative approach would be to collect information from patients/parents using survey methods.

Strengths

- allows collection of data on when the first concerns occurred, which may be missing from clinical records;
- good method for identifying time at which the diagnosis was communicated to the patient/parent, which may be an important component of the odyssey;
- captures not only the patient/parents' objective view of the length of the odyssey but also their subjective judgement as to the acceptability of it;
- could also collect information on the quality of the odyssey (eg emotional impact of 'looping' through different specialties and hospitals with unnecessary repeat tests,

whether or not their condition is taken seriously, number of wrong diagnoses that preceded the correct one);
- patients/parents likely to be highly motivated to participate so high response rates;
- likely to have additional benefits by empowering patients/parents and providing feedback of concerns to stimulate improvements in services.

Limitations
- expensive and resource intensive to collect new data routinely;
- patients/parents judgement of attribution of relevant symptoms/signs may be inaccurate;
- subject to recall bias as patients/parents can only be asked about the onset of symptoms/first presentation after the final diagnosis is made, in some cases several decades later.

Development opportunities
- lessons could be learnt from those rare disease databases that already incorporate patient/parent surveys.

7.6 National Congenital Anomaly & Rare Disease Registration Service (NCARDRS)

The NCARDRS is planning to start incorporating rare diseases during 2015. When it is fully operational it could monitor the diagnostic odyssey. It's difficult to assess its strengths and limitations until more detail becomes available so what follows is somewhat speculative.

Strengths
- it would provide a comprehensive, single national database covering the whole of England;
- data will have been checked, cleaned and shown to be meet certain quality standards;
- use of multiple sources to identify all cases should ensure high sensitivity and specificity for cases included;
- likely to have high credibility with patients/parents and clinicians;
- high volume of patients with a range of rare diseases;
- NCARDRS are amenable to addition of additional data variables on odyssey;
- database custodians are likely to be well motivated to make data available for monitoring diagnostic odyssey.

Limitations
- it is still at an initial stage and is designed to be implemented in stages. So the ability to measure diagnostic odysseys may be some way off;
- current plans do not include routine data from primary care which would be necessary to measure the diagnostic odyssey.

Development opportunities
- being at an initial stage of development, it offers an opportunity to include the measurement of diagnostic odyssey within its scope.

7.7 Summary of options

The options have been assessed against the following nine criteria:

- range of rare diseases included;
- *information on diagnostic odyssey:* extent to which data are included;
- *representativeness of cases included:* extent of selection bias;
- *accuracy of case recruitment:* sensitivity (no false negatives) and specificity (no false positives);
- *data completeness:* extent to which missing data might bias findings;
- *validity of data:* on diagnostic odyssey;
- *credibility:* how meaningful the data are to patient/parents and clinicians;
- *timeliness:* how up-to-date the data are;
- *burden and cost of additional data collection:* additional time and expense to provide data on diagnostic odyssey.

For each criterion, the extent to which each option does or could satisfactorily meet the requirement has been judged as:

Red = considerable limitation
Orange = some limitation
Green = no existing limitation

Given uncertainty as to what the capabilities of the National Congenital Anomaly & Rare Disease Registration Service will be, it was not possible to assess it.

Figure 4 Assessment criteria for six potential data sources

Criteria	GP information systems	Primary care research databases	Rare disease database	Specialist department database	Patient/ Parent Survey
Range of diseases					
Information on diagnostic odyssey					
Representativeness of cases					
Accuracy of case recruitment					
Data completeness					
Data validity					
Credibility					
Timeliness					
Additional burden and cost					

8. Recommendations

8.1 Key considerations in formulating a solution

No single data collection approach can accurately and cost-effectively collect routine measurements of the diagnostic odyssey for all 5000-8000 rare diseases across the whole of the UK. The heterogeneity of diseases as regards their symptoms, signs, pathology, and natural history means that patients' experiences and diagnostic pathways vary. This, combined with the rarity of each disease, means that **we recommend that monitoring of the odyssey should be retrospective in design and focus on a 'basket' of tracer diseases**.

i. Retrospective approach

Given the low incidence of rare diseases, assessment of the diagnostic odyssey will inevitably need to start with the endpoint (when the diagnosis is eventually made) and then retrospectively look back at the events and timings of steps along the journey. This means that the completeness and accuracy of the odyssey will depend on the data collected at the time (eg date of referral from primary care) or on the recall of such events by patients/parents or clinicians.

ii. Tracer conditions

It is not feasible to assess the diagnostic odyssey for all rare diseases. The selection of 'tracer' conditions needs to maximise the generalisability of the results to the wide range of rare diseases that exist. To achieve this, the following criteria should be observed in determining suitable rare diseases for consideration:

- *relevance:* evidence (which may well be anecdotal) that prolonged odysseys exist and that it has an adverse impact on patients/parents;
- *disease prevalence:* sufficient to provide an acceptable statistical power to detect the impact of policy/practice interventions;
- *diagnostic specificity:* sufficient to be able to isolate condition by codes used in routine databases;
- *existence of tell-tale presenting symptoms and signs:* to enable a date to be determined at which a health professional could reasonably be expected to actively consider a diagnosis of a rare disease.

In selecting tracer conditions from those that meet these criteria, it would be advisable to include a range that reflected not only the variety of diagnostic categories (eg musculoskeletal, metabolic, developmental etc) but also that involved a range of diagnostic specialties (eg clinical genetics, imaging, biochemistry etc).

Although there is no suitable single source of data available, a combination of existing sources, with some enhancements, could produce a feasible way forward. **We recommend the use primary care data as the foundation and to build on that through more specialist data sources such as rare disease databases and specialist department databases. In addition, patient/parent surveys could enhance knowledge and understanding of the diagnostic odyssey still further.** Details of such an approach are outlined below.

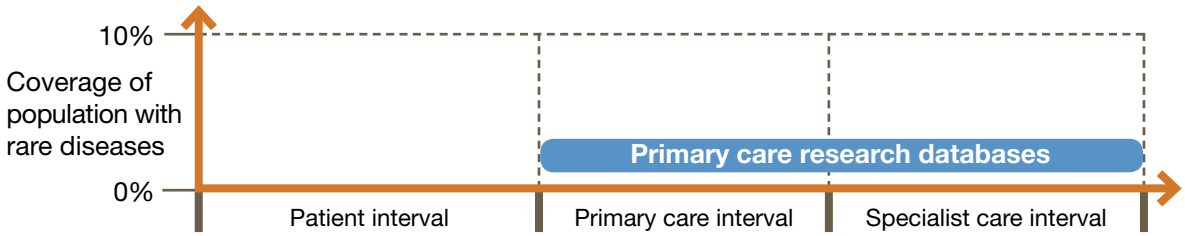
8.2 Primary care databases

Ideally, information systems in all general practices would be used so that everyone with a diagnosis of a rare disease could be identified. However, currently that is not feasible due to technical limitations with extracting data remotely (without burdening general practice staff with additional work), and political concerns about patient confidentiality that are restricting access to and the use of such data. Until these issues are resolved, alternative approaches must be used. Whilst not perfect, they may be fit-for-purpose if the data are handled cautiously.

We recommend the use of primary care research databases. The feasibility of identifying patients has already been demonstrated for tuberous sclerosis and Huntington's disease, and the cost is relatively low (Figure 5). The principal limitations are:

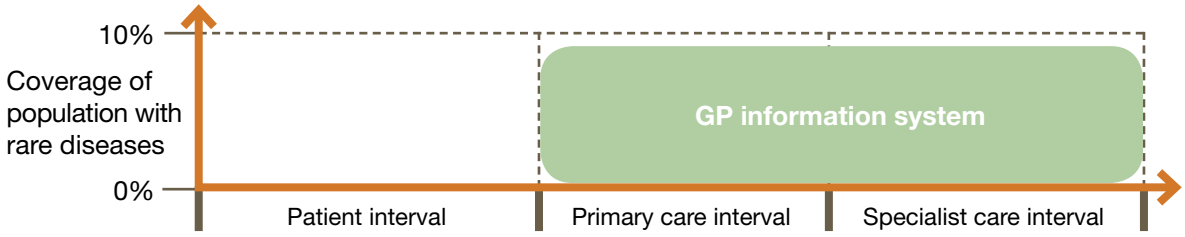
- the range of diseases to be included in the basket would be limited by the specificity and sensitivity of Read codes;
- the restricted coverage of the UK population to self-selected general practices may bias the findings (though this could be minimised by combining data from several research databases);
- the lack of data on the patient interval would preclude measuring the effects of interventions aimed at reducing it.

Figure 5 Diagnostic intervals for rare diseases covered by primary care research databases and coverage of population



As and when it becomes possible to extract data from all general practices (using the General Practice Extraction Service), the sample sizes will be much enlarged and selection bias will be minimal (Figure 6). There will still be the issue of the lack of specificity and sensitivity of Read codes for some rare diseases. The work to design the queries for data extraction will be able to capitalise on experience from working with the primary care research databases.

Figure 6 Diagnostic intervals for rare diseases covered by GP information systems and coverage of population



8.3 Supplementary sources

The foundation provided by primary care data can be enhanced and validated by the addition of data from three other sources: rare diseases databases; specialist department databases; and patient/parent surveys.

Rare diseases databases

Although relevant for only a limited number of diseases, **we recommend the use of rare diseases databases to enhance the data from primary care**. Using patient identifiers, data from rare diseases databases could be linked to primary care research databases at the individual level (subject to meeting confidentiality requirements). This would help inform the primary care and specialist care intervals in the diagnostic odyssey. Meanwhile, the custodians of rare diseases databases should be encouraged to include data that allows all three intervals in the odyssey to be determined.

Specialist department databases

In a similar way, **we recommend that patients identified in primary care research databases be sought in databases run by specialist departments**. The strengths of these databases are the high number of patients with rare diseases included. We recommend including:

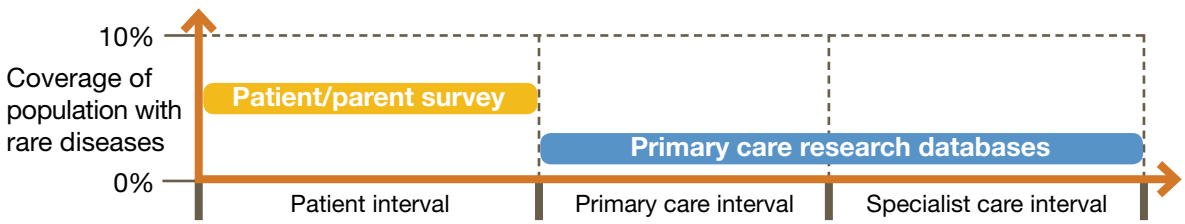
- genetic sequencing centres: a large and increasing number of rare diseases are diagnosed using genetic tests carried out by a small number of regional or national reference laboratories. Utilising their electronic records, supplemented by a small number of specific questions concerning time to diagnosis on test request forms, gives access to a large number of patients with rare diseases;
- quaternary care centres specialising in rare diseases: their patients are likely to be those with a relatively long diagnostic odyssey. Although not generalizable to all patients with a rare disease, the most severely affected patients are those for whom it is arguably most important to improve time to diagnosis.

Patient/parent survey

The principal gap in the information available from routine databases is data on the time of patients'/parents' initial concern that there might be a problem (the start of the patient interval). **We recommend the use of a patient/parent survey to help establish the patient interval.**

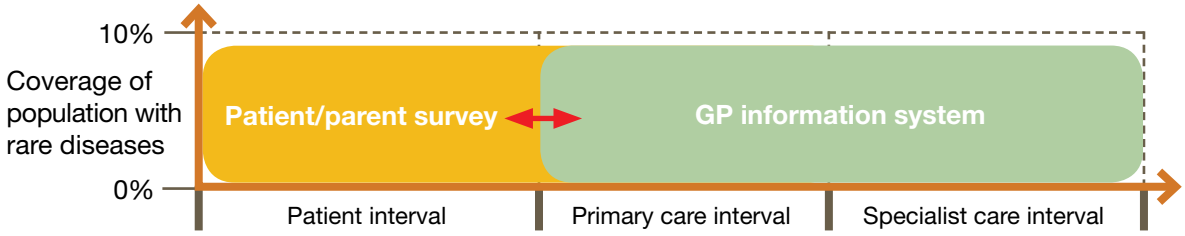
General practice research databases can't be used to identify individual patients so it will not be possible to try and generate linked data. Instead, patients would need to be recruited through patient associations, rare diseases databases or specialist department databases. As data from different sources would be based on different patients, the assumption would have to be made that both sources were representative of the odysseys of all patients (Figure 7).

Figure 7 Diagnostic intervals for rare diseases covered by primary care research databases and survey, and coverage of population



As and when primary care information systems can be utilised, patients/parents could be invited to participate in a survey by their GP, avoiding any information governance obstacles. Responses could then be linked to the routine databases at the individual level (ie data from both sources would relate to the same patients) (Figure 8). The survey need not be limited to the patient interval but could seek to validate the clinical records of the other two intervals. In addition the survey could obtain information on the ways the odyssey had affected patients'/parents' quality of life, not just quantifying the length.

Figure 8 Diagnostic intervals for rare diseases covered by GP information systems and survey, and coverage of population



There would be additional work for participating practices but the low prevalence of patients with rare diseases would mean it was slight. Given the importance of the odyssey for most of those surveyed, a high response rate would be expected. However, given the large number of general practices (over 8000 in England), the work involved in managing a survey would be considerable, as would be the cost.

8.4 The way forward

We recommend that these proposals be subject to widespread consultation among all those with an interest in and expert knowledge of the clinical, diagnostic and management aspects of the conditions and among those with expert knowledge of the relevant information systems. Whatever course of action is subsequently decided upon will need to be rigorously tested before widespread implementation.

We recommend that the feasibility of any proposals are tested in pilot studies of two or three rare diseases. This will enable a number of suppositions to be tested including:

- the ability to identify the diseases in the general practice research databases;
- the feasibility of using more than one GP research database and whether there is sufficient added value to justify such a strategy;
- the amount of information on the diagnostic odyssey that can be obtained from the GP research database/s;
- the cost and benefit of supplementing such data with that obtained from rare diseases databases;
- the cost and benefit of supplementing such data with that obtained from specialist department databases;
- the feasibility and response rates of patient/parent surveys;
- the feasibility of rare diseases databases and specialist department databases extending their datasets to include information on the odyssey.

Finally, whatever policy is adopted, it will need to be reviewed in the light of two promising prospects. Both the General Practice Extraction Service and the National Congenital Anomaly & Rare Disease Registration Service may provide better options for monitoring the diagnostic odyssey than the short-term solutions being proposed.

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Appendix 1 Systematic review protocol and search strategies

Protocol registered at PROSPERO, registration number CRD42014013877

Research aim

To identify and synthesise existing quantitative research into the diagnostic odyssey of long-term, non-communicable rare diseases in OECD countries, with a primary focus on how studies have defined, collected and analysed time to diagnosis.

A secondary aim of the review is to identify and extract data on what is known about the length and determinants of time to diagnosis. However, this will not be the primary focus of the synthesis and findings will be presented in the synthesis only where they aid interpretation of the usefulness of different research methods used. Data extracted on study findings will, however, be presented in results tables to allow their use by interested academics or clinicians.

Review Methods

Inclusion and Exclusion Criteria

Rare diseases will be defined as any disease identified as a rare disease by www.orpha.net, www.eurordis.org or any condition that meets the criteria for a rare disease set out in the UK Strategy for Rare Diseases, namely 'a life-threatening or chronically debilitating disease that affects 5 people or fewer in 10,000'.[1]

The aim of this review is to investigate methods for assessing diagnostic odysseys in patients with rare diseases that are often inherited or congenital, and may go undiagnosed for months or years. The causes and consequences of such diagnostic delays are sufficiently different from delays measured in minutes or hours in diagnosing acute conditions such as meningococcal meningitis (classified as a rare disease by orpha.net) to warrant separate consideration. The scope of the review will therefore be further limited to long term conditions of a non-infectious origin.

'Diagnostic odyssey' will be defined as: *a time to definitive diagnosis longer that what the natural history of the disease and available technologies would allow, and whose delay may affect the health or emotional wellbeing of the patient or their family, their clinical management including secondary prevention and symptomatic treatment, or their access to social support services.* The review will only include studies that measure time to diagnosis of a rare disease from an explicitly defined starting point in the disease pathway to a defined diagnosis date.

The review will not be limited by language, place of publication or publication date. Foreign language texts will be translated by a member of the research team or colleague fluent in that language. All quantitative study designs will be considered, including descriptive designs, except case studies of one or a small number of patients which will be excluded as not sufficiently informative. However, given that in some ultra-rare diseases an entire country may only have a small number of cases of a particular disease, case series of the entire case population of a facility, region or country over a specified time period will be included in the review.

In summary, studies will be included if they:

1. Were conducted in a World Bank defined OECD country

2. Measure, evaluate or seek to understand time to diagnosis, defined as length of time from onset of disease, onset of symptoms or presentation to any level of the health services until the correct diagnosis is made.

1 Department of Health. The UK Strategy for Rare Diseases. London, UK; 2013.

Included: only age at diagnosis measured, where it was used by study authors as a marker of time to diagnosis in a congenital condition
Excluded: only age at diagnosis measured, where used by study authors as a marker of disease onset.

3. Investigate one or more non-communicable, chronic rare diseases.
   Excluded: time to diagnosis of a complication resulting from an underlying disorder, whether rare or not; rare subtypes of a common disease

4. Report explicitly defined quantitative measures of time to diagnosis in a population of patients with a rare disease.
   Excluded: studies that do not explicitly define the start or end points of the time to diagnosis measure
   Excluded: case study designs unless representing a complete case population of a facility, region or country over a specified time period

Search Strategy

Medline, Embase and PsychINFO will be searched using search strategies based on the following broad logic:

[rare disease] AND **[diagnostic odyssey]** AND [**quantitative study design]** AND **[OECD country]**

Full search strategies for each database are given below. Of note, synonyms of rare diseases alone were felt unlikely to retrieve all relevant articles, while it was not feasible to include specific terms for the several thousand rare diseases currently known. As a pragmatic compromise, eight rare diseases (namely Crohn's disease, cystic fibrosis, Duchenne's muscular dystrophy, Ehlers-Danlos Syndrom, Marfan syndrome, Prader-Willi Syndrome, Tuberous Sclerosis and Fragile X syndrome) that were the focus of an early EURORDIS report[2] plus an additional seven conditions explicitly named in the UK Strategy for Rare Diseases1 (sickle cell anaemia, spina bifida, phenylketonuria, congenital hypothyroidism, medium chain acyl-CoA dehydrogenase deficiency, long QT syndrome and infantile epilepsy) were added to the search strategy as 'tracer' conditions. However, study eligibility was not limited to these 15 conditions.

In addition, institutional repositories of key organisations concerned with rare diseases will also be searched, as well as contacting key experts, screening the references of included studies and screening studies previously known to the authors.

Screening and Data Extraction

After de-duplication, the titles and abstracts of a random 10% of retrieved articles will be independently dual screened by two members of the review team using EPPI-Reviewer software. Differences in screening outcome will be reconciled through discussion and mutual agreement between the two screeners with reference to the study inclusion criteria, with input from the third reviewer if needed to solve any outstanding disagreements. Following reconciliation, the remaining abstracts will be screened by a single reviewer. The full text of the remaining eligible articles will then be screened in a similar manner, with 10% dual screened and the remainder single screened following reconciliation.

Data will be extracted by a single reviewer and checked for accuracy by a second. Data will be extracted on:

2 Eurordis. Survey of the delay in diagnosis for 8 rare diseases in Europe ('Eurordiscare 2'). 2009.

- study characteristics;
- rare disease investigated;
- population sampled, including sampling method and sampling frame used;
- Definition of time to diagnosis, including how this definition is operationalised within data collection instruments;
- Data collection method, including whether routine data is used;
- Data analysis method;
- Findings and key conclusions;
- Author-specified methodological limitations.

Synthesis and Quality Appraisal

A narrative synthesis will be followed. Given the heterogeneity of the diseases included and the focus on research methods rather than findings, it is not expected that an additional meta-analysis will be appropriate.

As the primary aim of this review is to synthesise research and data collection methods rather than their results, quality appraisal is seen as an integral component of the synthesis and discussion rather than a standalone process. Quality appraisal will be entirely narrative and no formal quality appraisal tool will be used, for the following reasons. Commonly used quality appraisal tools are designed for assessing effectiveness studies whereas we may include descriptive studies. Furthermore, quality appraisal tools primarily assess the validity of generalising the results of each study based on reported methods, rather than the appropriateness of the data collection methods themselves. Finally, the validity of a particular method may be different depending on the nature of the disease and diagnostic odyssey investigated. Therefore summarising a study's quality using a generic scoring system will provide less useful information that a narrative critique.

However, data will be extracted and reported separately for each study on their choice of study methods, author-identified and reviewer-identified limitations with a particular focus on potential biases resulting from: participant sampling and sampling frame, data collection instruments, conceptual definitions of time to diagnosis and statistical analysis techniques.

Two subgroups will be analysed in addition to the overall synthesis: studies using routine data only, and studies measuring time to diagnosis as a continuous rather than categorical variable.

Database search strategies

Medline and Embase:

#	Concept	Search terms	Hits (11/9/14)	Notes
1	Key focus of review	diagnostic odyssey.mp	71	Included without further filters
2	Rare disease	Exp Rare Diseases/	24431	[MeSH] introduced 2003
3		Rare disease?.mp	49980	
4		Orphan disease?.mp	1235	
5		((rare or orphan or low prevalence or low incidence or uncommon or infrequent) adj1 (disease? or illness$ or condition?)).mp	85313	
6		**Or/2-5**	85313	
7	Tracer conditions	exp crohn disease/ or exp cystic fibrosis/ or exp Muscular Dystrophy, Duchenne/ or exp Ehlers-Danlos Syndrome/ or exp Marfan syndrome/ or exp Prader-Willi Syndrome/ or exp Tuberous Sclerosis/ or exp Fragile X Syndrome/	222245	Diseases included in Eurordiscare rare diseases survey
8		(crohn or crohn's or cystic fibrosis or duchenne or duchenne's or Ehlers-Danlos or marfan or marfan's or prader willi or tuberous sclerosis or fragile X).mp	280105	Conditions spec. mentioned in Ch3/4 of UKRDS re: early detection/ diagnosis
9		Anemia, Sickle Cell/ or exp Spinal Dysraphism/ or exp Phenylketonurias/ or exp Congenital Hypothyroidism/ or exp Lipid Metabolism, Inborn Errors/ or exp Long QT Syndrome/ or exp Spasms, Infantile/	356880	
10		(Sickle cell or spina bifida or phenylkenoturia or congenital hypothyroidism or medium chain acyl-CoA dehydrogenase deficiency or MCADD or MCAD or long QT syndrome or infantile epilepsy).mp	94337	
11		**Or/6-9**	655274	
12	Diagnostic odyssey	Exp delayed diagnosis/	8363	
13		((odyssey? or late or delay$ or prolong$ or long or interval) adj3 (diagnos$ or identif$) or time to diagnosis or lag-time or symptom interval or patient interval).mp	140960	
14		((onset or start$ or duration) adj3 (symptom? or disease or condition or illness)) adj7 diagnos$.mp	17770	
15		Or/22-24	155723	
16	**RD + DO**	6 and 15	2745	
17	**(RD or Tracer) + DO**	(6 or 11) and 15	8824	
18	OECD	exp Australia/ or New Zealand/ or exp Japan/ or korea/ or "republic of korea"/ or Austria/ or Belgium/ or Czech Republic/ or exp Scandinavia/ or Estonia/ or Finland/ or exp France/ or exp Germany/ or Greece/ or Hungary/ or Iceland/ or Ireland/ or exp Italy/ or Luxembourg/or Netherlands/ or Poland/ or Portugal/ or Slovakia/ or Slovenia/ or Spain/ or Switzerland/ or exp Great Britain/ or Israel/ or exp Canada/ or exp United States/	4795730	

Medline and Embase:

#	Concept	Search terms	Hits (11/9/14)	Notes
19	OECD	Australia or new Zealand or japan or austria or belgium or (korea not ((democratic adj3 korea) or north korea)) or czech republic or (scandinavia or denmark or norway or Sweden) or estonia or finland or france or germany or greece or hungary or Iceland or (ireland or eire) or italy or luxembourg or (netherlands or holland) or poland or portugal or (slovakia or slovak republic) or slovenia or (spain or balearic islands or canary islands) or switzerland or (great britain or GBR or united kingdom or UK or england or scotland or wales or northern ireland or channel islands or isle of man) or israel or canada or ((united states adj2 america) or united states or USA) or (oecd countr* or "Organisation for Economic Co-operation and Development").mp.	6337110	
20		**Or/28-29**	6772971	
21	**RD + DO + OECD**	**6 and 15 and 20**	416	
22	**(RD or Tracer) + DO + OECD**	**(6 or 11) and 15 and 20**	1582	
23	Study design/ article type	Exp Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab or case control.tw	1619423	
24		cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.tw or prospective.ti,ab or retrospective.tw or (cohort adj (study or studies)).tw or Cohort analy$.tw or (Follow up adj (study or studies)).tw	3822380	
25		Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.	518045	
26		"clinical trial".pt. or "clinical trial, phase i".pt. or "clinical trial, phase ii". pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or "multicenter study".pt. or "randomized controlled trial".pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab.	1895823	
27		Epidemiologic Studies/ or (observational adj (study or studies)).tw	271211	
28		Intervention$ or control$ or evaluat$ or effect?.tw	18567518	
29		**Or/23-28**	20655421	
30		Animals/	6984680	
31		Humans/	28685331	
32		30 not (30 and 31)	5104444	
33		(News or comment or editorial).pt	1460015	
34		comment on.cm	602974	
35		**29 not (32 or 33 or 34)**	18231468	

Medline and Embase:

#	Concept	Search terms	Hits (11/9/14)	Notes
36	**RD + DO + OECD + design**	**29 not (32 or 33 or 34) (6 and 15 and 20 and 35) or 1**	318	Embase – 204 Medline – 114
37	**RD or Tracer) + DO + OECD + design**	**((6 or 11) and 15 and 20 and 35) or 1**	**1207**	Embase – 848 Medline - 359

PsychINFO:

#	Concept	Search terms	Hits (8/9/14)
1	Key focus of review	diagnostic odyssey.mp.	1
2	Rare disease	Rare disease?.mp.	304
3		Orphan disease?.mp.	17
4		((rare or orphan or low prevalence or low incidence or uncommon or infrequent) adj1 (disease? or illness$ or condition?)).mp.	740
5		or/2-4	740
6	Tracer conditions	**exp cystic fibrosis/ or exp Muscular disorders/ or exp Prader Willi Syndrome/ or exp Fragile X Syndrome/**	7875
7		(crohn or crohn's or cystic fibrosis or duchenne or duchenne's or Ehlers-Danlos or marfan or marfan's or prader willi or tuberous sclerosis or fragile X).mp.	4198
8		exp Sickle Cell Disease/ or exp Spina Bifida/ or exp Phenylketonuria/ or exp Lipid Metabolism Disorders/	1867
9		(Sickle cell or spina bifida or phenylkenoturia or congenital hypothyroidism or medium chain acyl-CoA dehydrogenase deficiency or MCADD or mcad or long QT syndrome or infantile epilepsy).mp.	2081
10		or/6-9	12207
11	Diagnostic odyssey	**((odyssey? or late or delay$ or prolong$ or long or interval) adj3 (diagnos$ or identif$) or time to diagnosis or lag-time or symptom interval or patient interval).mp**	3574
12		((onset or start$ or duration) adj3 (symptom? or disease or condition or illness)) adj7 diagnos$.mp	438
13		or/11-12	3940
14		(5 and 13) or 1	13
15		((5 or 10) and 13) or 1	96

Appendix 2 Results of systematic review

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Bygum 2013 Acquired angioedema--occurrence, clinical features and associated disorders in a Danish nationwide patient cohort	Denmark **Acquired Angioedema**	8	Retrospective De novo	Clinical case note review, Direct clinical examination/ history, Patient/family questionnaire Hospital records	Onset of symptoms Diagnosis	The mean duration from the onset of symptoms to the diagnosis of AAE was 1 year and 8 months (0 months to 5 years).
Evensen 2006 Epidemiology and outcome of adult-onset Still's disease in Northern Norway	Norway **Adult-onset Still's disease**	13	Retrospective De novo	Clinical case note review Hospital records	Not specified Diagnosis	Mean diagnostic delay was 5.4 months (range 0.5–18).
Huber 2010 [Alpha1-antitrypsin deficiency in Austria: analysis of the Austrian Alpha1-international-registry database]	Austria **Alpha1-antitrypsin deficiency**	139	Retrospective Routine	Registry Disease registry	Age at onset of respiratory complaints Age at diagnosis	The mean duration between the onset of symptoms and the final diagnosis was 6.5 years.
Greulich 2013 Alpha1-antitrypsin deficiency - diagnostic testing and disease awareness in Germany and Italy	Germany, Italy **Alpha1-antitrypsin deficiency**	Not supplied	Prospective Routine	Registry Disease registry	Showing symptoms of disease Receiving a diagnostic test/test result communicated	The median time interval between the onset of symptoms and diagnosis was 6 years (IQR 11; range, 0-40) and 7 years (IQR, 13; range, 0-73).
Rocchetti 2012 Modeling delay to diagnosis for Amyotrophic lateral sclerosis: Under reporting and incidence estimates	Italy **Amytrophic lateral sclerosis**	1799	Prospective Routine	Registry Disease registry	Date of first occurrence of symptoms that can be unequivocally linked to the disease Diagnosis	Mean delay to diagnosis from sypmtom onset is 458 days (SE = 11.53); median delay is 316 days.
Crow 1997 Batten disease in the west of Scotland 1974-1995 including five cases of the juvenile form with granular osmiophilic	Scotland **Batten Disease/ neuronal ceroid lipofuscinosis**	12	Retrospective De novo	Clinical case note review Clinical database	Age at which symptoms were first noted Age at diagnosis	Mean delay to diagnosis from sypmtom onset is 458 days (SE = 11.53); median delay is 316 days.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Anwar 2013 Phenotyping adults with non-cystic fibrosis bronchiectasis: A prospective observational cohort study	England **Bronchiectasis**	189	Prospective De novo	Direct clinical examination/history	Age at symptom onset Age at diagnosis	Mean diagnostic delay 17 years. Excellent non-invasive diagnostic techniques have been widely available for two decades, suggesting that index of suspicion fo rthis condition remains low.
Twiss 2005 New Zealand national incidence of bronchiectasis “too high” for a developed country	New Zealand **Bronchiectasis**	65	Prospective Routine	Specialist questionnaire, Surveillance unit Surveillance database	Age at onset of cough Age at diagnosis	At diagnosis (median 5.2 years) 40% of cases had cough for >2 years.
Pilo-de-la-Fuente 2011 Cerebrotendinous xanthomatosis in Spain: clinical, prognostic, and genetic survey	Spain **Cerebrotendinous xanthomatosis**	25	Retrospective De novo	Clinical case note review, Direct clinical examination/history Patients diagnosed wat the main reference centres for genetic diagnosis of CTX in Spain	Age at first neurological symptom/presenting symptom Diagnosis	An average delay of 19 years was observed between symptom onset and clinical diagnosis (range 2–44). This long delay may be partially because of the heterogeneity of neurological symptoms that characterize CTX, the lack of specificity of early features (diarrhea, cataracts), and the unawareness of rare diseases in clinical practice.
Jankovic 2011 Rationale and design of a prospective study: Cervical Dystonia Patient Registry for Observation of OnaBotulinumtoxinA Efficacy (CD PROBE)	USA **Cervical Dystonia**	609	Prospective Routine	Patient/family questionnaire or structured interview Disease registry	Symptom onset Diagnosis	Time to diagnosis 5.4 ± 8.6 years.
Peretti 2009 Chylomicron retention disease: A long term study of two cohorts	France, Canada **Chylomicron retention disease/ Anderson’s disease**	16	Retrospective De novo	Clinical case note review Hospital records	Age at onset of symptoms Diagnosis	Delay in diagnosis was considerably longer in the French cohort (6.3 ± 1.3 years) compared to the Canadian cohort (1.3 ± 0.04 years). This delay was likely due to lack of awareness for the disease and perhaps to poor accessibility to a competent gastroenterology service.

Author-Yr Title	Country **Rare diseases(s)**	**Sample size**	**Prosp/retro** **Routine/de novo**	**DataColl method** **Sampling Frame**	**Starting point: TTD** **Ending point: TTD**	**Findings and key conclusions**
Kapoor 2010 Idiopathic systemic capillary leak syndrome (Clarkson's disease): the Mayo clinic experience	USA **Clarkson's disease/Idiopathic systemic capillary leak syndrome**	24	Retrospective De novo	Clinical case note review Hospital records	Onset of symptoms Diagnosis	Median time to diagnosis from symptom onset was 1.1 years (interquartile range, 0.5-4.1 years). In 3 patients, a formal diagnosis was made more than 5 years after the onset of symptoms (after 5.5, 8.0, and 32.0 years). delay in diagnosis and/or misdiagnosis led to increased patient morbidity in our series.
Kachko 2008 Complex regional pain syndromes in children and adolescents	Israel **Complex regional pain syndrome**	14	Retrospective De novo	Clinical case note review Hospital records	Onset of symptoms/ initiating event, time from seeking medical help Referral to pain clinic	The median time from onset of symptoms to seeking medical help was 4.46 weeks (range 2 – 82 weeks). The median time to referral to pain clinic was 24.51 weeks (range 1.2 – 94).
Bader-Meunier 2005 Clinical and laboratory manifestations of congenital dyserythropoietic anemia type I in a cohort of French children	France **Congenital Dyserythropoietic Anemia Type I**	12	Retrospective De novo	Specialist questionnaire Existing cohort/study sample	Onset of anaemia Correct diagnosis	The mean time elapsed from the onset of anemia until the correct diagnosis was established was 5.1 years (range 0.2–18).
Alm 1978 Congenital hypothyroidism in Sweden. Incidence and age at diagnosis	Sweden **Congenital Hypothyroidism**	112	Retrospective De novo	Clinical case note review	Birth, age of onset of symptoms Diagnosis	The diagnosis was delayed until after an age of three months in 52 % of the cases. The age at onset of symptoms compatible with hypothyroidism could be evaluated in 84 of the 112 children with CH. Of these, 76 (91 %) had one or more symptoms before the age of three months.This fact supports the view that mass screening of newborns for congenital hypothyroidism has to be introduced in Sweden.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Wilcken 1983 Diagnostic delay in cystic fibrosis: Lessons from newborn screening	Australia **Cystic Fibrosis**	33	Retrospective De novo	Clinical case note review, Direct clinical examination/history Not specified	Age of initial presentation to medical attention Age at diagnosis	Mean delay between presentation with symptoms and diagnosis of CF in clinically diagnosed infants was 2.6 years. Our investigation shows that without screening there are appreciable delays between onset of symptoms and diagnosis.
Lai 2005 The survival advantage of patients with cystic fibrosis diagnosed through neonatal screening: Evidence from the United States cystic fibrosis Foundation Registry data	USA **Cystic Fibrosis**	27692	Unclear/no info Routine	Registry Disease registry	Birth Diagnosis	Within MI and SCREEN groups, greater than 50% were diagnosed before 1 month, and greater than 75% were diagnosed before 3 months of life (Table I). In contrast, less than 20% of patients in the SYMPTOMgroup were diagnosed before 3 months, and almost half were diagnosed after age 1 year.
Sanders 2012 Comparing age of cystic fibrosis diagnosis and treatment initiation after newborn screening with two common strategies	USA **Cystic Fibrosis**	1288	Unclear/no info Routine	Registry Disease registry	Birth Time of diagnosis	Compared to infants born in IRT/IRT states, infants born in IRT/DNA states were younger at the time of diagnosis (median 2.3 weeks versus 4.0 weeks in IRT/IRT states, pb0.001).
Farrell 2007 Diagnosis of cystic fibrosis in the Republic of Ireland: Epidemiology and costs	Ireland **Cystic Fibrosis**	649	Unclear/no info Routine	Registry Disease registry	Birth Diagnosis	The average age of diagnosis was delayed to 24.6 months. Longer delays when diagnosis followed respiratory symptoms, rather than gastrointestinal signs, and also in girls compared to boys, particularly those presenting with respiratory symptoms.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Nick Jerry 2010 Effects of gender and age at diagnosis on disease progression in long-term survivors of cystic fibrosis	USA **Cystic Fibrosis**	3120	Prospective, De novo, Routine	Clinical case note review, Facility database, Registry Disease registry	Birth Diagnosis	Colorado database: childhooddiagnosed age at diagnosis ranging from birth to 10 years (median, 2.0 yr) and an AD cohort (n=109; range, 18–84 yr; median, 52.0 yr) CFF registry: median age at diagnosis for the CD cohort (n=1,436) was 1.7 years, compared with 37.4 years for the AD cohort (n=1,178), with age at diagnosis ranging from 18 to 80.7 years (median, 37.4 yr).
Jackson 2010 Delayed cystic fibrosis presentation in children in the absence of newborn screening	Ireland **Cystic Fibrosis**	601	Unclear/no info Routine	Registry Disease registry	Birth Diagnosis	Modes of presentation were each significantly associated with delayed presentation. Children with respiratory symptoms had the greatest likelihood of delayed diagnosis (median age: 20.4 months), followed by those with respiratory and gastrointestinal symptoms (9.2 months). Gender was not significantly associated with a delayed presentation when presentation mode was taken into account.
Spencer 1994 Cystic fibrosis in children from ethnic minorities in the West Midlands	England **Cystic Fibrosis**	16	Unclear/no info Routine	Clinical database	Birth Diagnosis	The median age of diagnosis was similar in the white European and nonwhite patients (0.42 vs. 0.33 years, 95% CI for the difference of the medians -0.15, 0.37).

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Chong 2000 Retrospective estimation of the birth prevalence for delayed onset disorders: application to cystic fibrosis in Nova Scotia	Canada **Cystic Fibrosis**	98	Prospective Routine	Registry Disease registry	Birth Diagnosis	It was found that 25 of the 77 were diagnosed in their first week of life, 21 were diagnosed between one week and three months, 17 between three months and six months, and 14 between six months and one year. Accordingly, the age-at-diagnosis probability estimates for these time periods are 0.241, 0.203, 0.164 and 0.135, respectively, with approximate standard errors 0.043, 0.040, 0.0367 and 0.034.
Lim 2014 Diagnosis of cystic fibrosis in London and South East England before and after the introduction of newborn screening	England **Cystic Fibrosis**	347	Prospective De novo	Clinical case note review, Facility database All patients under care of one of the CF specialist centres in the region	1. Age at first symptoms 2. Birth 3. Age at first presentation of CFrelated symptoms to a health professional Diagnosis	Unscreened children - median TTD from initial Sx = 1 year, 10% >6 years Screened children - median age of diagnosis 3 weeks.
Prapphal 1989 Cystic fibrosis in blacks in Washington, DC: fifteen years' experience	USA **Cystic Fibrosis**	188	Retrospective De novo	Clinical case note review Hospital records	Onset of symptoms Diagnosis	There were no statistically significant differences in average duration of symptoms prior to diagnosis between blacks and whites (blacks X = 1.26 +/- 3.00 years; whites X = 0.96 +/- 3.03 years; p>0.05).
Steinraths 2008 Delays in diagnosing cystic fibrosis: can we find ways to diagnose it earlier?	Canada **Cystic Fibrosis**	122	Retrospective De novo	Clinical case note review Hospital records	Onset of symptoms Diagnosis	Excluding the adult patients and patients with meconium ileus, mean age at diagnosis of CF was 3.6 years, and mean delay in diagnosis after first symptoms was 2.1 years. Considerable delays in diagnosis of children with CF occur when the disease is identified solely on clinical presentation.

Author-Yr Title	Country **Rare diseases(s)**	**Sample size**	**Prosp/retro** **Routine/de novo**	**DataColl method** **Sampling Frame**	**Starting point: TTD** **Ending point: TTD**	**Findings and key conclusions**
Balnaves 1995 The impact of newborn screening on cystic fibrosis testing in Victoria, Australia	Australia **Cystic Fibrosis**	167	Retrospective De novo	Clinical case note review, Facility database Administrative database, Hospital records	Birth Diagnosis	The age at diagnosis before 1989 varied from 1 to 10 years. In general, this time is now approximately six weeks, when the sweat tests are performed in AF508 heterozygous infants.
Farrell Philip 2003 Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis	USA **Cystic Fibrosis**	103	Prospective De novo	Clinical case note review Existing cohort/study sample	Birth Diagnosis	In the screened group (56 patients), diagnosis was made at a younger age of 12.4 weeks, compared with the diagnosis in control group (47 control patients) at the age of 95.8 weeks ($p<0.001$).
Tadic 2012 Dopa-responsive dystonia revisited: Diagnostic delay, residual signs, and nonmotor signs	Germany **Dopa-responsivedystonia**	23	Retrospective De novo	Clinical case note review, Direct clinical examination/history, Patient/family questionnaire or structured interview Hospital records	Age at onset Age at diagnosis	Theaverage (SD) delay in diagnosis was 15.5 (16.3) years.
Mohamed 2000 Delayed diagnosis of Duchenne muscular dystrophy	England **Duchenne muscular dystrophy**	21	Retrospective Routine	Clinical case note review Hospital records	Age at first specialist (non-GP) medical contact Age at diagnosis	Mean age at diagnosis for those not picked up by a screening programme or under the age of 6 months was 4.5 years (range 1.9-6.8). Age at first specialist presentation) was 1.9 years (1.3-4.2 years).
Van Ruiten 2014 Improving the diagnosis of duchenne muscular dystrophy	England **Duchenne muscular dystrophy**	20	Retrospective De novo	Clinical case note review Single tertiary centre	1. Age of first symptoms 2. First engagement with a health professional Diagnosis	The total delay from parental concern to diagnosis was 19.2 (4–50) months. improvement in the age of diagnosis of DMD although there continues to be a delay in presentation to a health professional and a delay in obtaining a CK test.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Jog 2011 Causes for treatment delays in dystonia and hemifacial spasm: A Canadian survey	Canada **dystonia or hemifacial spasm**	866	Retrospective De novo	Patient/family questionnaire or structured interview	Age at onset of movement disorders Age at diagnosis of movement disorders	The mean lag time between symptom onset and diagnosis was 5.4 years. Most of these patients had consulted a family physician and, on average, more than three physicians in total before the diagnosis was made. Thus delays in diagnosis may not be due to a lack of availability of physicians, but rather, points to the diagnostic uncertainty of initial mild clinical findings, and the nonspecific and highly variable symptoms reported by patients. Patients living further than 50km away from a movement disorders clinic were more likely to wait for more than a year for diagnosis compared with those living less than 50km away.
Alhadad 2012 Erythromelalgia: Incidence and clinical experience in a single centre in Sweden	Sweden **Erythromyalgia**	27	Retrospective De novo	Clinical case note review Clinical database	Symptom onset Diagnosis	The mean delay from the onset of the symptoms to the time of diagnosis was 4.5 (SD ± 3.9) years.
Barba-Romero 2011 Fabry disease in Spain: description of Spanish patients and a comparison with other European countries using data from the Fabry Outcome Survey (FOS)	Spain **Fabry Disease**	92	Prospective Routine	Surveillance database	Age at symptom onset Age at diagnosis	Mean delay of 11 years to the diagnosis in adult patients of both genders (SD 12 for men, 13 for women). In under 18s - delay in the diagnosis of 1 year (SD 2) for boys, and 0.3 years (SD 0.58) for girls
Ramaswami 2006 Clinical manifestations of Fabry disease in children: Data from the Fabry Outcome Survey	11 european countries **Fabry Disease**	51	Retrospective Routine	Clinical case note review Surveillance database	Age at onset of symptoms Age at diagnosis	The mean delay between the onset of symptoms and diagnosis of Fabry disease was approximately 3 years.

Author-Yr Title	Country **Rare diseases(s)**	**Sample size**	**Prosp/retro** **Routine/de novo**	**DataColl method** **Sampling Frame**	**Starting point: TTD** **Ending point: TTD**	**Findings and key conclusions**
Mehta 2004 Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry Outcome Survey	11 european countries **Fabry Disease**	366	Retrospective Routine	Clinical case note review Surveillance database	Onset of symptoms Diagnosis	Mean delay from onset of symptoms to correct diagnosis was 13·7 and 16·3 years in males and females, respectively. For some patients there was a delay of > 50 years before correct diagnosis, and delays of > 20 years between onset of symptoms and diagnosis were common.
Andrikos 2010 Evolution of Fabry disease in male patients: the Greek experience	Greece **Fabry Disease**	16	Prospective De novo	Direct clinical examination/history Not specified	Age at onset of symptoms Age of diagnosis	Diagnosis was delayed for a mean of about 18 years.
Luigetti 2013 Ttr-related amyloid neuropathy: Clinical, electrophysiological and pathological findings in fifteen unrelated patients	Italy **Familial amyloid polyneuropathy**	15	Retrospective De novo	Clinical case note review	Symptom onset Diagnosis	Mean age at onset was 66.1 ± 4.8; mean age at diagnosis was 70.3 ± 5.2; mean interval between symptoms onset and diagnosis was 4 years (4.3 ± 2.4). The delay from symptom onset to final diagnosis could be partially explained by the difference between the phenotype that we observed and the classical “Portuguese” one.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Bailey Donald 2009 No change in the age of diagnosis for fragile X syndrome: Findings from a national parent survey	USA **Fragile X Syndrome**	249	Retrospective De novo	Patient/family questionnaire or structured interview	First concern by someone about the child, time that a professional first confirmed a developmental delay Confirmed diagnosis of Fragile X	On average, someone first became concerned at 11.6 months. A professional confirmed a delay 8 months later. Soon thereafter, children began early intervention. The diagnosis of FXS was confirmed 12 to 14 months later. The average length of time between first concern and diagnosis was 24 months. Children with more co-occurring conditions were given the diagnosis earlier (B=1.64; SE=0.76; P=.03) and had shorter delays between first concern and diagnosis (B=1.81; SE=0.73; P=.01).
Bailey Donald 2000 Family experiences and factors associated with the diagnosis of fragile X syndrome	USA **Fragile X Syndrome**	41	Retrospective De novo	Patient/family questionnaire or structured interview	Initial concern about development expressed by someone/diagnosis of developmental delay made Diagnosis of Fragile X made	The average family had developmental concerns at 9 months of age. Developmental delay was determined at 24 months on average and Fragile X was diagnosed at 35 months on average.
Centers for Disease 2002 Delayed diagnosis of fragile X syndrome - United States, 1990-1999	USA **Fragile X Syndrome**	15	Retrospective De novo	Patient/family questionnaire or structured interview Existing cohort/study sample	First concerns about the child's development or behaviour Diagnosis	Median age at the imte someone first became concerned about the child's development/ behaviour: 12 months (range 0-50 months). Age at diagnosis - median 26 months, range 6-101 months).

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Blankart 2012 Does healthcare infrastructure have an impact on delay in diagnosis and survival?	Germany **Gastric Cancer**	2175	Prospective Routine	Administrative database Administrative database	Onset of disease/ first symptoms Initial diagnosis	The likelihood of being diagnosed increased with an increase in general practitioners ($p < 0.0001$) and gastroenterologists ($p < 0.0001$) in rural areas. In urban areas a higher density of general practitioners reduced delay in diagnosis ($p = 0.0262$), while a higher density of gastroenterologists did not ($p = 0.2480$). Delay in diagnosis can be reduced by higher availability of general practitioners and gastroenterologists in rural areas. Given the already very high density of physicians in urban areas there is no effect of additional gastroenterologists.
Smith Nicholas 2012 GM2 gangliosidosis in a UK study of children with progressive neurodegeneration: 73 cases reviewed	UK **GM2 gangliosidosis**	73	Prospective Routine	Specialist questionnaire, Surveillance unit Surveillance database	Age at symptom manifestation, excluding those identified following diagnosis in a sibling Diagnosis	A delay of 6.8 months (range 1–25mo) and 7.8 months (range 2–12mo) from symptom onset to diagnosis was seen in infantile-onset TSD and Sandhoff disease respectively (overall average of 7.4mo). Time to diagnosis averaged 7.4 months and 28.0 months in infantileand juvenile-onset disease respectively.
Bygum 2009 Hereditary angio-oedema in Denmark: a nationwide survey	Denmark **Hereditary angio-oedema**	82	Retrospective De novo	Clinical case note review, Patient/family questionnaire Clinical database, Disease registry	Onset of symptoms Diagnosis	The mean duration from the onset of symptoms to the diagnosis of HAE was 16Æ3 years (range 0–63). The time from the first symptom to the diagnosis was 18Æ6 years (0–63) in the period 2001–2002 and 10Æ3 years (0–45) in the period 2007–2008. there was no significant difference in the diagnostic delay in index cases and relatives: 15.6 years (0–45) vs. 16.6 years (0–63) although the diagnosis in nine relatives was established before the onset of clinical symptoms).

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Best Kate 2012 Hirschsprung's disease in the North of England: prevalence, associated anomalies, and survival	England **Hirschsprung's Disease**	100	Prospective Routine	Surveillance unit Surveillance database	Birth Diagnosis	The median time of diagnosis was 5 days after birth, but ranged from birth until the age of 5 years.
Cruysberg 1996 Delay in diagnosis of homocystinuria: retrospective study of consecutive patients	Netherlands **Homocysteinuria**	34	Retrospective De novo	Clinical case note review Hospital records	First major sign of the disease Diagnosis	Mean delay of 11 (0-43) years between the first major signs of the disease (at mean age 13 (1-40) years) and the ultimate diagnosis of homocystinuria.
Glass 2006 A study on the nature of genetic metabolic practice at a major paediatric referral centre	Canada **Inborn errors of metabolism**	220	Retrospective De novo	Clinical case note review Hospital records	Presentation to metabolic specialist Date of presumptive diagnosis	Most patients seen by the metabolic service were not diagnosed with a metabolic disease. Of the 42 in whom a diagnosis of genetic metabolic disease was confirmed, 34 (81%) were diagnosed within one month of presenting to a metabolic specialist; in another five cases (12%), the diagnosis was established within 1–3 months and in one case (2%), it was established in 3–6 months. In two cases (5%), diagnosis was established over 6 months after presentation. When a diagnosiswas actually possible, it was generally made within one month of being seen by the genetic metabolic consultant. In those cases where testing did not reveal a diagnosis within 3 months, a diagnosis was rarely made.

Author-Yr Title	Country **Rare diseases(s)**	**Sample size**	**Prosp/retro** **Routine/de novo**	**DataColl method** **Sampling Frame**	**Starting point: TTD** **Ending point: TTD**	**Findings and key conclusions**
Napuri 2010 Factors associated with treatment lag in infantile spasms	France **Infantile Spasms**	156	Retrospective De novo	Clinical case note review, Patient/family questionnaire or structured interview Hospital records	Time of first symptom/Time of first presentation to health care Time of treatment	The median time lag from first symptom to first visit to a medical practitioner was 2 weeks (range 0–24wks; mean 3.7wks; SD 3.8wks). It was shorter for those who had previously exhibited normal development than for those with psychomotor delay (p=0.028). The time lag from first visit to diagnosis and initiation of treatment (median 2wks; mean 4.8wks, SD 7.3wks; range 0–36wks) was shorter for those presenting to paediatricians (3.7wks) than for those presenting to general practitioners (6.5wks; p=0.002). The total time lag from first symptom to diagnosis and initiation of treatment ranged from a few days to 44 weeks with a peak at 4 weeks (Fig. 2). The diagnosis was established within a month of the first symptoms in 78 infants (49%) and within the 2 months in 38 infants (34%).
Patwardhan 2012 Is juvenile dermatomyositis a different disease in children up to three years of age at onset than in children above three years at onset? A retrospective review of 23 years of a single center's experience	USA **Juvenile dermatomyositis**	78	Retrospective De novo	Clinical case note review Administrative database	Onset of symptoms Diagnosis	The mean times between onset of symptoms to diagnosis in the younger and older age groups was 5.6 months and 4.5 months, respectively, not a statistically significant difference.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
MacCormick Judith 2009 Misdiagnosis of long QT syndrome as epilepsy at first presentation	New Zealand **Long QT syndrome**	31	Retrospective De novo	Clinical case note review Disease registry	First presentation with loss of consciousness Diagnosis	Thirteen patients (39%) experienced diagnostic delay after presentation with syncope or seizure: median delay 2.4 years (2 months to 23 years). For those labeled epileptic, diagnostic delay was significantly longer than with other misdiagnoses: estimated median difference 9.75 years (95% confidence interval 7.6 to 20.7 years).
Oprescu 2013 Clinical predictors of mortality and cause of death in lymphangioleiomyomatosis: A population-based registry	USA **Lymphangioleio-myomatosis**	410	Prospective Routine	Registry Disease registry	First lung-related symptom Physician diagnosis	The median time between symptom onset and diagnosis was 2 years (IQR 0.33, 6).
Roll 2012 The influence of regional health care structures on delay in diagnosis of rare diseases: the case of Marfan Syndrome	Germany **Marfan Syndrome**	447	Prospective Routine	Administrative database Administrative database	Onset of disease Diagnosis	174 insurers (44.7%) experienced an immediate diagnosis (TtD = 0) of Marfan Syndrome and the remaining 215 insurers (55.3%) were diagnosed after a time period greater than 0 days, with an average time to diagnosis of 607 days, a median of 641 days, and a maximum of 1095 days. The quantity of physicians and the nearest available health care center do not play an important role in determining the probability of an immediate diagnosis for Marfan Syndrome.

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Oopik 2008 Clinical and laboratory-reconfirmed myasthenia gravis: a population-based study	Estonia **Myasthenia gravis**	70	Retrospective De novo	Patient/family questionnaire or structured interview Hospital records	Age at onset, age at referral to the doctor for specific myasthenic symptoms Age at original diagnosis	There was relatively more men (n = 12; 92%) than women (n = 36; 68%) whose diagnosis was established within 1 year from the time of referral to the physician (|z| = 2.49, P = 0.013). In all women with non-confirmed MG the diagnosis was established within 1 year from referral to the physician, whereas 68% of women with confirmed MG received the diagnosis within 1 year (|z| = 5.00, P < 0.0001). Relatively more women with nonconfirmed MG (n = 11; 92%) had an established diagnosis within 1 year after onset of symptoms than women with confirmed MG (n = 29; 55%) (|z| = 3.52, P < 0.0005). The opposite was true for men and the difference became significant at 18 months, at a time when the diagnosis was established in 11 men with confirmed MG (85%) compared to three (43%) with non-confirmed MG (|z| = 1.97, P = 0.049).
Hilbert 2013 Diagnostic odyssey of patients with myotonic dystrophy	USA **Myotonic dystrophy**	811	Retrospective De novo	Registry Disease registry	Time from onset of first symptom Diagnosis	Average age of onset of symptoms was significantly greater in DM2 members (34.0 ± 14.1 years) compared to DM1 members (26.1 ± 13.2 years; p<0.0001). DM members with initial symptoms reported before age 18 years had greater diagnostic delay (13.0 ± 11.3 years) compared to members with onset after age 18 years (delays of 6.9 ± 8.2 years; p<0.0001).

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Patterson Marc 2013 Disease and patient characteristics in NPC patients: findings from an international disease registry	14 European countries, Australia, Brazil and Canada **Niemann-Pick disease type C**	163	Prospective Routine	Clinical case note review, Direct clinical examination/ history, Registry	Neurological onset Diagnosis	In general there was a long lag time between the mean (SD) age at neurological onset (10.9 (9.8) years) and age at diagnosis (15.0 (12.2) years). Delayed diagnosis can have a considerable impact on quality of life for patients and/or their family and primary caregivers. In addition, it has been recommended that diseasespecific therapy with miglustat should be started as early as possible in the course of neurological disease in order to stabilise neurological function.
Stampfer 2013 Niemann-Pick disease type C clinical database: Cognitive and coordination deficits are early disease indicators	Switzerland, Germany **Niemann-Pick disease type C**	42	Prospective De novo	Clinical case note review, Patient/family questionnaire	First neurological symptom Diagnosis	Mean delay from first neurological symptom to diagnosis was 5.7 years.
Mykletun 2013 Porphyrias in Norway	Norway **Porphyria**	680	Prospective Routine	Registry Disease registry	Onset of disease Diagnosis	Median diagnostic delay was one year for porphyria cutanea tarda, 4y for acute intermittent porphyria and 17y for erythropoietic protoporphyria. 13% with AIP and 36% with EPP had a diagnositic delay >20 years.
Ghosh 2013 Primary myoclonus-dystonia: A diagnosis often missed in children	USA **Primary myoclonus-dystonia**	9	Retrospective De novo	Clinical case note review Hospital records	Age of onset of symptoms, age at presentation to clinic Age at time of diagnosis	There was a mean time lag of 4.5 years between the onset of symptoms and diagnosis. The delay in arriving at a definitive diagnosis (sometimes spanning more than a decade) resulted in patient and parental anxiety for prolonged periods, poor motor development, unnecessary investigations, use of inappropriate therapy with potential side effects, and increase in health care costs.

Author-Yr Title	Country **Rare diseases(s)**	**Sample size**	**Prosp/retro** **Routine/de novo**	**DataColl method** **Sampling Frame**	**Starting point: TTD** **Ending point: TTD**	**Findings and key conclusions**
Basura Gregory 2009 Clinical features and the management of pyridoxine-dependent and pyridoxineresponsive seizures: review of 63 North American cases submitted to a patient registry	USA, Canada **Pyridoxine dependent seizures**	63	Prospective Routine	Patient/family questionnaire or structured interview, Registry, Specialist questionnaire Disease registry	Age of presentation Age at initiation of pyridoxine therapy	A delay in diagnosis and pyridoxine treatment was not uncommon, with the lag in the diagnosis for the entire group averaging 311 days (range 0 days to 8.5 years). This delay was substantially reduced to 39 days (range 0 to 145 days) for the ten kindreds where an older registered child had been previously diagnosed with PDS..
Karageorgaki 2009 Takayasu arteritis: Epidemiological, clinical, and immunogenetic features in Greece	Greece **Takayasu arteritis**	42	Retrospective De novo	Clinical case note review Hospital records	Date of disease onset Date of diagnosis	Median delay in diagnosis was 24 months. Fatigue at the time of diagnosis was associated with increased risk for delay in diagnosis (odds ratio=11.7; 95% CI: 1.5–89.1, p=0.018).
Vanoli 2005 Takayasu's arteritis: A study of 104 Italian patients	Italy **Takayasu's arteritis**	104	Retrospective De novo	Specialist questionnaire Administrative database, Clinical database, Disease registry	Symptom onset Diagnosis	Median diagnostic delay was 15.5 months (range 0–325 months). With the logistic regression model, we were able to identify only 2 variables as predictors of diagnostic delay: age at onset <15 years, associated with a higher probability of a delay >=2 years (OR 3.9, 95% CI 1.2–12.8), and ESR at onset >30mm/ hour, associated with a lower probability of delay (OR 0.35, 95% CI 0.15–0.82).

Author-Yr Title	Country Rare diseases(s)	Sample size	Prosp/retro Routine/de novo	DataColl method Sampling Frame	Starting point: TTD Ending point: TTD	Findings and key conclusions
Heath 2011 Diagnosing variant Creutzfeldt - Jakob disease: A retrospective analysis of the first 150 cases in the UK	UK **Variant Creutzfeldt-Jakob Disease**	150	Prospective Routine	Surveillance unit Surveillance database	Age at onset, first point of medical contact, point of neurological referral, point of neurological review Diagnosis of definite or probable vCJD	Median time from onset to the first point of medical contact was 2.5 months (mean 3.4; range 0-12 months). The time to presentation to a medical practitioner was dependent on the nature of the early clinical features. Those presenting with neurological features (ie cases with isolated neurological symptoms or a combination of neurological and psychiatric symptoms) presented earlier to a medical practitioner in comparison with those with isolated psychiatric features (neurological onset, 2 months; psychiatric onset, 3.3 months; combined, 1.7 months; p=0.04). Mean time from onset to referral to a neurologist was 7.4 months (95% CI 6.5 to 8). Mean time from neurological referral to review was only 16 days. Mean time for vCJD to be considered the most likely diagnosis in life (or in 10 cases pathologically proven following cortical biopsy) was 10.5 months (95% CI 9.8 to 11.2 months). Significant interval between illness onset and presentation to a primary care physician, which is influenced by the nature of the initial clinical features. Neurological review is invariably sought following the development of clinical signs and a diagnosis is then established relatively quickly. Despite the progressive clinical course, a confident clinical diagnosis is not usually achieved until a relatively advanced stage of illness (mean time to diagnosis 10.5 months) with a more rapid clinical progression accounting.
Auvin 2012 Diagnosis delay in West syndrome: misdiagnosis and consequences	France, Italy, USA **West syndrome**	83	Retrospective De novo	Clinical case note review Clinical database	First symptoms Diagnosis of infantile spasms	Twenty-eight infants (34 %) were diagnosed more than 30 days after initial presentation. The median time from the beginning of spasms to the diagnosis of IS was 10 days (Q1–Q3, 4–32; Fig. 1). A diagnostic delay of more than 30 days was a risk factor for poor outcome (RR, 31.70 [2.30–437.68] on multivariable analysis)

Appendix 3 Review of rare disease databases

English label of the activity	Coverage	Affiliation	Included / excluded	Working website	Website with private area	Website providing information about data	Website providing detailed list of data	Time of onset of symptoms	Time of diagnosis
AOMIC: adult onset myositis immunogenetic collaboration	National	Public	Included	YES					
Batten Disease Neuronal Ceroid Lipofuscinosis (NCL) Patient Registry	National	Public	Included						
BINOCAR: British Isles network of congenital anomaly registries	National	Not defined	Included	YES	YES	YES			
BPOLD: British Paediatric Orphan Lung Disease Registry	National	Public	Included	YES		YES			
CARIS - Welsh registry of congenital anomalies - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
CAROBB - congenital anomalies registry for Oxfordshire, Berkshire & Buckinghamshire - part of the BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
CRANE: patients registry with cleft lip and/or cleft palate in England and Wales	National	Public	Excluded (obvious or screened for)						
DRN 377: Clinical Register for Transient Neonatal Diabetes	National	Public	Included	YES					
DYSCERNE's dysmorphology diagnostic system (DDS)	European	Public	Excluded (obvious or screened for)						
EBV associated NK/T cell malignancies registry	National	Public	Excluded (acute or cancer)						
ECARUCA: European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations	European	Public	Excluded (acute or cancer)						
ECFS: European Cystic Fibrosis Society patient registry	Global	Private non-for-profit	Excluded (obvious or screened for)						
EHDN: registry of juvenile Huntington's disease D	Global	Public	Included						
EHR: European Haemoglobinopathy Registry	European	Public	Included	YES		YES			

English label of the activity	Coverage	Affiliation	Included / excluded	Working website	Website with private area	Website providing information about data	Website providing detailed list of data	Time of onset of symptoms	Time of diagnosis
EMSYCAR - East Midlands & South Yorkshire congenital anomalies registry - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
English alpha-1 antitrypsin deficiency registry - contributes to the Alpha One International Registry (AIR)	National	Public	Included	YES					
English central hypoventilation syndrome registry - will contribute to the European CHS	National	Public	Included	YES	YES				
English cystic fibrosis database	National	Public	Excluded (obvious or screened for)						
English cystic fibrosis patient registry - contributes to the EUROCARE CF and ECFS registries	National	Public	Excluded (obvious or screened for)						
English cystinosis registry	National	Not defined	Included	YES	YES				
English hereditary angioedema patient registry - part of the HAE European registry	National	Public	Included						
English hyperoxaluria registry	National	Not defined	Included						
English juvenile dermatomyositis registry and repository	National	Public	Included						
English mucopolysaccharidosis registry	National	Not defined	Included						
English phenylketonuria registry	National	Public	Excluded (obvious or screened for)						
English registry for lymphangioleiomyomatosis	National	Public	Included						
English registry of biliary atresia - contributes to the EBAR registry	National	Public	Included						
English registry of syndromes with abnormal vertebral segmentation	National	Public	Included						
English registry of Wolf-Hirschhorn syndrome	National	Public	Included						

English label of the activity	Coverage	Affiliation	Included / excluded	Working website	Website with private area	Website providing information about data	Website providing detailed list of data	Time of onset of symptoms	Time of diagnosis
English severe chronic neutropenia registry - contributes to the SCN international registry (SCNIR)	National	Public	Included	YES		YES	YES	YES	YES
EUMDS: European Registry for Myelodysplastic Syndromes - part of EuroLeukemiaNet (ELN)	European	Public	Included	YES		YES	YES		YES
EUROCARE CF: European cystic fibrosis registry (FINISHED)	Global	Public	Excluded (obvious or screened for)						
EUROmediCAT: Safety of Medication use in Pregnancy in Relation to Risk of Congenital Malformations	European	Not defined	Excluded (obvious or screened for)						
EUROPAC: the European registry of hereditary pancreatitis and familial pancreatic cancer	European	Public	Included	YES	YES	YES			
European Prader-Willi syndrome database	European	Public	Included						
EURO-WABB: An EU Rare Diseases Registry for Wolfram syndrome, Alström syndrome, Bardet-Biedl syndrome and other rare diabetes syndromes	European	Public	Included	YES		YES	YES	YES	YES
EUROWILSON: European network on Wilson disease (registries)	European	Not defined	Included	YES					
Familial Ovarian Cancer Register (FOCR)	National	Public	Excluded (acute or cancer)						
Glasgow registry of congenital anomalies - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
Global FKRP (Fukutin-Related Protein) defects registry - part of TREAT-NMD Alliance	Global	Public	Included	YES	YES	YES			
Great Ormond Street Hospital Congenital Melanocytic Naevus Registry	National	Public	Excluded (obvious or screened for)						
Hunter Outcome Survey (HOS): patient registry	Global	Public	Included						

English label of the activity	Coverage	Affiliation	Included / excluded	Working website	Website with private area	Website providing information about data	Website providing detailed list of data	Time of onset of symptoms	Time of diagnosis
I-DSD: Disorders of sexual development registry	Global	Public	Included	YES		YES	YES		
LCH: English Langerhans cell histiocytosis registry	National	Public	Included						
Merseyside and Cheshire registry of congenital anomalies -part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
Myotonic dystrophy patient registry in United Kingdom - part of the TREAT-NMD network	National	Public	Included	YES		YES	YES		YES
National Congenital Anomaly System (NCAS) - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
NDSCR - National Down syndrome cytogenetic registry - part of BINOCAR and EUROCAT network	National	Public	Excluded (regional)						
NHD: the national haemophilia database	National	Not defined	Included	YES		YES	YES	YES	YES
NHR: National Haemoglobinopathy Registry	National	Public	Included	YES		YES	YES		YES
NorCAS - Northern registry of congenital anomalies - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
Regional spinocerebellar ataxia registry	Regional	Public	Excluded (regional)						
SWCAR - South West congenital anomalies registry - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (regional)						
The Alström syndrome UK (ASUK) Clinical Research Database	National	Public	Included	YES					
The MTM and CNM Registry - The Myotubular and Centronuclear Myopathy Patient Registry	National	Public	Included	YES	YES	YES			
The National Chronic Granulomatous Disease Registry	National	Public	Included	YES					
The regional paediatric cardiology database	Regional	Public	Excluded (regional)						
TREAT-NMD: Accelerating Treatments for Neuromuscular Diseases (registries)	Global	Public	Included	YES					
UK & Ireland Fanconi Anaemia Registry	National	Public	Included	YES					

English label of the activity	Coverage	Affiliation	Included / excluded	Working website	Website with private area	Website providing information about data	Website providing detailed list of data	Time of onset of symptoms	Time of diagnosis
UK and Ireland Duchenne and Becker muscular dystrophy patient registry (part of the TREAT-NMD network)	National	Not defined	Included	YES	YES	YES			
UK and Ireland Spinal muscular atrophy (SMA) patient registry (part of the TREAT-NMD network)	National	Public	Included	YES		YES	YES		
UK Dyskeratosis Congenita (DC) registry	National	Public	Included						
UK Huntington disease registry (collaborating with the EHDN/Euro HD Registry)	National	Public	Included	YES	YES				
UK Neurofibromatosis 2 (NF2) Patient Registry	National	Public	Included						
UK Paediatric ITP (Immune Thrombocytopenic Purpura) Registry	National	Public	Included	YES	YES	YES			
UK renal rare disease registry	National	Private for-profit	Included	YES	YES	YES			
UK Thrombotic Thrombocytopenia Purpura (UKTTP) Registry	National	Public	Included	YES		YES	YES	YES	YES
UKAITPR: United Kingdom adult idiopathic thrombocytopenic purpura registry	National	Public	Included	YES		YES	YES	YES	YES
UKCCCR: English familial ovarian cancer patient registry	National	Not defined	Excluded (acute or cancer)						
UKESR: United Kingdom Evans Syndrome Registry	National	Public	Included	YES		YES	YES	YES	
UKFITPR: United Kingdom familial idiopathic thrombocytopenic purpura (ITP) Registry	National	Public	Included	YES		YES	YES		
United Kingdom neuromyelitis optica registry	National	Public	Included						
WANDA - Wessex registry of antenatally detected anomalies - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (Regional)						
West Midlands registry of congenital anomalies - part of BINOCAR and EUROCAT network	Regional	Public	Excluded (Regional)						

Appendix 4 Interview participants

Name	Position	Organisation
Robin Lachmann	Consultant in Metabolic Medicine	Univeristy College London Hospital
Hywel Williams	Senior Research Associate, Centre for Translational Research, Genetics and Genomic Medicine	Institute of Child Health, London
Jim Bonham	Clinical Director of Diagnostics, Pharmacy & Genetics	Sheffield Children's NHS Foundation Trust
Fiona Stewart	Consultant in Genetic Medicine	Belfast City Hospital
Liam Smeeth	Professor of Clinical Epidemiology/ General Practitioner	London School of Hygiene and Tropical Medicine
Mark Bale Colin Pavelin Melanie Peffer	Deputy Director of Health Science & Bioethics Head of Genomics and Rare Diseases Programme Policy Manager Genomics, Science and Emerging Technologies	Department of Health Health Education England Department of Health
Iain Mellis	Accountable commissioner – Metabolic Diseases	NHS England
Edmund Jessop	Specialist Commissioner	NHS England
Jacquie Westwood Jane Deller	Director Programme Manager	UK Genetic Testing Network
Lara Bloom	Chief Operations Officer	Ehlers-Danlos Syndrome UK
Tess Harris	Chief Executive	Polycystic Kidney Disease Charity
Jayne Spink	Chief Executive Officer	Tuberous Sclerosis Association
Graham Lipkin	Consultant Nephrologist/Lead at Rare Diseases Centre	Institute for Translational Medicine, Queen Elizabeth Hospital Birmingham
David Goldblatt	Director of Clinical Research and Innovation, Academic Lead for future Centre for Rare Diseases	Institute of Child Health, London
Sarah Stevens	Public Health Consultant National Disease Registration	Public Health England
Dirk Demuth Paola Nasuti Lara Lucchese	Clinical Project Director Senior Consultant Senior Consultant	IMS Health
Willie Hamilton	Professor of Primary Care Diagnostics	University of Exeter Medical School

Appendix 5
Interview topic guide

Adapted to suit each interviewee and in response to themes emerging from previous interviews.

Start of interview: Thanks, consent, introduction and presentation of study aim

Topic questions (to be adapted to the particular interviewee and in response to the flow of discussion during the interview):

- What is your day to day interaction/experience with people with rare diseases?
- What for you are the key issues around diagnostic odysseys/delayed diagnosis in rare diseases?
- What are the key causes/contributors to these delays?
- When do you consider to be the start of a diagnostic odyssey?
- When do you consider a diagnostic odyssey to have ended?
- What would be the best way of capturing data on time to diagnosis in rare diseases? Do you know of any existing data?
- What rare diseases would it be reasonable to generalise across in terms of changes to time to diagnosis? Are there any particular categories of rare disease that we should consider?
- Given the impossibility of analysing all 6000 rare diseases, we have considered selecting a small number of tracer conditions to focus on. Are there any conditions that you feel would be particularly important to include or exclude? What criteria would be sensible to use to select tracer conditions?
- How meaningful would it be to collect data on all patients with rare diseases that are admitted/seen at/tested at a particular facility that commonly manages people with rare diseases?

End of interview: is there anything else you think I should know about diagnostic odysseys in rare diseases? Thank you for your time and insights.

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Appendix 7 Presenting symptoms for rare diseases previously used to measure time to diagnosis

Disease	Presenting symptoms indicative of start of diagnostic odyssey
Alpha1-antitrypsin deficiency[1]	Age at onset of respiratory complaints: Mostly dyspnoea and non-productive cough, also cough with sputum, dyspnoea at rest and paroxysmal dyspnoea.
Batten Disease/neuronal ceroid lipofuscinosis[2]	Motor deterioration, visual deterioration, first seizure noted
Bronchiectasis[3]	Age at onset of cough
Cerebrotendinous xanthomatosis[4]	Age at first neurological symptom/presenting symptom: Symptoms found at presentation generally neurological (mental retardation most common), also a history of chronic diarrhoea or juvenile cataracts
Congenital Dyserythropoietic Anemia Type[5]	Onset of anaemia
Congenital Hypothyroidism[6]	Most frequent symptoms found were obstructive constipation, lethargy and feeding difficulties
Duchenne muscular dystrophy[7]	First parental concerns: most common symptoms waddling gait, difficulty with steps, falls, delayed motor development, speech delay
Dystonia or hemifacial spasm[8]	Age at onset of movement disorders
Fabry disease[9, 10]	Ramaswami et al (2006): Clinical manifestions categorised into neurological, gastrointestinal, ophthalmological, auditory, dermatological and 'various' Andrikos et al (2010): presenting symptoms included Angiokeratomas, Abdominal pain-Diarrhea, Hypohidrosis, Lymphedema, Pain crises, Acroparesthesias, Hypohidrosis, Hearing loss, Cold-Heat Intolerance, Arthritis, Lymphedema
Fragile X[11]	Initial concern about development expressed by someone/diagnosis of developmental delay made: ascertained during interview by asking ‘How did you first learn about fragile X syndrome?’
Gastric Cancer[12]	Named codes for gastric cancer-related symptoms: benign neoplasm of other and ill-defined parts of digestive system (stomach); neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs (stomach); oesophagitis; special screening
GM2 gangliosidosis[13]	Symptoms cited included developmental delay or regression, strabismus or perceived visual impairment and hyperacusis
Haemophilia[14]	Attendance to a doctor with bleeding, bruising or joint pain
Lymphangioleiomyomatosis[15]	First lung-related symptom: included dyspnoea, cough, pneumothorax, pleural effusions.
Marfan Syndrome[16]	Named symptom codes: constitutional tall stature, other disorders of lens, astigmatism, floppy mitral valve syndrome, non-rheumatic aortic valve disorders, endocarditis
Myotonic dystrophy[17]	6 symptoms based on 'core manifestations' of MD and 'high impact on quality of life': mytonia, weakness, cataracts, pain, fatigue, sleep disturbances
Niemann-Pick type C[18]	First neurological symptom: questionnaire with 270 questions on medical history
Primary myoclonus-dystonia[19]	myoclonus or dystonia
Takayasu arteritis[20]	Onset of first symptom, categorised as: vascular, cardiac, CNS, Musculoskeletal, Constitutional and Laboratory.
West syndrome[21]	Beginning of spasms. Identification on structural lesions of the brain or a genetic disorder was considered a ‘symptom’.

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