

Proposed framework on a networked service model for care of adults with rare bone conditions in England

A Kyowa Kirin initiative in collaboration with an expert steering committee of rare metabolic bone experts and representatives of people living with rare bone conditions.



This framework was developed by a steering committee of healthcare professionals and patient group experts specialising in rare bone conditions, set up following a meeting organised and funded by Kyowa Kirin. Participants received an honorarium to attend the initial meeting for their expert insights and advice. Kyowa Kirin fully funded and led on the development of this Proposed Framework, in collaboration with the steering committee and a wider group of experts, along with writing support from Evoke Incisive Health. The steering committee had final editorial control and received no payment for their contribution to the development and review of the Proposed Framework, except honorarium for the initial meeting mentioned above.

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Introduction

Over the last few years, significant progress has been made in the arena of rare bone conditions. Nonetheless, like many rare diseases, people living with rare bone conditions experience multiple challenges when accessing care, including difficulty in receiving the correct diagnosis, a lack of understanding among non-specialist clinicians and society, and a sub-optimal approach to disease management due to a healthcare infrastructure that doesn't always meet the needs of those living with these conditions and their loved ones.

Furthermore, although paediatric services have tended to be well-organised for children living with rare bone conditions, the quality of support available to adults is more variable and reactive, and less proactive and effective. As therapeutic innovations advance, there is growing interest at both the national policy level and the clinical and patient group communities to design solutions which deliver highly specialised, flexible, multidisciplinary care for adults with rare bone conditions.

This interest has been further supported by the UK Rare Diseases Framework, and the subsequent England Rare Diseases Action Plan 2022, which address some of the key issues facing people with rare bone conditions, including helping individuals get a final diagnosis faster, increasing awareness of rare diseases among healthcare professionals, achieving better coordination of care and improving access to specialist care.^{1,2}

With the aim to identify the specific care challenges affecting people living with rare bone conditions, including X-linked hypophosphataemia (XLH), and potential system solutions, Kyowa Kirin Ltd (Kyowa Kirin) brought together a group of clinicians and patient organisation representatives specialising in rare bone conditions in early 2021 to discuss ways of improving care for adults with rare bone conditions. Participants received honorarium to attend this initial meeting and to provide their expert insights and advice.

Following this initial discussion, a smaller steering committee was convened to develop this *Framework* on how a networked service model of care could improve the experience of adults living with rare bone conditions in England. This *Framework* outlines the challenges faced, and provides potential system solutions that set out how care could be improved and who should be involved in delivering it, to ultimately enable access to high quality care and support for all individuals living with these conditions.

The development of this *Framework* was led and fully funded by Kyowa Kirin with writing support from Evoke Incisive Health, a healthcare policy and communications consultancy who provides integrated support across a range of audiences including policymakers, healthcare providers and patients. Nonetheless, the steering committee had full editorial control of its content, and received no payment for their contribution to the development and review of the *Proposed Framework*, except honorarium for the initial meeting mentioned above.

What are rare bone conditions?

Rare bone conditions are described in literature as being rare, chronic, genetic conditions that affect bones, cartilages, and teeth of their carriers.³ These conditions comprise around 5% of all rare diseases, affecting millions of patients worldwide.⁴ This group of diseases varies in their symptoms, onset, and severity, and can include as many as 461 different diseases.^{3,5} However, the principles of diagnosis, management and follow-up frequently overlap, allowing for greater coherence and consistency for categorising as follows:

- 1 Rare primary bone fragility conditions**, which include Osteogenesis imperfecta (OI), Multiple osteochondromas (MO), Hajdu-Cheney, pregnancy and lactation associated osteoporosis, and undiagnosed severe primary fragility disorders after specialist multidisciplinary care
- 2 Rare bone mineral and vitamin D disorders**, including X-linked hypophosphataemia (XLH), Tumour-induced Osteomalacia (TIO), Vitamin D-dependent rickets (VDDR), tumoral calcinosis, and Hypophosphatasia (HPP)
- 3 Rare skeletal dysplasias**, including Achondroplasia (ACH), Pseudoachondroplasia, Multiple Epiphyseal Dysplasia (MED), and Cleidocranial Dysplasia (CCD)
- 4 Rare high bone mass and sclerosing conditions**, such as osteopetrosis, pycnodysostosis, melorheostosis and Juvenile Paget's
- 5 Rare ectopic bone formation disorders**, including Fibrous dysplasia/McCune-Albright syndrome (FD/MAS), Fibrodysplasia Ossificans Progressiva (FOP), Hereditary Multiple Exostoses (HME) and Ollier disease
- 6 Vascular Bone Disorders**, including Gorham-Stout disease (GSD) and systemic generalised lymphangiomatosis with bone disease
- 7 Miscellaneous rare bone disorders associated with periostitis**, for example, Hypertrophic osteoarthropathy also called pachydermoperiostosis, and Caffey disease

A detailed description of the most common rare bone conditions, as outlined by the European Reference Network on Rare Bone Diseases, can be found in [Appendix 1](#).⁶

What is the prevalence of these conditions?

Prevalence is defined by the Centre for Disease Control as the proportion of a population who is affected by a specific characteristic or condition in a given period.⁷

Even though one would expect this to be calculated to a very accurate value, for rare conditions such as rare bone diseases, prevalence can be quite difficult to determine. This occurs because some of these conditions are difficult to diagnose and, in some cases, clinicians are unfamiliar with the condition, leading to many cases going undetected.⁸

Nonetheless, it is estimated that the prevalence for these conditions varies between less than 1/100,000 and 50/100,000, with some conditions such as XLH having an estimated prevalence of between 15 in 1,000,000 people and others, such as FD/MAS, having an estimated prevalence of 50 in 100,000.^{9,10,11,12,13,14,15,16,17}

Due to this very low prevalence amongst the general population these conditions can be categorised as rare or, in some cases, such as PHP and HPP, ultra-rare diseases.

Detailed prevalence for the most common rare bone conditions, as outlined by the European Reference Network on Rare Bone Diseases, can be found in **Appendix 2**.⁶

What do the current services look like?

As described by the European Reference Network on Rare Bone Diseases, these conditions tend to share a common care pathway, which we have described below.⁵ Nonetheless it should be noted that care differs from individual to individual, depending on their condition, symptoms, and circumstances.

› Entrance into the system

Some people with rare bone conditions enter the system as infants, with diagnosis sometimes occurring as early as before birth, as can be the case with ACH and OI.^{18,19} However, for other conditions, such as XLH, even though diagnosis occurs in childhood it is frequently delayed due to the rarity of the condition and the diversity of its clinical manifestations, especially in spontaneous cases which account for 20-30% of overall XLH cases.^{20,21} The same can happen with PHP and HPP, with some people living with HPP facing a diagnostic delay of over 10 years.^{22,23} For people with MO, the average age of diagnosis is three years old; however, some individuals only receive a diagnosis at 12 years old.¹⁴

Diagnosis can be further delayed, as it often relies on the suspicion of a particular condition and the correct referral to a specialist site. Due to the lack of knowledge around rare conditions, patients can be referred to the incorrect specialist unit or to a site which lacks expertise on the condition, therefore leading to a longer diagnostic process and a delay in access to the appropriate care.¹

Methods utilised

When it comes to the diagnostic methods utilised, these can also vary between conditions. Most individuals present with some sort of physical bone deformity which can be identified through radiological findings or through blood tests.

However, genetic testing tends to be required to provide a final diagnosis. For example, when there is no established family history of XLH, an analysis of the PHEX gene is performed to confirm the diagnosis.^{16,24,25} Genetic testing is also available for individuals with OI and carrier testing is available for relatives of affected individuals, when the causative gene in the OI patient has been identified.¹⁹

Transiliac bone biopsy may also be required in the diagnosis of conditions such as idiopathic juvenile osteoporosis and Juvenile Paget's disease.^{26,27}

Other conditions, such as HPP, require an analysis of the levels of an enzyme which when existing in low levels can indicate the presence of the condition.²⁸

Diagnosis may also depend on a careful review of an individual's family and medical history,^{8,19} as is recommended for any first-generation family member of a person living with XLH or with OI.^{19,20}

Clinicians involved

Given the rarity of these conditions and their symptoms, it is also recommended that, where possible, diagnostic results are reviewed by specialists in the field, such as rheumatologists, endocrinologists, radiologists, and pathologists with experience in managing rare bone conditions.²⁵

In some cases, children may present to paediatric dental services first if they experience premature exfoliation, spontaneous abscessed, or delayed eruption.²⁹ They may then be referred to a specialist for an official diagnosis to be conducted, if the dental health specialist recognises the symptoms presented as abnormal.

› Paediatric care

Paediatric care for rare bone conditions varies depending on the condition being addressed and its severity.

Disease management

Treatments are available for some children, such as those with infant onset of HPP, MO and XLH.^{13,20,30,31,32} However, for most children with a rare bone condition the focus is predominantly on managing the symptoms, for example, through:^{13,33,34,35}

- Surgery to address fractures that don't heal or to remove bone and cartilage deformities
- Management of dietary calcium and vitamin D
- Physiotherapy and occupational therapy
- Chronic pain management
- Regular dental reviews
- Mental health support
- Control of obesity and overweight

Clinicians involved

This disease management tends to be led by a multidisciplinary specialist team, with additional support from other healthcare professionals, as necessary. However, for some rare disorders there is a lack of peer-reviewed management guidelines, which could lead to inappropriate care being provided to children.³⁶

Children with XLH, for example, are seen on a regular basis by a multidisciplinary team at a specialist centre, organised and led by an expert in metabolic bone diseases, which is usually a paediatric endocrinologist. The care is tailored to each child's circumstances and clinical manifestation. The clinical lead is also responsible for liaising with the local care team, including GPs and paediatricians, radiologists, orthopaedic surgeons, physical therapists, rheumatologists, and dentists.^{20,37}

Likewise, the management of children with ACH is led by a paediatrician, orthopaedic surgeon, and neurosurgeon, depending on the severity of the condition. Children with ACH also have access to a paediatric otolaryngologist or a speech therapist if they suffer from hearing impairments.^{38,39}

The care for individuals with infantile-onset HPP is also led by a paediatrician. Individuals are followed at a specialist centre, where besides having access to a range of specialist clinicians, they also have access to a treatment that has shown significant improvements in growth, respiratory function, and motor development.⁴⁰

A similar situation occurs with OI with children having regular follow-ups with specialised clinicians and having access to several specialist centres across the country.^{41,42}

Although paediatric dentists are not always part of a child's care team, they should be part of the multidisciplinary team for all children with rare bone diseases to monitor the impact of their condition on their dental health.

For other conditions, such as MO, individuals may receive yearly follow-up by a paediatrician or be counselled to wait until puberty before a corrective surgical intervention is performed, depending on the condition's severity.³²

Overview of current paediatric care pathway

The below figure provides an overview of the current paediatric care pathway for rare bone conditions, inferred from the information collated through desk research and feedback provided by expert clinicians, patient groups and people living with rare bone diseases. As noted above, some conditions do not go through all the steps of the pathway:

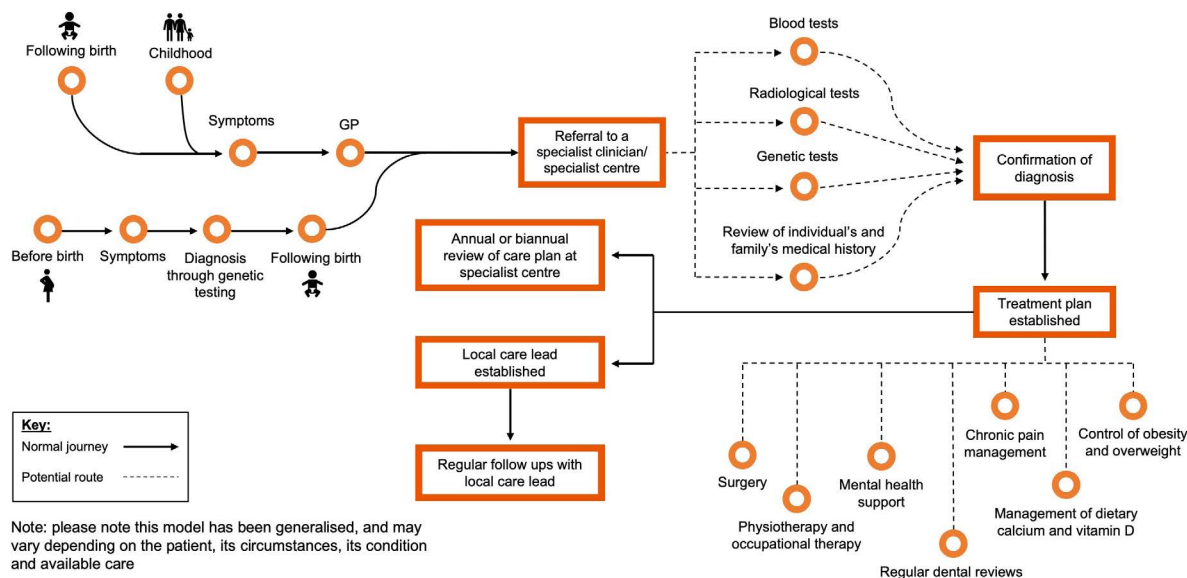


Figure 1. Current paediatric care model for rare bone conditions.

> Adult care

Research shows that 70% of rare diseases, which were seen as childhood conditions, have since become diseases recognised as being present in adults.⁴³ The same happens for most people living with rare bone conditions, who, due to the debilitating and chronic nature of their conditions require ongoing care throughout their lives. As such, they end up having to be moved into adult services for most of their patient journey. XLH is an example of a condition that requires constant management, with the morbidity associated with this condition increasing as individuals get older, due to people experiencing a reduction in mobility, joint stiffness, fatigue, muscle weakness and severe musculoskeletal pain.^{16,44,45}

Clinicians involved

Whilst most children have access to multidisciplinary care at several locations throughout the country, care for adults tends to not follow the same pattern with varied access to specialist and multidisciplinary teams. For example, whilst adults living with HPP do have access to specialist centres,^{22,42} conditions such as OI only have access to some 'hub and spoke' arrangements for multidisciplinary care across multiple providers.

These arrangements are inconsistent across England, despite the fact that many of those under the care of a specialist centre also require support from services which are closer to their home.^{46,58}

Unfortunately, it is difficult to measure and assure the quality of care provided in specialist centres due to a lack of agreed patient pathways for these conditions.

Furthermore, people living with rare bone conditions also face a lack of equity in care with some care centres having services led by endocrinologists and some by rheumatologists, depending on the speciality that has taken an interest in the condition. This can lead to the condition being cared for differently, across the country.

Overview of current adult care pathway

The below figure provides an overview of the current adult care pathway for rare bone conditions, inferred from the information collated through desk research and feedback provided by expert clinicians, patient groups and people living with rare bone diseases. It should be noted that this pathway may differ from patient to patient and between conditions, with variations existing across England, which can lead to health inequalities.

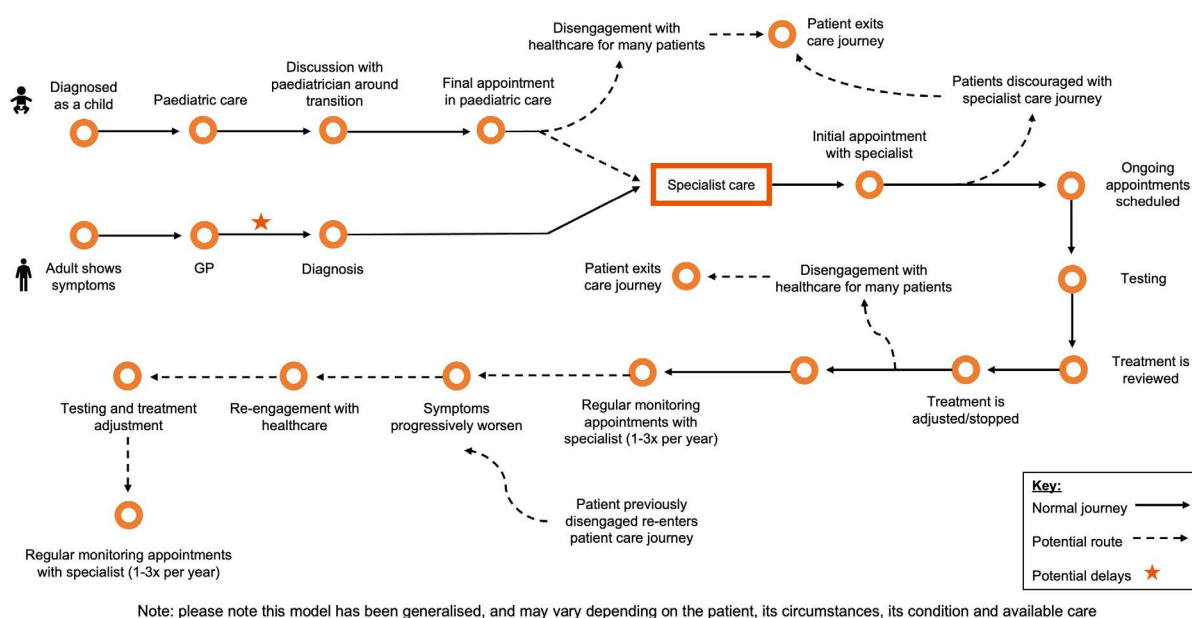


Figure 2. Current adult care model for rare bone conditions.

Transition between paediatric and adult care

Transition between paediatric and adult care is defined as “the purposeful and planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult orientated healthcare systems”.⁴⁷ This process is key to ensure patients and their families are prepared to have their care transferred and should take place between the ages of 14 and 18.^{44,48,49}

However, many people with rare bone conditions do not go through an appropriate transition and instead experience an uncoordinated transfer of care. For example, in a survey conducted by Rare Disease UK (the national alliance for people with rare diseases and all who support them), 16% of respondents that had transitioned from the paediatric to adult services experienced problems in transition.^{50,51}

Among other things, lack of coordination between paediatric and adult services, as well as between clinical and social care teams contribute to making the transition experience challenging. This can lead to a loss in continuity of care during transition.⁵⁰

Insufficient transparency and communication between clinicians and their patients can also be a cause for concern. According to a recent report by Beacon for Rare Diseases (UK based charity that is building a united rare diseases community with patient groups at its heart), several individuals living with rare diseases as well as their parents reported a lack of engagement and information of what to expect of their transition of care, including no information on what would change and who would be involved in leading their care. As the transition process can be extremely stressful for patients and their families, it is key that they are informed of what changes in care to expect and when these should happen.⁵⁰

People with rare conditions also reported a lack of early conversations to prepare them and their families for transition. Most noted that their transition was rushed or simply happened, without notice, when they were considered eligible for adult care.⁵⁰

In some occasions, a referral letter was used to move people living with rare bone diseases between paediatric and adult care.⁵² This can be insufficient and lead to poorer care, as individuals may have to wait longer to get an appointment with their new clinical care lead, and, in some cases, may even fall through the cracks of the healthcare system entirely.

People living with rare bone conditions face multiple mental and emotional difficulties which can be exacerbated during the transition period. Patients can feel isolated and not able to deal with the change in care.⁵² However, individuals living with rare diseases have reported that their mental health needs are often neglected, with clinicians focusing solely on their physical needs.⁵⁰

In some cases, transition is further complicated as it often comes just before or near the same time a young person is looking to leave home, whether for work, university, or travel. This makes it more difficult for individuals to stay in touch with their care team and to ensure support is in place as needed. It is also a time at which they transition into taking responsibility for their own care and being treated as an adult, despite many times having the understanding of the care pathway of a child.⁵²

› Management of pregnant women with rare bone disorders

Pregnant women who live with rare bone conditions can experience additional pain throughout pregnancy due to wound healing, bone loss, hypertension or acquired heart defects.^{53,54,55,56} Due to the impact of rare bone conditions, patients should receive close surveillance by healthcare professionals, beginning at preconception, however this is not always the case.

What is working well?

As stated above, paediatric services tend to be well organised for most conditions, with children having access to a care lead, specialised centres and a multidisciplinary team, when needed.

Additionally, groups such as the British Paediatric and Adolescent Bone Group (BPABG) organize bi-annual meetings where they peer review the development of treatment guidelines for rare bone disorders.⁵⁷

Furthermore, some adults living with rare bone conditions do have access to specialised clinicians who provide them with ongoing care. For example, an OI multidisciplinary clinic, which includes access to a specialist nurse and a physiotherapist, was set up at the Royal National Orthopaedic Hospital and a local rare bone radiology multidisciplinary team was also created with input from

a specialist radiologist.⁵⁸ However, even though these services are available, these were set up due to the commitment of local clinicians to provide the best care to their patients, despite facing lack of provision for implementing and running the services.

What are the system challenges?

People living with rare conditions face countless system challenges compared to those living with common chronic conditions.⁵⁹

› Delay in, or incorrect, diagnosis

These challenges include the time it takes to get a correct diagnosis, which for rare diseases, on average, can take up to four years.⁶⁰ During this time, people living with rare conditions have reported being seen by up to eight clinicians and receiving two to three misdiagnoses.⁶¹

For some conditions, including rare bone diseases, this agonising period of time can be even longer. For example, owing to the rarity of XLH and the diversity of clinical presentation, diagnosis may be delayed, particularly in people with de novo variants resulting in mild disease,^{20,62,63,64} as illustrated by the experience of a woman living with XLH who was misdiagnosed with dwarfism as a child and only diagnosed with XLH in her mid-teens.⁶⁵ As a result, she was unable to access specialist services as a child.⁶⁵

Delays and misdiagnosis can frequently be attributed to a general lack of understanding of rare bone diseases within the clinical community.^{60,66,72} For example, the parent of a child with HPP reported that when their son started to exhibit symptoms, the clinicians following the case couldn't diagnose the condition and prepared them for palliative care. It was only after one consultant did extensive research that they were able to identify a drug trial for the condition.⁶⁷ Similarly, patient group leaders from eleven European countries rated awareness amongst clinicians as a top unmet need for adults living with XLH.⁴⁴

› Lack of understanding of the condition

Challengingly, even when an individual receives a correct diagnosis, they may not be referred to a specialist centre of care. In a report that looked at the burden of care on adults with XLH, several patient groups highlighted that referral to adult services was one of the biggest challenges people with XLH face.⁴⁴ For example, people living with XLH have frequent dental issues resulting from poor mineralisation of teeth and gum disease. If these individuals don't have access to a specialised dentist who is aware of how to treat these issues, they may suffer a high rate of tooth loss.⁴⁴ In some situations, this is due to insufficient understanding at the local level of the complex needs people with rare bone conditions have and the support they require.⁷⁸ Alternatively, it may be due to a lack of awareness of specialist centres and the process of referral.

The lack of understanding within the clinical community can also lead to inappropriate medical interventions. For example, giving local anaesthetic injections prior to dental prescription for people with FOP can lead to 'locked jaw' and malnutrition.⁶⁸

Often it also means people living with a rare condition and their carers are not provided with the personalised information and educational materials they need.⁶⁹ A recent survey by Rare Disease UK found that nearly half (49%) of respondents didn't feel they were given enough information about their condition and the care they needed, post-diagnosis.⁷⁰ This can lead to patient's not knowing the care they should receive and not advocating for it.

› Lack of care coordination

Another central challenge facing individuals with rare bone diseases, is care coordination. Lack of access to a care coordinator is sometimes due to insufficient funding being allocated to setting up specialist centres and care coordinators.

According to the CONCORD study, in the UK only 12% of people living with a rare condition and 14% of parents or carers have access to a formal care coordinator.⁷¹ In the same study, only 10% of people with a rare condition reported having a care plan related to their rare condition. This means that in addition to the chronic burden of their condition, most individuals with a rare disease need to manage their own care. This includes having to call providers and services to arrange for their care and ensuring different healthcare professionals have access to relevant information regarding their condition and treatment plan.⁶⁰ Individuals may also need to attend numerous appointments at different clinics and hospitals, all of which have to be coordinated by themselves.

Without care coordinators, managing a rare bone disease can be a full-time job. As illustrated by a recent study on the burden of XLH in adults, this in turn can lead to people leaving their employment and facing social and economic challenges.^{60,72} Indeed, unemployment and early retirement have been shown to be more frequent amongst adults with this condition than in the general population.⁴⁴

These challenges can be further exacerbated if these individuals are not provided with access to, and awareness of, their disability rights and social benefits, as highlighted by several XLH patient group leaders.⁴⁴

The lack of access to the appropriate care close to home can also lead to families uprooting themselves, as exemplified by the story of a parent of a child with HPP, who had to move to another city to ensure their son had access to a specialist centre where the care he needed was provided.⁶⁷

All together, these issues can have a heavy emotional and physical charge on one's wellbeing, which only deepens the already difficult circumstances individuals with rare bone conditions live with.

› Lack of research opportunities

Rare conditions, including rare bone conditions, also face several challenges in research and clinical trials due to the size of the population affected by each condition.

For efficacy to be analysed in a clinical trial, the trial usually needs to be randomized and controlled, however this requires time, funding, and large patient population sample sizes, which can all be less attainable in rare conditions.⁷³

Furthermore, using control groups helps strengthen the trial, however ethical concerns may arise in placebo-controlled trials, especially in rare diseases where patients may have shortened lifespan.⁷⁴ Parents may also be reluctant to enrol their child in a trial where they may not receive the therapy being reviewed but a placebo instead.⁷³

Additionally, the small patient population sizes and their geographic dispersion also hinder the timely and adequate recruitment of eligible patients.⁷³ Traveling to research centres, may pose a further barrier to research, especially when patients live with significant physical impairments.⁷³

These challenges ultimately lead to a lack of research opportunities, lack of access to data sets and reliable epidemiological data. This can impair the knowledge and information available to patients and clinicians, including on potential models of care.

Future of care for rare bone conditions

Who and what should be involved in the care moving forward?

As outlined above, rare bone conditions present several challenges for the clinical community around providing the appropriate care, including a great variety in clinical presentation and different levels of severity the diseases present amongst those affected. Furthermore, due to their rarity, clinicians are sometimes unable to correctly diagnose these conditions leading to severe delays in diagnosis and access to care.

According to several studies, improvements in care for people with rare conditions should include:^{28,32,44,60,75,76,77}

- detailed and tailored care plans
- access to a multidisciplinary team (MDT), including a care coordinator
- improved capacity and capability across healthcare through, for example, the introduction of a data driven healthcare system
- improved communication between patients and their care team and between local and regional teams, which can be done through technology
- tailoring care to a patient's needs
- access to patient support groups and appropriate information about their condition

› Early diagnosis

Regardless of whether a treatment is available, early diagnosis can help those afflicted with these conditions put an end to the diagnostic odyssey they face. It can also enable them to access the right patient support groups and better family planning, which is especially key when several family members may be affected by the same condition, such as in the case of XLH and OI. Access to prenatal genetic counselling diagnoses can help parents assess the risk of having children with the same condition. Early diagnosis can also help these individuals and their carers to receive the social and educational support they need to manage their condition appropriately.^{78,79}

Reducing the costs of genetic testing and improving access to this accurate diagnostic method, could help genotyping become a frequently used method to support early clinical diagnosis.⁸⁰

› Multidisciplinary care team

While the care provided to people living with rare bone conditions may often be led by an expert in bone health, their care ultimately needs to involve other clinical experts due to their condition's complexity. Having access to an extensive network of experts and researchers can help clinicians keep up to date with any advances that can help support and improve a patient's management and care.

It is thus necessary that for people with rare conditions to have access to high quality care, care coordination is at the centre of disease management. Indeed, coordinated care has been shown to deliver significant improvements to the lives of people living with rare conditions, as seen with Alström's and Huntington's disease.^{81,82,83}

For the purposes of this report, the below NHS England’s definition of multidisciplinary care was adopted:⁸⁴

“ A multidisciplinary approach involves drawing appropriately from multiple disciplines to explore problems outside of normal boundaries and reach solutions based on a new understanding of complex situations. Multidisciplinary and Multiagency working involves appropriately utilising knowledge, skills and best practice from multiple disciplines and across service provider boundaries, e.g., health, social care or voluntary and private sector providers to redefine, re scope and reframe health and social care delivery issues and reach solutions based on an improved collective understanding of complex patient need(s). ”

In line with the above description, and as outlined in Figure 3, this framework proposes that care for people living with rare bone conditions should be driven by a core multidisciplinary specialist team, who are experts on these conditions and can advise other clinicians on the appropriate care plan to undertake. This core multidisciplinary team should be supported by a range of affiliated specialists who should be called upon when needed, as well as local health and social care professionals to ensure care is delivered close to home, whenever possible. These three teams should work closely together to deliver improved care.

The below figure provides an overview of who should be involved in these teams:

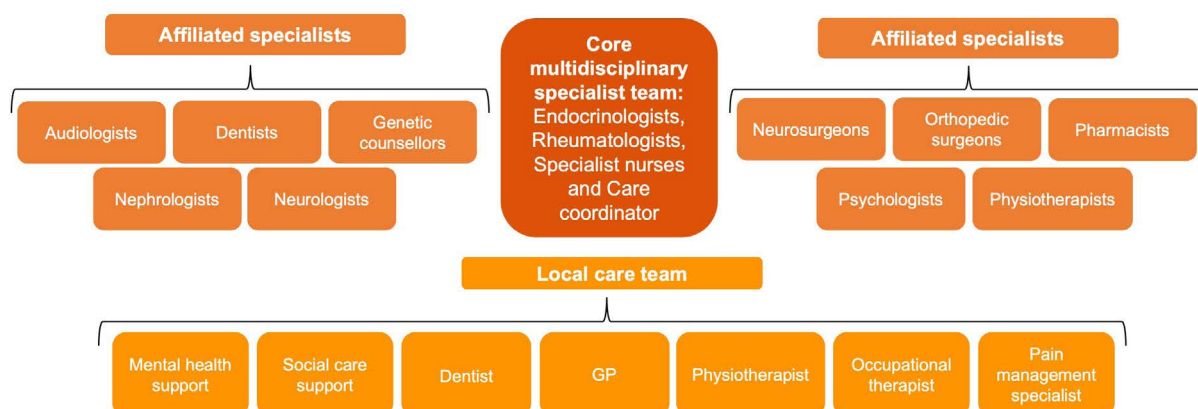


Figure 3. Proposed multidisciplinary care coordination model for adults with rare bone conditions.

› Dental health support

As highlighted previously, people with rare bone conditions suffer from severe dental health issues.^{8,15,16,17} As such it is key that they have access to specialist dentistry, through the NHS, from the point of diagnosis and throughout their lives.

› Transition

Transition is a highly critical period in one’s care, given that if not undertaken appropriately it can lead to the deterioration of care provided during infancy. As such, it is key that certain measures are in place to ensure it is coordinated and appropriate to one’s needs.

A transition coordination team or a transition coordinator could be assigned, as suggested by the Beacon for Rare Diseases report and by the CONCORD study,^{50,71} to oversee the transition process and facilitate the communication between the adolescent, their family and their care teams, at both the paediatric and adult settings. This role can be undertaken by a specialist nurse, a paediatric specialist or another healthcare professional involved in delivering the adolescent's paediatric care, to help ensure a smoother transition and a clearer communication of the adolescent's needs between care settings. This could also help them and their families feel more supported and confident about this new phase of care.

If a formal transition coordinator or coordinating team is not available, this coordination of care during the transition period could be undertaken by an informal care coordinator, as suggested by the CONCORD study.⁷¹ This informal coordination could include a referral to a specialist centre by a GP or a nurse coordinating some aspects of care during treatment or hospital visits.

Adolescents or their families could also be encouraged to take more of a leading role in their care, if they feel comfortable doing so. They should; however, always be given key information on what care they are entitled to receive, who they should receive it from and when.

Given this period tends to be very stressful for both adolescents and their families, the transition process should start as early as possible and regular meetings should be held throughout the process between the paediatric MDT and the adult MDT. Where possible these should be attended by the adolescent with the rare bone condition, their family, and the transition coordinator or the coordination team, so that they are fully aware of the changes in care to be expected. Timing for transferring adolescents between services should also be flexible to accommodate for their needs.

Finally, care teams in both paediatric and adult settings should follow existing guidelines for transition, such as those provided by NICE and NHS England Improvement Standards.⁵⁰ Regular reviews should also occur to ensure both settings are held accountable for the quality of transition pathways available.

› **Management of pregnant women with rare bone disorders**

Pregnancy for women with rare bone conditions can be extremely challenging. As such, a MDT of healthcare professionals should also be formed to support women with rare bone conditions throughout pregnancy.

This team should include a perinatologist, obstetrician, maternal-foetal specialist, paediatrician, anaesthetist, orthopaedist, geneticist, surgeon, psychologist and midwife, and other specialists that may deem to be needed to provide the highest standard of care possible. Biochemical monitoring should also be considered for those who are receiving treatment.

› **Psychological support**

Special attention also needs to be given to psychological and mental health support provided to those living with rare bone conditions, from paediatric to adult services, as it can be difficult to overcome day-to-day challenges, such as going to school, university or work, or even building relationships.

Research has indeed shown that even when medical care for people living with rare bone conditions is good it often doesn't include the psychological and mental health support that these people and their carers need.^{85,86,87} These studies also demonstrate that the overall quality of life of people living with rare bone conditions, their families and their carers is lower when compared to the general population.

For example, in a study looking at the quality of care provided to people living with HPP, 33.4% of the people surveyed stated that emotional problems were impeding their ability to perform daily activities.⁶⁷ The study concluded that if psychological support was adequately provided this percentage could be much lower and patients would have a higher quality of life.

Psychological support should therefore be provided to help these people, their carers, and their families prepare for the day-to-day challenges they may face, throughout their journey, from paediatric to adult care.

› **Care coordinator**

As highlighted previously, having a care coordinator could substantially improve the care and quality of life of people living with a rare bone condition and their families and carers. This is supported by the CONCORD study's findings, with more than 70% of people with rare diseases, their parents and carers, as well as healthcare professionals who responded to the survey agreeing with this proposal.⁷¹

Each individual should have access to a care coordinator, a trained healthcare professional that would help manage their care, monitor their treatment plan, provide them with personalised information on their condition and care, liaise with their team (both at local and core team level) and, where appropriate, coordinate between health and social care.⁶⁹ The role of this coordinator is crucial as it provides each individual and their family with a support system as they undergo extended therapy, potentially helping them achieve effective self-management.

This role can be occupied by a variety of healthcare professionals such as a clinician, a specialist nurse, a GP or a key worker, as long as they have received the appropriate training.⁶⁹ Unfortunately, current healthcare services don't offer healthcare professionals access to specialised training on rare bone disease management. So, to enable patient access to high quality care it is crucial that an investment is made in developing a curriculum for nurses, healthcare professionals, student nurses and student doctors focused on diagnosing and managing these conditions.

Having a care coordinator has been shown to provide patients with significant benefits. For example, people living with Sickle Cell and Thalassaemia (SC&T) reported having less emergency hospital admissions and being able to manage their anxiety better when they had specialist nurses coordinating their care and providing them with psychosocial support.⁸⁸ In England, there are 41 SC&T specialist nurses responsible for the acute sector. Their work is regularly reviewed by external (non-nurses) management consultants and they are provided with training across a range of different areas, such as counselling of at-risk couples and SC&T clinical nursing care, the latter being accredited by the Royal College of Nurses.⁸⁸ This model of care provides a potential source of inspiration for the specialist nursing role in coordinated care for rare bone conditions.

› **Nationally coordinated expert centres**

As rare bone conditions care requires a range of different expertise to be appropriately delivered, we are proposing that nationally coordinated expert centres are established to enable the recruitment of qualified professionals and to ensure that they receive the training needed to maintain their expertise. Specialist clinicians, detailed in Figure 3's core multidisciplinary specialist team section, should be available at these centres.

This is supported by the findings of the CONCORD study, where more than 80% of people with rare conditions, their families and carers, as well as healthcare professionals who responded to the survey believe having access to a specialist centre would improve quality of care.⁷¹

This model of delivery of care also enables a more efficient management of resources and wider access to the technology needed that allows the appropriate delivery of the services.

Nonetheless, to ensure equitable access to services, given the small number of expert centres and the fact that some patients may live far away from centres, we propose that patients who are suitable for shared care should be followed by one specialist centre and their care reviewed (annually or biannually, depending on the patient's condition) by their lead physician.

Additionally, and in line with the guidance for commissioning highly specialised services developed by NHS England, we recommend that there is monitoring of the geographical access to these services to ensure equity of access.⁸⁹ This should be measured through the standardised co-efficient of variation (SCV) which indicates if variation is unlikely not to have occurred by chance (SCV above 20) or if the variation can be considered random (SCV below 20). This variation is measured by mapping patients that have received an intervention or have a confirmed diagnosis of the relevant condition, thus highlighting where genuine clusters of patients are observed. Where these clusters are identified, a review of the information collated should be undertaken to understand the possible causes and explore solutions to reduce inequalities. Furthermore, this geographic analysis should be repeated regularly to ensure all patients have access to the highest standard of care they need and deserve, regardless of their location.

Further details on how this care should be organised can be found in the section **“How should care be organised?”**.

› IT infrastructure and data specialists

Furthermore, and as highlighted previously, when care is uncoordinated, patients must ensure clinicians have access to the correct medical information, which can sometimes mean having to relay the same information over and over again to different specialists and, in some cases, crucial information being missed. Thus, to avoid delays in care and ensure patients receive the highest standard of care, clinicians across all three teams should have access to the patient's medical history and medical records in an easy way. Only when communication and information sharing across all parties exists, can the service truly be coordinated and address the current system gaps.

To achieve this, an investment needs to be made in IT infrastructure and data specialists, which would be responsible for monitoring and sharing this data. This data system should be informed by patient data from GP records, radiologist appointments and core MDT appointments.

Additionally, for patient data to be easily identified and analysed, diagnostic coding for outpatient appointments should be improved. Improving the coding for overall outpatient data, for example through implementing a code such as Orphanet's orphacode,⁹⁰ could also help automatically lift benchmarking data from hospital settings, which can be used to improve patient care in other settings.

Machine learning algorithms can also help accelerate diagnosis as they are able to screen X-rays and compare them to previously diagnosed patients, to quickly identify calcifications or ossifications in patients.⁹¹

› Patient data registry

With 461 rare bone diseases, or skeletal dysplasias, identified, data registries are key to help support better understanding of the natural progression of these conditions and enable expertise and data sharing which can ultimately improve access to higher quality of care and help close the evidence gap that rare diseases care faces.

As stated previously, research in rare diseases face several challenges including the small patient population affected, patients being dispersed geographically and, in some cases, the lack of interest in research due to the inability to set up an appropriate efficacy clinical trial. Research collaboration can help address some of these challenges. This collaboration can be enabled through, for example, the establishment of a clinical registry, which can collate data from several rare bone conditions such as the symptoms, diagnostic methods used, number and location of patients and genomic data. This registry can serve as a source for historical controls and for overall data sharing, as well as a recruitment tool for potential clinical trials.^{92,93}

Indeed, a great example of how this collaboration can lead to improvements in patient care is the global registry created by the International Fibrodysplasia Ossificans Progressiva (FOP) Association, which has led to broad consensus on the methods to diagnose FOP and prevent flare-ups, and to the development of guidelines which propose a family-centred care.⁹⁴

A patient registry is already available for rare diseases across the whole of England, the National Congenital Anomaly and Rare Disease Registration Service.⁹⁵ Amongst other things, the registry provides a resource for clinicians, it supports and empowers patients and carers, and it informs the planning and commissioning of health and social care.⁹⁵

Some disease specific registries already exist, such as the international XLH registry, which is aimed at collecting data to characterise the treatment, progression, and long-term outcomes of XLH in both adult and paediatric settings,⁹⁶ and the US-based FD/MAS patient registry, which is used by UK clinicians and allows for patients and their families to share their experiences with the condition from how the diagnosis is made to what therapies work best.⁹⁷ Thus, leveraging large datasets from other countries or from the [Online Mendelian Inheritance In Man](#) (a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily) can help with improving the overall understanding of these very rare conditions and in establishing disease prevalence in the country, which in turn can help improve access to care.

However, we recommend that a UK-based patient registry for all rare bone conditions is set up and that funding is provided, so that patient data can be better shared across multiple settings so that all people living with these conditions, regardless of their location, have access to better disease management and the highest quality of care.

› Education for primary care clinicians

According to a recent report that looked at what care for people living with rare bone conditions looks like in the EU and the US, bone health is underrepresented in undergraduate medical education and largely centred on fractures.⁹⁸ Patient advocates and bone health experts, interviewed by the authors called for medical school's curriculums to include additional learning time dedicated to bone conditions.⁹⁸ This measure would provide primary care clinicians with a better understanding of bone abnormalities and how to diagnose them, so that faster referral to specialists and faster diagnosis can be achieved.

Additionally, the UK Rare Diseases Framework also recommends that primary care clinicians become more widely 'aware of rare diseases' and 'alert to considering them' when diagnosing a patient, and that they are 'provided with the education and resources that can help them recognise rare diseases and be aware of potential specialist treatment needs.'¹

We fully support these recommendations, and believe that if at a primary care setting diagnosis can be fastened, ultimately patient outcomes and their quality of life can be dramatically improved.

› Access to patient group support

The role of patient groups can be critical in providing information to patients, their families, and their carers, and in encouraging them to be actively involved in the decisions of their care. Patient groups also provide individualised support to people with rare conditions and their carers, as well as enabling people with lived experience to form a collective voice, which can be key especially for those living with rare diseases.

As recommended by the Beacon for Rare Diseases report,⁵⁰ patient groups can also help support patients and their families during their transition in care. They can help doing so through educating them about their rights to a coordinated transition, facilitating the communication between clinicians and families, working with MDTs and support the development of age-appropriate care, so patients feel comfortable when moving care settings.

It is therefore key that all people living with rare bone conditions are referred to a patient support group following diagnosis. This referral could be led by the care coordinator; however, an approved list of patient advocacy groups is developed and made available to all the clinicians and care coordinators leading on, or involved in, the care provided to people living with rare bone conditions.

How should care be organised?

Vital to the success of multidisciplinary care will be greater care coordination. To deliver this we recommend that a networked model of care is set up with the aim of providing consistent care, both regionally and locally.

This model could ultimately improve efficiency and avoid duplication of services, while increasing cost efficiency and improving patient access to services. This model has been successfully implemented in other rare and ultra-rare conditions, such as Alström and pulmonary arterial hypertension.^{81,82,99} As such, we propose that care is organised the following way:

1 Care organisation within an umbrella of a rare bone disease network

- A network of specialised centres should house the core MDTs for rare bone services
- Each MDT should have access to affiliated specialists that can be called on as needed, both to support the core MDT as well as local care teams, who provide the day-to-day support and care as illustrated in Figure 3
- Designation of these specialist centres should be driven by minimal service standards based on clinical criteria, supported by peer review
- The designation process for the previously established European Reference Network (ERN) on Rare Bone Diseases could be used as a starting point for establishing accredited specialist centres. At present the UK has twelve ERN designated specialist centres already set up in Birmingham, Bristol, Cambridge, Glasgow, Liverpool, London, Manchester, Newcastle, Oxford, Sheffield, Southampton, and Stanmore
- Where possible, existing paediatric centres specialised in providing care to people living with rare bone conditions should also house specialised care for adults with these conditions. This can enable continuity of care once individuals transition into adult care
- While highly specialised prescribing could drive further specialisation within the network (for example a smaller number of prescribing centres for different rare bone diseases), the UK rare bone disease network could provide equality of access for adults around the UK living with rare bone conditions
- Where possible, IT systems should be aligned, to support improved data collection and allow for interoperability across national and local teams to inform quality improvement and guidelines/pathway optimisation

2**Patient management**

- Care should be delivered as close to home as possible
- To enable this, patients who are suitable for shared care should be followed by one specialist centre and their care reviewed (annually or biannually, depending on the patient's condition) by their lead physician. These appointments should be used to determine which treatments and specialists the individual needs during the MDT clinic appointment and the day-to-day support the individual will need at a local level. Where appropriate, these should be held virtually to lessen the burden on patients
- A care coordinator should be assigned to each individual, and be responsible for coordinating the care recommendations made by the core multidisciplinary team and affiliated specialists, and provide urgent unplanned access for the patient to specialist care and triage
- Patients should have regular appointments with their care coordinator to ensure progress is being made in their disease care. Where possible and appropriate, these appointments should be held virtually to lessen the travel and economic burden on patients. If however, a physical examination or blood testing is required, this appointment should be held in person
- When an individual is receiving treatment, multidisciplinary clinic appointments should be increased in regularity to ensure appropriate follow up
- Individuals living with these conditions and their carers should be given written and/or digital information material where available about the condition and informed of the local/national/international patient groups for additional support. Treatment-specific patient support programmes might also be needed
- Where appropriate, individuals living with rare bone conditions should have access to a social care officer to help them with issues regarding work, social care support, etc.
- Patients should have ongoing mental health support at a local level, under the guide of affiliated mental health specialists
- Where needed, patients should have regular access to physiotherapy and occupational therapy and to pain management services at a local level
- Genetic counselling should also be available for affected families who are considering having children. The value of family mapping should be shared amongst clinicians
- Where needed, regular training should be provided to local teams on how to appropriately manage the care of individuals living with rare bone conditions. One option for this may be encouraging local clinicians to rotate through specialist MDT clinics, to build their knowledge and improve awareness of rare bone diseases

3**Referral pathways**

- Local healthcare professionals should be educated on common signs, symptoms and red flags of rare bone conditions to support early identification and referral
- Individuals living with rare bone conditions should be referred to a specialised clinic via their consultant physician or their GP within 18 weeks of their diagnosis as per NHS England's RTT target¹⁰⁰
- Local healthcare professionals should be supported in understanding where to refer patients and what information would be needed as part of the referral letter to support continuity of care and minimise the coordination burden on people living with these conditions and their families. This could be enabled through the development of an online portal for referrals, which could contain details on the local centres and referrals proformas. This would also allow for data capture on referral patterns and numbers, enabling for better planning of care across the pathway
- To support GPs and local centres referral, a national directory of specialist centres should be developed for different rare bone conditions. This could be web-based with a referral system in place
- Referral can be further improved if access to accurate patient data is easy and efficient. As mentioned above, this can be achieved through a national patient registry and through providing better funding for IT infrastructure and data specialist

4 Transition

- Where possible, co-located services should be established to enable individuals to meet with both teams (paediatric and adult care) on multiple occasions before care is transferred to adult services
- Common standards should be set across rare bone diseases to ensure joint management of the handover, especially where services are not co-located. These standards should be based on existing guidelines for transition, such as those provided by NICE and NHS England Improvement Standards
- Regular reviews of the quality of transition pathways should be undertaken
- Specialist centres should seek to build relationships with local clinicians to ensure they understand that it is critical to refer individuals to the right services
- Where possible, a transition coordinator should be appointed to ensure transition between services is seamless and integrated. This role could be led by radiologists, specialist nurses, pathologists or paediatric clinician
- If a formal transition coordinator isn't available, informal coordination should be strived for, through for example referrals from GPs
- Where possible, additional administrative support should also be provided to paediatric services to ensure adult services receive the appropriate patient information and patients are referred to the services they need to achieve the highest quality of care possible
- Transition should start as early as possible to ensure patients, their families and the care teams have enough time to outline an appropriate transition pathway
- Regular meetings should be held between the MDTs at both paediatric and adult settings. Where possible, patients, their families and the transition coordinator should be in attendance

The below figure provides a visual overview of how we propose care should be organised for adults with rare bone conditions:

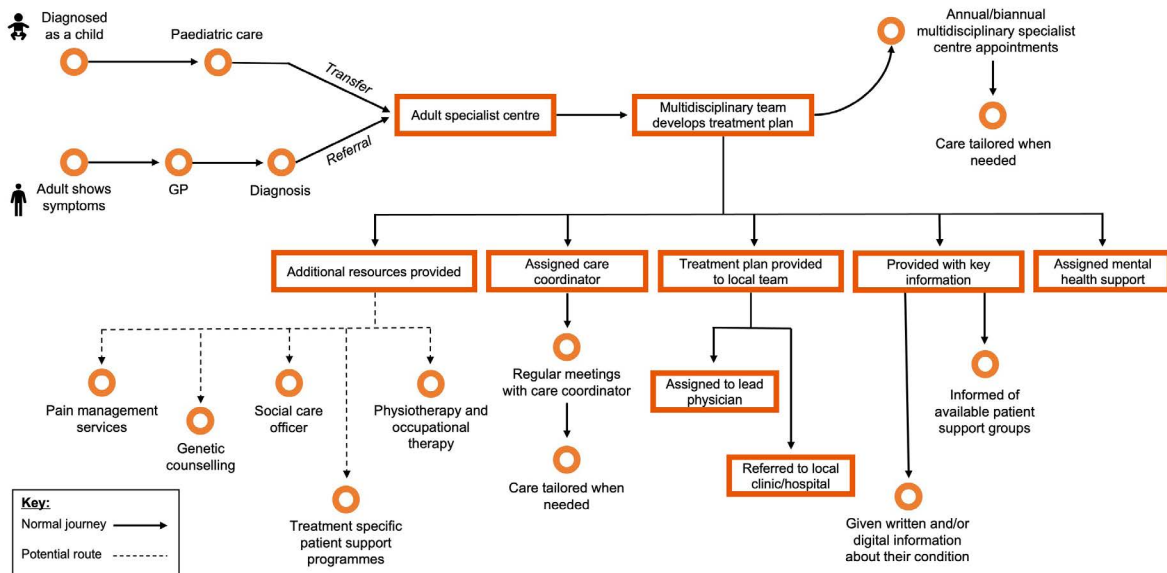


Figure 4. Proposed adult patient pathway for rare bone conditions.

Conclusion

Due to the complexity and burdensome nature of rare bone conditions, people living with these diseases and their families face several issues throughout their lives, including when trying to access appropriate adult care services. These challenges include delays in receiving a correct diagnosis, lack of awareness from clinicians of these diseases and their symptoms, lack of transition pathways from paediatric to adult services, and no access to specialist multidisciplinary teams and specialist treatment centres.

Nonetheless, progress is under way to improve the quality of life of these people and the care pathways they access. Although some of these steps are being built into the healthcare infrastructure, more work still needs to be done to help provide the highest quality of care.

This *Proposed framework* aims to be a step in the right direction, by suggesting how care for adults with rare bone conditions could be improved and delivered in England, and who should be involved in providing it.

We, thus, urge the wider rare bone community, from clinicians to patient representatives, to join us in advocating for these recommendations to be considered for implementation so that ultimately everyone living with these conditions can have access to the timely and affordable care they deserve.

Appendix 1

Below we provide a detailed description of the most common rare bone conditions, as outlined by the European Reference Network on Rare Bone Diseases:⁶

- **Achondroplasia (ACH)**, characterised by short stature (usually under 4 feet 6 inches); an unusually large head with a prominent forehead and flat nasal bridge; short arms and legs; prominent abdomen and buttocks and short hands with fingers that assume a “trident” or three-pronged position during extension. This condition can also lead to spinal cord damages and upper airway obstructions, which can make breathing harder¹¹
- **Fibrous dysplasia/McCune-Albright syndrome (FD/MAS)**, characterised by skeletal lesions, skin hyperpigmentation, hyper-functioning endocrinopathies, enlargement or deformity of the bone, and fractures due to the weakened bones. This condition can also lead to scoliosis and severe pain^{12,101}
- **Hypophosphatasia (HPP)**, a condition which weakens and softens the bones, leading to skeletal malformations including short limbs, an abnormally shaped chest, and soft skull bones. Infants may have difficulties with feeding, respiratory problems, and high levels of calcium in the blood, which can lead to recurrent vomiting and kidney problems. Adult forms of HPP can also include recurrent fractures in the foot and thigh bones, which can lead to chronic pain. Affected adults are at increased risk for joint pain and inflammation and may lose their secondary teeth prematurely¹³
- **Multiple osteochondromas (MO)**, usually characterised by multiple benign bone tumours that are covered by cartilage, which can lead to bone deformities, skeletal abnormalities, short stature, nerve compression and reduced range of motion. In 1 to 5% of cases patients can develop malignant tumours, known as chondrosarcomas¹⁴
- **Osteogenesis imperfecta (OI)**, characterised by increased bone fragility, low bone mass, and predisposition to bone fractures which may vary in severity. This condition can also result in spinal curvature, short stature, joint dislocation, deafness, pain and dental problems^{8,15}
- **Pseudohypoparathyroidism (PHP)**, presents in infancy and is caused by an inadequate response to the parathyroid hormone which leads to low levels of calcium, faulty bone growth, headaches, weakness, easy fatigue, lack of energy, blurred vision, and hypersensitivity to light⁹
- **X-linked hypophosphataemia (XLH)**, a lifelong, progressive condition characterised by chronic low levels of phosphate in the blood. XLH symptoms include rickets and weakened skeletal bones that result in lower limb deformities, stunted growth, and dental abscesses. These lead to further debilitating morbidities that have a deleterious impact on multiple body systems throughout adult life, including fractures, pseudo fractures, osteoarthritis, enthesopathies, hearing problems as well as ongoing serious dental problems^{16,17}

Appendix 2

The prevalence for each individual rare bone condition outlined in Appendix 1, can be found below:

- **ACH:** birth prevalence for ACH has been estimated to be around 1 in every 25,000 – 30,000 individuals.³⁸ In England, it is estimated that between 1,885 and 2,262 people have been diagnosed with ACH^a
- **FD/MAS:** the exact prevalence of fibrous dysplasia is unknown, but it is estimated to be less than 1 in every 2,000 individuals.¹² In England, it is estimated that less than 28,275 people live with FD/MAS^a
- **HPP:** the prevalence of severe forms of HPP in Europe is estimated to be 1 per 300,000 live births. Milder forms, in which signs and symptoms have a later onset, are more common and are estimated to be present in 1 per 6,370 of the population.⁴⁰ In England, it is estimated that around 188 people have been diagnosed with severe forms of HPP, whilst over 8,870 people are estimated to have been diagnosed with milder forms of the condition^a
- **MO:** the prevalence of MO has been estimated to be about 1 in every 50,000 individuals within the general population.^{14,25} In England, it is estimated that around 1,134 people live with MO^a
- **OI:** the number of people with OI in the UK and Ireland is unknown. However, it is estimated to be approximately 1 in every 15,000 people.^{8,15} In England, it is estimated that approximately 3,770 people live with OI^a
- **PHP:** the exact prevalence of PHP is unknown; however, it is estimated to range between 1 and 9 individuals in 1,000,000.⁹ In England, it is estimated that between 56 and 508 people live with PHP^a
- **XLH:** the prevalence of XLH is estimated to be around 15 in every 1,000,000 people.¹⁰ In England, it is estimated that around 848 people live with XLH^a

^a Calculations were made based on annual population estimates provided by the Office for National Statistics on 25 June 2021 for England. Available [here](#)

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About Kyowa Kirin

Kyowa Kirin commits to innovative drug discovery driven by state-of-the-art technologies. The company focuses on creating new values in the four therapeutic areas: nephrology, oncology, immunology/allergy and neurology. Under the Kyowa Kirin brand, the employees from 40 group companies across North America, EMEA and Asia/Oceania unite to champion the interests of patients and their caregivers in discovering solutions wherever there are unmet medical needs.

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