E13/S(HSS)/b

2013/14 NHS STANDARD CONTRACT
FOR CRYOPYRIN ASSOCIATED PERIODIC SYNDROME (ALL AGES)

PARTICULARS, SCHEDULE 2 – THE SERVICES, A – SERVICE SPECIFICATION

Service Specification No.	E13/S(HSS)b
Service	Cryopyrin associated periodic syndrome (All Ages)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

The cryopyrin associated periodic syndromes (CAPS) comprise a specific type of inherited periodic fever syndrome, which are now also known as inherited autoinflammatory diseases. The aim of the service is to provide a national centre for diagnosis, assessment, treatment and monitoring of patients with CAPS, an extremely rare life-long inflammatory disease that interferes with growth and development, causes serious morbidity and is often fatal. Treatment will comprise eight-weekly injections of canakinumab, which is a new profoundly effective but high cost monoclonal antibody therapy.

The service will be based at the National Amyloidosis Centre (NAC), which is located in University College London Medical School at the Royal Free London NHS Foundation Trust and has been providing diagnostic services for patients with inherited periodic fever syndromes since 1999. NAC is the only UK centre with specialist expertise in CAPS, and it has internationally recognised expertise in diagnosis, genetic analysis, and clinical management of this extremely rare disorder. The causative role of excessive interleukin 1 production in causing the symptoms of CAPS, and the remarkable efficacy of canakinumab were discovered at the NAC.

Canakinumab is the only licensed treatment for CAPS, and there is no specific expertise or other clinical services available throughout the UK for patients with this ultra-orphan disease.

The prevalence of CAPS is thought to be ~ 1 in 1 million, and therefore given the very small number of affected patients, a designated national treatment centre for CAPS will facilitate collection of patient data and maximise expertise in the use of

canakinumab, thus improving the provision of ongoing and future patient care. Novartis are creating a registry to further facilitate this process, which will be used by the centre.

Fundamental to this service, national commissioning of the CAPS treatment service represents the only feasible route in England by which CAPS patients will be able to equitably access this new highly effective high cost therapy.

Evidence base

Canakinumab is a new fully-human IgG1 anti-interleukin 1β antibody produced by Novartis, which, when administered subcutaneously every 8 weeks, leads to complete remission of the disabling inflammation in the skin, eyes, joints and brain and flu-like symptoms and fevers in CAPS. The overwhelming fatigue that impedes employment and social activities is abolished, corroborated in clinical trials through normalisation of the SF-36 quality of life and FACIT-F© fatigue scores. Median FACIT-F© score was 29.5 in the pivotal phase III study of canakinumab, far below the healthy score of 52. In the long term, there is every expectation that prolonged treatment with canakinumab will completely prevent the skeletal deformities, blindness, deafness and amyloidosis that commonly occur. Catch-up growth and age appropriate sexual maturation have been observed in adolescents with CAPS who have been treated with canakinumab

The efficacy of canakinumab in CAPS has been studied from its outset at the NAC. A phase II trial first demonstrated its truly remarkable efficacy, showing complete and almost overnight resolution of fever, anaemia, rash, arthritis, conjunctivitis and headache caused by chronic meningitis. Established amyloidosis causing renal dysfunction has completely resolved in affected patients as a result of reduced serum amyloid A protein (SAA) production. An international phase III study led by the NAC team proceeded to formally confirm this remarkable efficacy, which was coupled with excellent safety and tolerability. Various analyses of the results from the phase II and III studies conducted at the NAC have been published and presented at meetings, and the phase III trial was published in full in the world's leading general medical journal the New England Journal of Medicine in 2009.

In brief, this placebo controlled randomised withdrawal phase III study demonstrated complete clinical remission in 97% of patients with CAPS, associated with no reported adverse events in terms of injection site reactions and an otherwise excellent safety and tolerability profile. During the randomized placebo-controlled withdrawal part of the trial, none (0/15) of the patients randomized to canakinumab experienced a disease flare, compared to 81% receiving placebo (OR: 0.00, 95%CI:0.00, 0.14, ρ=<0.001). Two treated patients demonstrated qualitative improvements in their hearing test. Median SAA levels in the blood normalized in canakinumab treated patients (<10mg/L), and by contrast were ~80mg/L in those receiving placebo. These latter findings are extremely important since SAA levels below 10 mg/L are normal, and are not associated with susceptibility to amyloidosis, and indeed SAA levels below 10mg/L often lead to reversal of established amyloidosis and improved renal function.

Canakinumab treatment was well tolerated, not associated with any deaths and few serious adverse effects.

Analysis of the phase II study provided major new insights into the pathogenesis of CAPS, and indentified the basis for the unparalleled efficacy of canakinumab. This study was published in the Journal of Experimental Medicine. (In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, Wittkowski H, Bek S, Hartmann N, Bosset S, Hawkins PN, Jung T. J Exp Med. 2009 May 11;206(5):1029-36).

Additional clinical studies of canakinumab are ongoing at the NAC and elsewhere.

2. Scope

2.1 Aims and objectives of service

CAPS is an extremely rare genetic disease caused by mutations in the gene for a newly discovered protein called cryopyrin. This results in excessive production of interleukin 1β (IL-1β), which potently causes disabling multi-system inflammation from birth. Patients suffer severe fatigue, fever and muscle pains on a daily basis that mimic influenza (the symptoms of which are also caused by transient excessive production of IL-1β), along with chronic anaemia and inflammation in the skin, eyes, joints and brain that present as severe rashes, conjunctivitis, arthritis, chronic meningitis, blindness, deafness and neurological impairment generally. About 25% of patients develop AA amyloidosis that results in renal failure and death within 5-10 years. Growth and development are impaired, and puberty is delayed as a result of chronic severe systemic inflammation.

2.2 Service description/care pathway

Canakinumab is a new monoclonal antibody treatment produced by Novartis that inhibits interleukin 1β and usually leads to complete remission of CAPS. The CAPS treatment service will be accommodated within the NAC at University College London/Royal Free London NHS Foundation Trust. The service will comprise clinical evaluation of patients with known and suspected CAPS with a view to treatment with cankinumab, and their long-term surveillance and follow-up. . It is thought that there may be about 60 cases of CAPS in the UK in total, i.e. a prevalence of ~ 1 in 1 million. It is estimated that a child is born with CAPS about once every 2 years in England.

Patients will attend the NAC for evaluation of their disease, and their suitability for canakinumab therapy will be determined. It is anticipated that contra-indications to treatment will be exceptional. The drug will be prescribed at the NAC and administered by subcutaneous injection every eight weeks, during the first year of

treatment, with the hope that four-monthly follow-up will prove feasible in subsequent years, with interim dosing performed at home. Patients will undergo long-term surveillance and follow-up at the NAC, including quality of life studies and entry into a register that is currently being developed by Novartis.

Patients with CAPS will undergo genetic testing, expert clinical assessment, quality of life evaluations, and annual audiometry, ophthalmic and neurologic assessments, and brain magnetic resonance imaging (MRI) where indicated. The sensitive blood markers of systemic inflammation will be measured frequently.

It is hoped that clinic visits may be reduced from two to four-monthly after the first year or two commencing treatment in most patients. This will depend on adequate local arrangements to formulate and deliver this novel drug, and to perform the necessary monitoring procedure.

Since canakinumab is a new drug, the possibility that it may be associated with as yet unreported adverse effects will be maintained under constant review. Further, little is yet known about the magnitude of its efficacy in patients with the most severe forms of CAPS, notably including those with severe central nervous system (CNS) disease. The possibility of a requirement for intensification of IL-1 inhibiting treatment will be reviewed in patients with active CNS disease, in whom it is possible that additional IL-1 blocking therapy, e.g. anakinra, might be beneficial.

Service model and care pathways

Patients will attend the NAC for evaluation of their disease, and their suitability for canakinumab therapy will be determined by two expert consultants. It is anticipated that contra-indications to treatment will be exceptional. The drug will be prescribed at the NAC and administered by subcutaneous injection every eight weeks, during the first year of treatment, with the hope that four-monthly follow-up will prove feasible in subsequent years, with interim dosing performed at home. Patients will undergo long-term surveillance and follow-up at the NAC, including quality of life studies and entry into a register that is currently being developed by Novartis.

Patients with CAPS proven by genetic testing and expert clinical assessment will undergo:

- baseline audiometric hearing test
- baseline ophthalmic assessment by ophthalmologist
- baseline brain magnetic resonance imaging (MRI), and neurologic assessment in those with central nervous system disease
- baseline quality of life assessment and entry of details into CAPS registry
- baseline SAP amyloid scan in selected individuals or later on in those in whom there is a suggestion of amyloidosis developing (~25% of all cases).

Two monthly injections of canakinumab at NAC with bloods for safety and efficacy; quality of life (QoL) assessment.

Monthly measurement of SAA protein in blood samples sent to the NAC (most sensitive marker of disease activity in CAPS, and predictor of development of

amyloidosis).

Annual follow-up Brain MRI in those with abnormalities, and ophthalmic assessment and audiometry in all cases.

It is hoped that clinic visits may be reduced from two to four-monthly after the first year or two commencing treatment in most patients. This will depend on adequate local arrangements to formulate and deliver this novel drug (a very meticulous procedure), and to perform the necessary monitoring procedure.

Treatment with canakinumab is expected to be life-long.

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Experience and expertise of the clinical team

The physicians at the NAC have been working with patients with CAPS for over ten years, both in terms of offering general help and support, and in conducting clinical research. This has underpinned a close and rather unique physician-patient relationship, in which many of the patients we now propose to with canakinumab can claim much credit in its development.

The NAC:

- began to characterise CAPS clinically at the NAC in 1998
- performed a genome wide genetic linkage study in 2000
- discovered the abnormal gene that causes CAPS in 2001
- undertook seminal scientific studies that implicated excessive IL-1 production as the cause of the disease in 2002
- treated the first patients in the world with an IL-1 inhibitor in 2002, which completely turned off the disease, and which was published in the New England Journal of Medicine
- began a collaboration with Novartis to investigate their completely novel super-potent IL-1 blocking drug (canakinumab) in 2003
- performed the first into man treatment of CAPS with canakinumab in 2003
- designed a phase II and then a phase III study with Novartis that demonstrated virtually 100% efficacy of canakinumab in CAPS. (Papers in the New England Journal of Medicine, and Journal of Experimental Medicine).

Patient involvement

The NAC has received much support from CAPS patients since the service was designated, including letters of support from most UK patients who have received canakinumab; these patients universally describe the extraordinary efficacy of this

drug, and the remarkable manner in which the treatment has turned around their lives.

CAPS is such a rare and recently characterised disease that no specific patient organisation has yet developed. However, CAPS (under the previous name of Muckle-Wells syndrome) is one of many inherited diseases supported by the patient organisation CLIMB (Children Living with Inherited Metabolic Disease) – see www.climb.org.uk

The NAC has lately been working with Novartis with an aim of developing an 'online community' to support both patients with CAPS and less experienced physicians.

There is also an online CAPS Community www.rarediseasecommunities.org/en/community/caps that is part of the Rare Disease Network, which is linked with EURORDIS (Rare Diseases Europe) www.eurordis.org

The provider will work with NHS England to ensure sufficient considerations are given to communications.

Risk management

It is widely recognised that an effectively planned, organised and controlled approach to the risk management process is the cornerstone of sound management practice, which aims to anticipate and wherever possible prevent, or manage risks to patients, staff, visitors and the organisation. Good risk management awareness and practice embedded in the service is an essential success factor in ensuring that risks are managed systematically and consistently.

The NAC recognises that identifying risks and managing these well provides invaluable opportunities to improve patient care and there are formal arrangements in place to support these principles. Risk management is covered in mandatory training programmes for staff and the monthly directorate risk and governance meeting provides the opportunity to review all clinical incidents and to ensure processes are revisited as a part of managing risk. This is also achieved by promoting a policy of openness and accountability and by effective communication both within the service and with the external community.

The service recognises that in the absence of a peer review opportunities from which shared learning can occur, this may create a risk element for the service and therefore it recognises the importance of having a sound risk management processes in place which allows the service to continually review performance and learning needs and to respond to these appropriately.

Discharge criteria & planning including any transition arrangements

CAPS is an inherited life-long disease, for which it is anticipated that life-long therapy will remain required. It is anticipated that CAPS patients will remain under the care of the CAPS treatment service indefinitely, although it will probably be possible to

reduce the frequency of clinic visits after the first year or two, in patients in whom the very high level of expected efficacy of treatment has been confirmed. It is anticipated that administration of canakinumab between visits to the NAC will be delivered by a specialist agency that administer and provide drugs in patient's homes.

Patients will remain under surveillance for the known and other potential long-term complications of CAPS, which include deafness, amyloidosis, CNS and visual defects etc, and if necessary will be referred for to other specialist services as appropriate on a case by case basis.

2.3 Population covered

This service covers patients registered with an English GP, resident in Scotland, resident in the European Union and eligible for treatment in the NHS under reciprocal arrangements.

Patients from Wales and Northern Ireland are not part of this commissioned service and the Trust must have separate arrangements in place for patients from these and other non EU referrers.

2.4 Any acceptance and exclusion criteria

Equal access to the service regardless of where patients live is not thought likely to represent a problem, other than travel costs in some instances, given the experience of the NAC and given the great willingness with which patients with CAPS have attended monthly during the course of the canakinumab clinical trials.

Although travel costs are generally modest, especially when clinic appointments can be scheduled electively several months ahead, a modest travel budget would ultimately guarantee equal access to the service.

Referrals are made directly to either of the two CAPS consultants at the NAC. The criteria that will be used for define the patients that will be treated are male and female patients at least four years of age with a diagnosis of CAPS confirmed clinically at the NAC. The diagnosis will be supported by DNA analysis and clinical investigations described above.

There are no specific exclusion criteria.

2.5 Interdependencies with other services

Patients with CAPS are usually identified in either paediatric, rheumatology or dermatology practice, and the patients are therefore referred predominantly by hospital consultants, although the service is open to all medical practitioners within the NHS in England and Scotland.

The CAPS treatment service will be provided within the Royal Free London NHS Foundation Trust by two senior consultants supported by specialist nurses, though very young children will be treated at the fever clinic held in paediatric rheumatology at Great Ormond Street Hospital for Children NHS Foundation Trust (where the two NAC consultants hold honorary clinical contracts).

Genetic testing for the service is performed in the NAC clinical diagnostic lab, and routine haematology and clinical chemistry are provided by the Royal Free London NHS Foundation Trust laboratories. Audiometric testing, pharmacy services, clinical neurology and ophthalmology, and MRI imaging are provided by colleagues at the Royal Free London NHS Foundation Trust.

Clinical assessment and treatment, i.e. administration of the canakinumab antibody therapy, will be performed my medical and nursing staff in the NAC.

At present the service has no dependencies external to the NAC/Royal Free London NHS Foundation Trust/Great Ormond Street Hospital for Children NHS Trust.

The Autoinflammatory Topic Specific Group (TSG) was created in 2009 by Professor Pat Woo, head of paediatric rheumatology at Great Ormond Street Hospital for Children NHS Foundation Trust, whose clinical team in the fever clinic includes the two CAPS expert consultants based at the NAC. This is one of the TSGs within the MCRN/ARC funded clinical trials strategy group (CSG) in paediatric rheumatology, developed by Professor Alan Silman and rheumatologists who have expressed an interest in autoinflammatory diseases.

CAPS is one of several autoinflammatory diseases that is being surveyed throughout Europe in the Eurofever project: www.printo.it/eurofever/ This project was promoted by the Autoinflammatory Diseases' Working Group of the Paediatric Rheumatology European Society (PRES) and is supported by the Executive Agency for Health and Consumers (EAHC, Project No2007332, http://ec.europa.eu/eahc/projects/database.html).

The general aims of the Eurofever project are to:

- sensitize paediatricians and paediatric rheumatologists to the prompt recognition of autoinflammatory diseases
- provide proper information to families affected by these conditions
- increase the knowledge on the clinical presentation, response to treatment and complications of theses rare disorders.

The Eurofever project includes the following actions:

- a survey on the prevalence of diagnosed or suspected autoinflammatory diseases among all European Paediatric Rheumatology Centres;
- an international Registry for Autoinflammatory diseases;
- a survey on the efficacy of treatment in these disorders;
- elaboration of outcome measures for possible future therapeutic trials;
- informative webpages for patients and physicians on each disorder.

CAPS also comes under the auspices of CLIMB, which is part of the British National Information Centre for Metabolic Diseases, a resource for young people, adults, families and professionals. www.climb.org.uk/

CLIMB is the United Kingdom's foremost provider of free metabolic disease information to young people, adults, families, professionals and other interested groups. CLIMB's vision is to provide Metabolic Disease specific information, advice and support to children, young people, adults, families and professionals in the United Kingdom and to provide information and support to families worldwide, to fund educational and primary research programmes and to investigate treatments and medical services.

There is also an online CAPS Community www.rarediseasecommunities.org/en/community/caps that is part of the Rare Disease Network, which is linked with EURORDIS (Rare Diseases Europe) www.eurordis.org

Other internet based resources are available to physicians e.g. Infevers http://fmf.igh.cnrs.fr/ISSAID/infevers/

Infevers is an online database for CAPS and other autoinflammatory disease mutations.

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

Canakinumab will be the only licensed treatment for CAPS. It will be prescribed by the only experts in this disease in the country through the Royal Free London NHS Foundation Trust. MHRA approved pharmacy in full compliance with the drug's licence, and any long term post-marketing surveillance measures that will be conducted. All patients will be presented and reviewed at the centre's weekly multi-disciplinary team meeting, attended by the department's nurses and four consultants. Patient data will be coded and entered on the drug registry that Novartis is creating; information form this will be fed back to prescribers on a regular basis.

The governance and risk arrangements for the Royal Free London NHS Foundation Trust generally were reviewed by the trust Board in support of establishing a new divisional structure in April 2009. This structure was proposed in order to develop and facilitate a more integrated approach to systems of quality improvement.

The integrated approach represents a move from a centrally managed process to one in which each of the four clinical divisions manage the devolved system of quality assurance through divisional governance and risk processes.

Each division has a number of specialist boards that monitor governance and risk

arrangements within their clinical directorate or speciality. A number of these report directly to the trust operations board, although most such boards provide updates to their respective divisional board meetings.

There is also a small corporate governance team comprises of: a central risk & safety team managed by the deputy director of risk & safety, and the clinical effectiveness & quality standards manager managed by the deputy director of clinical governance. Each of the four clinical divisions has aligned governance partners responsible for coordinating and managing locally the governance and risk processes. The governance partners are accountable to the divisional nurse directors with responsibilities to the central governance and risk leads.

Each clinical specialty is required to provide ratings to the divisional board meetings by means of a 'quality scorecard' in three areas of review: do no harm, effectiveness and patient experience. Corporately the quality scorecard provides disaggregated information for those target areas.

The quality scorecard is also populated with information from divisional 'audit scorecards', which are used as a monitoring tool and to collate information on clinical audit activity required for reporting the 'engagement in clinical audits' national priority indictor to the Care Quality Commission (CQC).

The audit scorecard is reviewed monthly at the clinical audit & effectiveness committee (CAEC) The role of CAEC is to enable the effective delivery of the local and national clinical audit and effectiveness agenda, support the delivery of significant improvements in the quality of patient care and improve patient safety through clinical audit and clinical effectiveness.

There is an expectation that practitioners will participate in continuous professional development and networking. Provide assurance that this will be built into roles within the service.

See also service standards for the national treatment service for Cryopyrin Associated Periodic fever Syndromes (CAPS).

4. Key Service Outcomes

The objectives of the service are to enable patients with CAPS to receive the new highly effective treatment with canakinumab.

It is anticipated that the vast majority of patients will respond dramatically to this treatment in terms of resolution of day to day symptoms caused by multi-system inflammation, with profound improvement in quality of life. It is anticipated that the risk of developing amyloidosis will be prevented in all responders, and there is a great hope that the developmental abnormalities (neurological, rheumatological, growth and development generally) that occur during childhood and adolescence will also be prevented following early introduction of the treatment.

Day to day symptoms caused by multi-system inflammation will be assessed every eight weeks using a 20 point CAPS activity score, and by monthly measurements of SAA and CRP in the blood. Audiometry, ophthalmology, neurology and brain MRI assessments will be performed annually. Development of amyloidosis will be sought using the various specialist techniques available at the NAC.

The florid disabling day to day clinical symptoms of this disease affecting performance and quality of life, grossly deranged blood markers of inflammation and anaemia, and long term sequelae (deafness, amyloidosis etc) provide hard outcome measures that can be tested robustly. It is proposed that measurements takes place over a 10 year period:

- quality of life
- Incidence/progression/possible improvement in deafness
- Incidence of new development of amyloidosis, and course of amyloidosis and renal failure in patients who already have this complication.

Patients will be invited to enrol in an international registry being developed by Novartis when this becomes available.

The service will provide an annual report on patient severity score.

5. Location of Provider Premises

The CAPS Treatment Service is wholly provided by University College London medical school staff, which holds honorary contracts with the Royal Free London NHS Foundation Trust and the Great Ormond Street Hospital For Children NHS Foundation Trust. A sub-contracting agreement, subject to annual review, has been drawn up between the two institutions, principally to define allocation of the budget. The Royal Free London NHS Foundation Trust is the legal entity responsible for the clinical amyloidosis service. No formal sub-contracts are held externally to the Royal Free – University College London partnership.

The National Amyloidosis Centre is located in University College London Medical School at the Royal Free London NHS Foundation Trust.