Arthritis Research UK

Providing answers today and tomorrow

NHS National Institute for Health Research

Clinical Research Network Children

NIHR CRN: Children / Arthritis Research UK Paediatric Rheumatology Clinical Studies Group (CSG)

Clinical Research Strategy

1st July 2015

Compiled and summarised by

Professor Michael W Beresford,
Chair of the NIHR: CRN Children /Arthritis Research UK
Paediatric Rheumatology CSG

On behalf of the entire CSG including
4 Consumer Members

1. Table of Contents

2. Aim, Goal, and Remit of the Strategy

Aim

The strategy's overall aim has been to answer **"What are the key clinical research priorities that will change clinical practice in Paediatric Rheumatology for the better?"**

Our Goal

"All children, teenagers and young adults in the UK with a rheumatological condition may be given the opportunity to be enrolled in a clinical trial or well conducted clinical study from point of diagnosis onwards. By doing so they have the chance to improve their own care and outcome as well as helping future patients with similar conditions; and to have the option of contributing towards a related, fully informed and consented Biobank (e.g. DNA and serum) for subsequent investigation into the causes of their conditions."

Remit

To develop a comprehensive portfolio of key research priorities for clinical trials and related studies covering the entire spectrum of major disease areas in paediatric rheumatology in the UK.

3. Overview

From its inception in 2007 the UK Paediatric Rheumatology Clinical Studies Group (CSG) was given the ambitious challenge of developing a comprehensive research strategy in support of the entire spectrum of paediatric rheumatic and musculoskeletal diseases.

In a unique partnership of expertise, the NIHR Clinical Research Network: Children (NIHR CRN: Children) - formerly the Medicines for Children Research Network (MCRN) - and Arthritis Research UK established in 2008 the "NIHR CRN: Children/Arthritis Research UK Paediatric Rheumatology Clinical Studies Group" within the existing structures of the NIHR CRN: Children and Arthritis Research UK Clinical Studies Groups (CSGs). This collaboration of expertise has established and delivered a major, comprehensive and long lasting clinical research programme for paediatric and adolescent rheumatology and musculoskeletal disease in the UK.

From the CSG's initial Research Strategy in 2008, and through its subsequent updates (the last formerly being undertaken in 2011), the CSG recognised the specific challenges of conducting clinical trials and related studies in children and adolescents, particular for rare diseases. For almost all the conditions relevant to the CSG's Strategy, there was very limited or no existing Level 1 Evidence and significant lack of robust biomarkers and outcome measures were identified as a key hurdle to overcome to enable such trials to be performed. Novel trial design and methodological approaches were identified as major requirements to address some of these barriers, that the CSG has been extremely successful in overcoming.

Over the subsequent 8 years, many of the original priorities of the initial CSG Research Strategy have been addressed by initiatives led by or supported by the CSG. During this period there has been a significant expansion of the UK paediatric rheumatology community with new and developing centres participating in collaborative research and significant growth of rheumatology trainees participating and developing their research skills, championed by the CSG. The CSG's Research Strategy seeks to continue to build on existing strengths in the UK paediatric rheumatology and musculoskeletal research community while supporting other key clinically important research areas needing development. Details of the CSG can be found on its website: http://www.arthritisresearchuk.org/research/research-funding-and-policy/our-clinical-study-groups/paediatric-rheumatology.aspx.

4. Stake Holder Involvement in developing the Research Strategy

The CSG Research Strategy 2015 has been developed by inclusion of the important input of many stakeholders and in many ways, including:

Topic-specific Research Strategy: Development, Prioritisation, and Proposed Studies

The principle methodology adopted by the CSG to inform, develop and support the task of formulating its Research Strategy has been through its ten, now well established "Topic-specific groups" or TSGs. The TSGs gather under disease-specific groupings or themes of intervention. Each scientific member of the CSG acts as a "link-person" for these TSGs to facilitate integration of the various activities of the TSGs into the overarching work and strategic portfolio development of the CSG. Consumer involvement in the activity of the TSGs is fostered in every way.

The TSG activities are open and inclusive to all interested stakeholders, and regular updates are included on the CSG's websites, along with e-mailings to BSPAR members. In view of this, and as they represent key stakeholders working in specific areas of clinical research relevant to the Strategy, the principle focus of identifying priorities was through them.

Development of PICOs covering each TSG area

To develop this revised Strategy, each TSG was tasked with developing a number of "PICOs" (Patient group; Intervention; Comparator; Outcomes). The specific challenge was that these were achievable within a reasonable time scale within a UK context (either alone or in collaboration with international colleagues). Following on from this, all proposed PICOs were discussed, refined, reviewed and revised by the whole of the CSG in its monthly teleconferences and at two face-to-face meetings. These was in order that the PICOs were in line with the overarching aims and remit of the CSG and maximally integrate the significant individual and collective expertise and experience of the CSG as a whole in finalising the PICOs for each TSG.

Once a pre-Final draft was formulated, the Board Members of the British Society of Paediatric and Adolescent Rheumatology (BSPAR) were formerly asked for their input and approval.

British Society for Paediatric and Adolescent Rheumatology (BSPAR)

BSPAR represents all health care professionals in the UK and Ireland involved in the care of children, teenagers and young adults with rheumatic disease, working in clinical services, educational and academic sectors. It is a specialist society within the Royal College of Paediatrics and Child Health. Its current membership is over 200 health care professionals, from doctors (paediatricians, rheumatologists and paediatric rheumatologists) and nurses through to therapists (physiotherapists and occupational therapists), podiatrists and other health care professionals.

BSPAR's aim is to advance paediatric rheumatology care in the UK and Ireland, by raising the standards of clinical care, enhancing the quality of training and promoting research in order to increase understanding, improve management and ultimately create better outcomes for children with rheumatic diseases. These are closely aligned to the aim and remit of the CSG. BSPAR therefore represents key health professional stakeholders and the CSG has worked hard to inform and work closely with BSPAR members.

To this end, the BSPAR Board Members were asked in the capacity as representatives of key communities within BSPAR for which they sit on the Board to:

- Rate on a scale of 0 (not important) to 10 (top priority) for inclusion in the CSG Strategy
- Should we include it in the CSG Research Strategy (Yes / No)?
- Any brief comments / refinements / suggestions

Based on feedback and ratification from the BSPAR Board, the CSG finalised the PICOs for each TSG, presented here in the final version of the Research Strategy. In a similar way, the PICOs have the support of other key stakeholder groups, including the British Paediatric and Adolescent Bone Group (BPABG).

Consumer Involvement

From its outset the CSG has actively included consumers in all its activities, particularly in relation to developing its Strategy. Four excellently qualified consumer representatives are members of the CSG. They

represent a broad geographical distribution including a devolved nation's representative. Models have been set up for consumer comment on the wider CSG agenda. These include:

- Child / parent consumer focus groups on setting the research priorities related to a specific TSG agenda
- Consumer group meetings to discuss the remit and wider agenda of the CSG (this has proved a useful way of co-ordinating consumer input into trial protocols and lay summaries for example)
- Fostering existing consumer links / representatives in a range of areas of clinical / research activity. Using these links, the CSG consumer representatives are establishing mechanisms through which wider consumer experience can be drawn on as necessary and appropriate. This will take place through: the use of existing contacts with external rheumatology groups; making consumer members of the CSG accessible to the public and other consumers through a consumer email account; and website information.
- Based on consumers increasing involvement in all CSG activity, identifying consumer training needs and exploring how consumers might be best supported to meet the objectives of the CSG strategy.
- The production of a detailed handbook for consumers involved with CSGs

Along with the consumer representatives on many of the TSGs, and in collaboration with the BSPAR Parent's Group and other established consumer groups within BSPAR, the voice of the child, young person and their families had proactively contributed to and directed the development of these priorities.

5. Development of the Strategy

Global Themes and Research Methods / Tools

The CSG identified has from the outset common priority "Themes" that have relevance across all paediatric and adolescent rheumatic diseases and therefore to each area of the CSG's research strategy. These remain relevant today. Common "Research Methods / Tools" needed to address these themes have also been identified as necessary in addressing the key strategic question: **"What are the key clinical research priorities that will change clinical practice for the better?"**

Theme	Tool
Rare diseases	To establish mechanisms for national / international collaboration with characterised phenotype cohort
Lack of predictors of outcome	To facilitate development of Biobanks and collection of material form all future studies such that biomarkers of activity and outcome, pharmacogenomics and genetics can take place
Lack of outcome measures	To develop minimum datasets to allow theses to be established and measured
Lack of suitable paediatric formulation or pharmacokinetic data	Specific focus on pharmacy and formulation in all studies in common use in paediatric rheumatology
Lack of research into tolerability of medicines	Specific focus on tolerability in all studies in common use in paediatric rheumatology
Cardiovascular risk of chronic inflammatory diseases	To develop biomarkers and tools to assess cardiovascular risk and outcome with a view to interventional trials for relevant disease areas
Lack of understanding of disease mechanism	Foster parallel studies exploring disease mechanism
Lack of knowledge of the process of puberty and brain development	Foster interdisciplinary collaboration to explore physiological and pathological processes in normal and teenagers with rheumatic diseases, integrating with research into facilitating transition to adulthood
Lack of evidence base for the interventions undertaken by allied therapists	To foster studies in order to develop an evidence base for these areas of primary importance to the care of patients in paediatric rheumatology

Lack of evidence base for young people with learning difficulties	Foster the development of guidance for best practice for the management of young people with learning difficulties and rheumatic disease
For international trials in an area identified as a priority in its Research Strategy, the CSG will work with relevant bodies (e.g. MCRN) to facilitate the various processes that are involved in allowing the UK Paediatric Rheumatology community to participate in them	

6. Research Priorities developed by CSG Topic Specific Groups

Juvenile Dermatomyositis JDM

TSG: JDM

Question to be addressed:

Can we achieve international consensus on a minimal core data (MCD) set (based on history and examination) for use in clinical care of patients with Juvenile Dermatomyositis (JDM) and to inform future clinical trials?

Strategy/Comment:

1. The final agreed MCD will be aligned with the UK JDM Cohort and Biomarker study (JDCBS).and incorporated into clinical care, in close collaboration with clinical and research teams as well as commissioning/funders to improve clinical care and outcomes
2. Where feasible integrate existing web based data collection system into electronic health record being used by hospitals for patients with JDM
3. Liaise closely with international efforts including International Myositis Assessment and Clinical Studies Group (IMACS) and Euromyositis collecting adult Dermatomyositis data to facilitate smooth data transition across to adult Juvenile Dermatomyositis care.

PICO

P: Patients with JDM recruited to the UK JDM Cohort and Biomarker study (JDCBS).
I: Creation of a consensus agreed minimal core dataset for JDM for use in standard clinical care and trials
C: No Comparator
O: Improved data for definition of JDM and its clinical state, improved ability to compare patients and define clinical improvements between centres, countries and different studies.

TSG: JDM

Question to be addressed:

Would kinase inhibition be an effective novel therapy in JDM?

Strategy/Comment:

Significant pilot data have been generated already to indicate that interferon-driven JAK/STAT activation is unregulated in JDM and therefore that this pathway may be a useful novel target for therapy

Safety and efficacy of an orally administered JAK inhibitor in patients JDM

P: UK children and young people, with newly diagnosed JDM recruited to the UK JDM Cohort and Biomarker study (JDCBS).
I: Open label uncontrolled Phase 2 study of JAK inhibition; study design to be agreed
C: No control arm; efficacy/safety data compared with standard treatment data already published
O: Treatment response: 20% improvement in at least 3 Paediatric Rheumatology International Trials Organisation (PRINTO) core-set variables with no more than one variable (muscle strength excluded) worse by 30% or more at 6 months using a modified; secondary exploratory endpoints also included.

Non-Inflammatory Musculo-Skeletal (MSK) Disorders
TSG: Non-Inflammatory MSK Disorders **Question to be addressed:** ***What is the UK clinical caseload of Complex Regional Pain Syndrome (CRPS)?*** ***[For Clinical Audit / Service evaluation in collaboration with BSPAR]***
Strategy/Comment: Collaboration with Pain TSG and BSPAR AHP group to survey the incidence of CRPS in paediatric practice.. A national survey of practise would be feasible in the mid-term. Agreed definition of CRPS in childhood with Pain TSG using Budapest Criteria. Develop robust methods to capture all patients via multi-professional engagement. Combined survey monkey, British Paediatric Surveillance Unit (BPSU) with key pain, physiotherapy, orthopaedic and paediatric rheumatology professionals.
P: UK children and young people with a diagnosis of Complex Regional Pain Syndrome. I: Undertake a national survey of the incidence of CRPS. C: Patients are referred to Rheumatology, Chronic Pain and Orthopaedic services with non-inflammatory musculoskeletal pain syndromes. It is unknown how many of these are presenting with CRPS. O: National incidence of CRPS in childhood and Adolescence.
TSG: Non-Inflammatory MSK Disorders **Question to be addressed:** ***In children and young people with symptomatic joint hypermobility does a physiotherapeutic intervention improve function compared with standard care?***
Strategy/Comment: Feasible in longer term Close liaison with AHP members of TSG. Working alongside, and informed by, support groups. Actions: 1. Describe intervention according to literature and agreed best practice 2. Design multicentre RCT
P: Children and young people (5-18 years) with non-inflammatory musculoskeletal pain ; associated with joint hypermobility I: Multicentre physiotherapeutic intervention study to improve muscle strength and function C: Standard Care O: Functional improvement
TSG: Non-Inflammatory MSK Disorders **Question to be addressed:** ***Evaluation of efficacy of gabapentin in children and young people with chronic pain CRPS***
Strategy/Comment: Feasible in mid term. Partner with industry and work alongside Pain CSG. Multi-centred intervention trial.
P: UK children and young people with diagnosis CRPS according to Budapest Criteria I: Patients randomised to receive gabapentin or placebo alongside normal care C: Normal care (plus placebo) O: Functional improvement (with reduced impact of pain on activity)
TSG: Non-Inflammatory MSK Disorders **Question to be addressed:** ***What is the evidence for current postulated criteria for diagnosing symptomatic joint hypermobility and***

postulated associated conditions in children and young people?

[Evidence synthesis]

Strategy/Comment:
Cochrane systematic review of evidence for diagnostic criteria for EDS3 (Ehlers-Danlos Syndrome type 3), BJHS (Benign Joint Hypermobility Syndrome), JHS (Joint Hypermobility Syndrome) and postulated associations such as postural orthostatic hypotension, gastrointestinal transit disorders. Incontinence etc. Feasible mid-term. Close liaison with Paediatric Pain CSG and Adult Pain TSG. Initial Horizon scan

P: All studies that target or include children and young people with a diagnosis of Ehlers Danlos type 3.
I: Cochrane review
C: Not applicable
O: Evaluation of current, graded evidence for EDS type 3 as a diagnosis and postulated associations

TSG: Non-Inflammatory MSK Disorders
Question to be addressed:
To develop a validated tool for the diagnosis of symptomatic joint hypermobility in children and young people.

Strategy/Comment:
There are very limited population data on joint hypermobility in different ages of childhood (<18). Moreover there are limited population data on whether distribution or severity of joint hypermobility is causally associated with musculoskeletal pain and other reported symptomatology.
Beighton and Brighton scores have both been developed and evaluated in adults.
These are not effective in the diagnosis of children and young people with non-inflammatory musculoskeletal pain and joint hypermobility, nor do they identify the clinical presentations, and hence do not help with targeting appropriate intervention.
Feasible in mid to long-term following horizon scan.

P: Children and young people with non-inflammatory musculoskeletal pain and joint hypermobility.
Evaluation of clinical characteristics (selected symptomatic joint mobility, strength, coordination, fatigue, pain, function, exercise levels, family history, illness behaviour, anxiety)
I: N/A
C: Population based evaluation of clinical characteristics in non-symptomatic children and young people to determine which factors should make up diagnostic criteria
O: To investigate if a discrete condition of joint hypermobility exists in childhood or whether this is just a component of non-inflammatory pain

Formulations

TSG: Formulations
Question to be addressed:
What do children and young people and parents of children with a chronic illness think is appropriate in terms of measuring acceptability of new medicines for children?

Strategy/Comment:
Understanding barriers and specific issues around medicines used in JIA and how barriers may be minimised.

P: Children and Young People, and their parents, with and without chronic illness
I: Questionnaire coupled to a case study to elicit patients and family views about studies on the acceptability aspects of new medications
C: Not applicable
O: Evidence synthesis to take to Regulatory Agencies and the Pharmaceutical Industry to ensure that patients views are considered in the design of acceptability tests.

Consumer led priorities
TSG: Consumer **Question to be addressed:** ***In children and young people with rheumatological conditions, does standardised data collection, compared to current practice where data isn't being collected or shared, reduce uncertainty for children and young people, families and healthcare professionals?***
Strategy/Comment: There is considerable uncertainty for children, young people, families and healthcare professionals (HCPs) as to the benefit of current data collection methods. It is important to review what data is currently collected and shared, along with any regional variations in collection and practice across the UK. Understanding how this data is used will inform the development of a standardised data collection protocol for all paediatric rheumatology settings across the UK, formulated and developed with involvement from HCPs, children, young people and their families, to enable them to feel in control of disease management by convenient access to data that is collected at clinic and during maintenance therapy. The proposed research will also benefit the healthcare system, enabling HCPs to monitor the progression of patients and for a central registry in the UK to record relevant information for enhancing healthcare provision for the future, in addition to collecting data such as epidemiology, treatments, disease control, adherence, burden of disease and the patient journey for all children and young people with rheumatological conditions.
P: Children and young people with rheumatological conditions I: Standardised data collection C: Current practice O: Reduced uncertainty for children, young people, families and health care professionals
TSG: Consumer **Question to be addressed:** ***Can we improve the tolerability of this relatively inexpensive drug with long term safety data, before we move to expensive biologics with shorter safety profiles?***
Strategy/Comment: Disease modification in rheumatology increasingly involves MTX as the first Disease-Modifying Anti-Rheumatic Drug (DMARD) of choice for children and young people. Intolerance to MTX is a considerable burden on the individual and their families. This research would address concerns of parents, carers, children and young people by assessing the current evidence base detailing the side effects of methotrexate and the effects of the incidence of these side effects amongst the under 18 population of individuals with JIA in the UK. The severity of the problem would need to be assessed and how solutions can be implemented to reduce the humanistic burden of treatment , with an enhanced quality of life for children and young people and improved disease control as a result of improved treatment adherence with fewer side effects.
P: Children and young people with inflammatory disorders currently receiving methotrexate I: Regular treatment with methotrexate, oral and subcutaneous formulations C: Treatment with other anti-inflammatories (DMARD, NSAID or biologic therapy) O: Quality of life for children, young people and families, increased disease burden and discontinuation rates
TSG: Consumer **Question to be addressed:** ***In children and young people with JIA and related conditions, how can qualitative research amongst the public improve visibility and understanding of long-term rheumatological conditions, identifying strategic drivers for improving early diagnosis and future service provision and research delivery in paediatric rheumatology?***
Strategy/Comment:

P: Children and young people (10-18) with JIA and other rheumatological conditions I: Qualitative research amongst the public and families of children and young people with JIA C: Not applicable O: Improved service provision and research delivery
Scleroderma
TSG: Scleroderma **Question to be addressed:** ***Development of outcome measures for Juvenile Localised Scleroderma JLS (needed for clinical trial design and clinical care)***
Strategy/Comment: Robust widely accessible outcome measures are lacking in juvenile localised scleroderma. Recently developed skin scores for this disease have not been assessed in comparison to less-widely available non-invasive imaging. An objective outcome marker would facilitate clinical trials and routine clinical practice.
P: Children and young people with localised scleroderma I: Use of skin scores together with non-invasive imaging (ultrasound, thermography) C; Standard clinical examination O: Improve the assessment of disease activity
TSG: Scleroderma **Question to be addressed:** ***Developing an evidence base for efficacy of treatments in Juvenile Localised Scleroderma:***
Strategy/Comment: Only one RCT exists to provide evidence of efficacy and safety for JLS (methotrexate and corticosteroids versus placebo and corticosteroids. Further studies are required to provide evidence for treatment of children who do not respond to methotrexate.
P: Children and young people with active localised scleroderma who are methotrexate and mycophenolate mofetil naive I: Mycophenolate mofetil and corticosteroids C: Treatment with methotrexate and corticosteroids O: Shows non-inferiority in efficacy and safety
JIA (including JIA-associated uveitis)
TSG: JIA **Question to be addressed:** ***What is the Impact of Treating to Target on Disease Related Outcomes in Children and Young People with Juvenile Idiopathic Arthritis?***
Strategy/Comment : To improve disease related outcomes in children with all ILAR subtypes of juvenile idiopathic arthritis (JIA).

P: Under 16s with a new diagnosis of JIA. All ILAR subtypes of JIA will be eligible for inclusion.
I: Treating towards pre-defined disease activity targets (JADAS or JADAS3 Cut-offs corresponding with evidence based disease states including remission), according to a pre-determined treatment algorithm. The treatment algorithm will vary according to the ILAR subtype.
C: Routine clinical care (decisions made as normal by the treating physician).
O: Time to low disease activity and inactive disease (disease activity measures). Secondary outcomes to include:

- Proportions of patients achieving the different disease targets by specific time points (eg 6, 12 months)
- Costs of medications
- Joint imaging
- Quality of life
- Patient reported outcome measures (PROMS) and patient reported experience measures (PREMS)
- Health economic outcomes

Drug toxicity (MTX associated nausea, elevated liver enzymes, low white cell counts)

TSG: JIA

Question to be addressed:

How can we optimise access to specialist care for children and young people with musculoskeletal disease through triage in primary care?

Strategy/Comment:

To improve access to care for children and young people with significant musculoskeletal disease utilizing a triage service based in primary care supported by paediatric specialist teams.

P: Children and young people (CYP) under the age of 18 with musculoskeletal presentations to primary care; the term 'musculoskeletal presentations' is to be defined as part of the project.
I: Triage of all CYP referrals meeting minimum criteria (to be defined) to be assessed in primary care and placed in the correct treatment pathway with the correct clinician. Health care professionals in primary care will perform triage, up skilled and supported by paediatric specialist teams. Referral guidance (to be defined) into the triage service will include targeted education and support for primary care through partnership working with paediatric specialists. Cost consequence analysis involving impact of the triage on primary care, specialist care and families.
C: Routine clinical care (decisions made as normal by the treating primary care doctor)
O: For the CYP and parents: Prompt triage, accurate diagnosis and to see the 'right clinician' for assessment and management, with better experience and satisfaction with care, for CYP and families through reduced interval to diagnosis and access to the right clinical care.
For Primary Care; Provide clear guidance on when and to whom to refer CYP with MSK problems, through targeted education to improve knowledge about MSK problems in CYP and further improve triage effectiveness.
For the Provider; Improve efficiency so that referrals are appropriate and timely, with improved effectiveness of clinical care through reduced interval from presentation to diagnosis and early initiation of treatments. This will optimize capacity and resource allocation to deliver clinical care meeting standards of care and targets for specialist commissioning. There will be improved engagement of multidisciplinary teams with primary care to develop targeted education to optimise referrals and collaborative working.
For the Commissioner; Optimise spend and reduce geographical variation ensuring the health budget is providing greatest value. Identify where further investment is needed, to improve services including increase in appropriately skilled and trained manpower.
For the NHS; Improved collaborative working at the interface between primary, community and specialist care
For the CSG and NIHR; An exemplar of working towards evidence based best practice with improved collaborative working between primary and secondary care to better the clinical outcomes for CYP.

TSG: JIA

Question to be addressed: ***Does an antiemetic drug given at time of starting Methotrexate reduce the incidence of methotrexate-related nausea and vomiting (both anticipatory and post methotrexate nausea and vomiting)?***
Strategy/Comment
P: Children and young people with JIA starting methotrexate (MTX) for the first time. I: Standard dose of Ondansetron (4 mg or 8 mg according to age) 1 hour before and 8 hours after weekly MTX dose prescribed when starting MTX C: Standard practice O: Reduction of incidence of post-MTX nausea and vomiting using patients reported validated tool (MISS questionnaire) Reduction of anticipatory and associative MTX-related nausea and vomiting using patients reported validated tool (MISS questionnaire) Drug survival and need to escalate to a biologic therapy Health economic analysis
Auto-inflammatory
TSG: Auto-inflammatory **Question to be addressed:** ***Can we develop an 'Inflammation Gene Panel' for routine diagnostic use amongst auto-inflammatory syndromes?***
Strategy/Comment: 1. Funding applications secured from: Rosetree's and SOBI (as a funding partnership)- Jan 2015; AMR/GOSH grant application: submitted 18.11.2014 result pending 2015
P**:** Patients with suspected monogenic inflammatory disease I: Diagnostic application of next-generation sequencing using a targeted panel capturing 175, known monogenic autoinflammatory and related diseases C: Sanger sequencing of 6 genes currently available routinely in NHS in the UK O: Diagnostic efficiency and yield of this novel diagnostic approach in a routine NHS clinical setting with specific reference to sensitivity, and specificity.
Vasculitis
TSG: Vasculitis **Question to be addressed:** ***Can we improve the care provided for patients with Kawasaki Disease (KD)in the UK by creating networks of excellence?***
Strategy/Comment: Set up and develop UK Kawasaki disease network of excellence . Preliminary discussions to bring together the British Heart Foundation project regarding cardiovascular health after KD, and the BPSU work- Feb 2015 meeting planned for potential NIHR or BHF programme grant
P: Children and adult survivors of KD in the UK I: Multi-professional approach to the routine care of KD from cradle to grave C: N/A O: Pragmatic reported and clinically relevant outcome measures examining impact of network of excellence, including a. CAA interventions and outcomes b. Impact of new UK treatment guideline on CAA rate c. Transition to adult care d. Late cardiovascular Health and building on results of BHF study (see point 4 in column 3) e. Risk factors for IVIG resistance in Caucasian patients f. Links to Academia (genetics, biomarkers, Imaging and new treatment [e.g. IL1 blockade]) and Industry

TSG: Vasculitis **Question to be addressed:** ***Is tocilizumab more effective in the treatment of Takayasu arteritis than standard therapy alone: RCT (Rare disease design)?***
Strategy/Comment: 1. Preliminary discussions with Roche, and adult partners (David Jayne and Justin Mason) 2. Manuscript accepted for publication in Arthritis Research submitted (Aug 2014; revised Nov 2014, result pending) regarding preliminary exploration of TA outcome measure tools in the young
P: Children and adults with TA: UK based population I: Tocilizumab, methotrexate (MTX), and corticosteroid (experimental arm) VERSUS C: MTX, and corticosteroid (standard arm) O: Clinical: PVAS, ITAS2010, DEI-TAK, MRA/MRI; exploratory secondary endpoints: pVDI
TSG: Vasculitis **Question to be addressed:** ***Is there a genetic contribution to Anti-neutrophil cytoplasmic antibodies ANCA associated vasculitis affecting children and young people?***
Strategy/Comment: Links to auto-inflammation gene work, also with 100 000 genomes team in Cambridge (new collaboration) 1. First paediatric patients recruited to 100 000 genomes (Ken Smith and Adrian Thrasher collaboration- Oct 2014) 2. This work links to the auto-inflammation TSG work stream and the 100,000 genomes project (in collaboration with Cambridge team).
P: Children and young people with ANCA associated vasculitis I: Not applicable C: Not applicable O: Whole genome sequencing as part of 100, 000 genome project
TSG: Vasculitis **Question to be addressed:** ***Is anakinra effective in the management of Kawasaki disease?***
Strategy/Comment: A Proof of concept (quasi experimental, non randomized cohort) study. This is a 2-year open-label, prospective multicentre trial of Anakinra in patients with acute KD who failed to respond to a first infusion of IVIG within 48h. CI Isabelle Kone Paut
P: Patients with KD who have persistent fever 24 hours post first IVIG infusion I: 2 mg/kg anakinra (can escalate up to 6 mg/kg) for 15 days C: no comparator O: Primary end point: body (temperature <38 within 48 hours of treatment by anakinra (after the last escalation dose, if any necessary) by day 15. Secondary end points: CRP, physicians and parents VAS, CAA, adverse events.
Bone
TSG: Bone **Question to be addressed:** ***In children and young people with Osteogenesis Imperfecta (OI), does TGFb pathway-directed treatment, as opposed to standard of care treatment, improve quality of life as measured by OI-specific assessment tools?***
Strategy/Comment:

Justification:- Bisphosphonate therapy improves bone size and mass but does not clearly reduce fracture risk in OI; TGFb antibody therapy increases bone mass and restores bone architecture, reduces bone turnover and restores normal osteocyte density in mouse models of OI. Strategy:- Possible funding source MRC DPFS, Genzyme.
P: Children with OI I: TGFb Antibody C: Standard Care O: Restoration of bone microarchitecture at the distal radius and tibia.
TSG: Bone **Question to be addressed:** ***In children and young people with OI, does antisclerostin antibody, as opposed to standard of care treatment, increase trabecular bone mass in the axial and appendicular skeleton?***
Strategy/Comment: Justification:- Bisphosphonate therapy improves bone size and mass but does not clearly reduce fracture risk in OI; antisclerostin antibody therapy increases bone mass in adult osteoporosis and in mouse models of OI. Increasing trabecular bone mass is a major step in reducing fracture risk both in childhood and adult OI. Possible funding sources MRC DPFS/industry (Amgen)
P: Children and young people with OI I: Antisclerostin antibody C: Standard Care O: Increase of trabecular bone mass in the axial and appendicular skeleton.
TSG: Bone **Question to be addressed:** ***In 4-18 year olds with symptomatic hypophosphatasia, does asfotase alfa as opposed to current standard of care treatment improve motor function and reduce fatigue and pain?***
Strategy/Comment: Justification:- Myopathy is a major component of both infantile and some juvenile cases of HPP; the cause of the myopathy is unclear but it improves significantly with ERT. Funding source – Alexion (pharma) and EU sources; insufficient UK patients to allow a meaningful study to be undertaken
P: 4-18 year olds with symptomatic hypophosphatasia I: Asfotase Alfa C: Standard care O: Improved motor function and reduction in fatigue and pain.
TSG: Bone **Question to be addressed:** ***In children and young people with primary hypoparathyroidism, does the use of human PTH as replacement therapy as opposed to standard of care (1 alpha calcidol) prevent hypercalcemia and nephrocalcinosis?***
Strategy/Comment: Funding strategy:- EME - Bone and PTH call. This is going forward via the NIHR RD TRC
P: Children and young people with hypoparathyroidism I: Human PTH as replacement therapy C: Standard care (1 alpha calcidol) O: Prevention of hypercalcemia and nephrocalcinosis
TSG: Bone **Question to be addressed:**

In the treatment of children with vitamin D deficiency is the use of single high dose treatment (I) as safe and effective as daily treatment?

Strategy/Comment:

Most children with vitamin D deficiency in the UK are treated with daily treatment for a duration of 8 to 12 weeks. However single high dose regimes are used effectively elsewhere in the world although there is some concern about potential side effects. Does single high dose treatment improve compliance and is it as safe and effective as daily treatment?

P: Children and young people with vitamin D deficiency
I: Single high dose treatment
C: Daily treatment
O: Safety and efficacy

TSG: Bone

Question to be addressed:

In children and young people with chronic recurrent multifocal (or unifocal) osteomyelitis, is pamidronate or adalimimab effective in reducing flares and healing lesions?

Strategy/Comment:

Chronic recurrent multifocal osteomyelitis (CRMO), is a poorly researched but potentially disabling condition with no evidence base for treatment but where major treatment with bisphosphonates or biologic drugs are used off license and with unit to unit variation. The immediate effect of local or multifocal osteitis is of pain, bony enlargement with effects dependent on site of inflammation for example causing thoracic outlet syndrome, difficulties in chewing if the jaw is involved, muscle atrophy and chronic pain. Systemic inflammation and arthritis occur in a significant proportion. In the long term as many as 49% are reported to suffer pathological fractures often with vertebral collapse. Skeletal deformities occur in 58%. A significant number evolve into spondylarthritis, psoriatic arthritis or with associated inflammatory bowel disease. The morbidity of the disease is such that treatment is required in at least 2/3rds of patients and as this is currently with drugs that have serious effects or are expensive it is important that we achieve an evidence base for management.

CRMO, either because of greater awareness and diagnosis appears to be on the increase. A variety of therapeutic interventions including; NSAID, steroids and more recently bisphosphonates are used to reduce the frequency and severity of the inflammatory episodes. Whilst the consensus amongst paediatric rheumatologists is that bisphosphonates are effective there is little evidence base for this assertion. Furthermore the impact of bisphosphonates on the young person's otherwise healthy bone remains unknown. At the same time, use of biologic agents have been noted to be of potential benefit. There is a need for a clinical trial to address this issue.

P: Children with CRMO or unifocal recurrent osteomyelitis
I: Treatment with a biologic agent in combination with NSAID treatment +/- a weaning dose of steroids
C: Treatment with Pamidronate with NSAID treatment +/- a weaning dose of steroids
O Reduction and severity of osteomyelitic events; Imaging lesion size, numbers and severity based on whole body diffusion weighted MRI

- Pain score: 0-10 VAS, 0= no pain, 10 = worst pain ever
- Cumulative prednisolone dose
- Disability score: CHAQ
- Quality of life score: CHQ
- Physician global assessment
- Health economics

JSLE

TSG: JSLE

Question to be addressed:
Are the new SLICC criteria for JSLE more robust than the ACR criteria in JSLE, and in patients with probable/evolving JSLE, what are the early predictors of meeting ACR criteria for SLE in the future?

Strategy/Comment:
To analyse the existing data (from 2006 -2015 onwards).
Results to be published / promoted to improve awareness of patients likely to develop true lupus and to warrant earlier treatment.

P: Patients recruited to the UK JSLE Cohort Study with probably/evolving JSLE.
I: N/A
C: Comparison of clinical features in patients with probable JSLE (who do / do not go on to develop SLE within 5 years) at 6 months, 12 months and 18 months post presentation to paediatric rheumatology.
O: Description of early features which are predictive of progression on to definite JSLE, helping to define those that warrant earlier / more aggressive treatment.

TSG: JSLE
Question to be addressed:
Are the individual system domains of the BILAG score sensitive to change in children and young people (CYP) with JSLE, and therefore suitable for use in the management of CYP with JSLE, and as an outcome in clinical trials which focus on particular organ systems?

Strategy/Comment:
Over next 3 years – To use Cohort data to undertake such analysis accompanied with retrospective case note review where necessary. Brunner et al (ARTHRITIS & RHEUMATISM, Vol. 42, No. 7, July 1999, pp 1354–1360) have looked at the sensitivity of the overall score as compared with SLEDAI / SLAM. They did not look at individual domain specific scores. Marks et al (Rheumatology 2004;43:1186–1189) compared the total BILAG scores, patient visual analogue scores and physician (VAS) in a lupus nephritis group (biopsy confirmed) and non LN patients cross-sectionally and identified important differences. They did not look at responsiveness over time.

P: Patients within the UK JSLE cohort study followed up for at least 6 months after the development of their first flare (domain specific BILAG A or B).
I: Review of UK JSLE Cohort database data BILAG scoring at up to 4 occasions during the disease course: at the time of diagnosis, 6 months post-diagnosis, at the time of a flare (a deterioration in clinical presentation or laboratory results requiring initiation or increase of either corticosteroids or “second-line” drugs), and 6 months post-flare.
C: Comparison between responsiveness of the scale for flares in different organs.
O: Domain specific BILAG score to be looked at in relation to 1) it’s responsiveness to change in treatment regimens used in real world clinical practice; 2) responsiveness to the change in the physicians’ global assessment; 3) responsiveness to change in patient global assessment.

TSG: JSLE
Question to be addressed:
To identify biomarkers for monitoring disease activity, defining areas of organ involvement and predicting outcome.

Strategy/Comment:
The methods of assessing disease severity are always open to discussion in relation to children and young people with lupus. Many believe that clinical assessment should take precedence over laboratory investigations. However, it is well recognized that laboratory markers may precede active disease whilst active disease may exist in the absence of laboratory markers”. Biomarkers that can help to monitor the disease and define areas of organ involvement are therefore required to improve monitoring and longer term outcomes. Areas which would particularly benefit (lupus nephritis, neurological involvement, CV risk, early predictors of damage to identify those in need of early / aggressive treatment).
This is linked in with outstanding priority - To Determine cross sectional and longitudinal biomarkers of

cardiovascular morbidity and mortality in JSLE.
P: Participants of the UK JSLE Cohort Study I: Identification and assessment of novel biomarkers within clinical samples collected from UK JSLE Cohort Study patients (urine, plasma, serum, genetic material, renal biopsy tissue (ethics pending)) C: Assessment of organ specific disease activity using investigation results collected within routine clinical care. O: Novel biomarkers which will improve the monitoring of global and organ specific JSLE disease activity (e.g. lupus nephritis, neurological involvement) and help stratify treatment dependent on individualized patient risk (e.g. CV risk, those at high risk of damage)
TSG: JSLE **Question to be addressed:** ***Can we achieve International consensus on a minimal core data set (from history examination and laboratory markers) for use in care of patients with JSLE and to inform future clinical trials?***
Strategy/Comment: A minimal core data set is essential to ensure that internationally data collection is standardized and fit for purpose in clinical care and the research setting.
P: A working group of internationally-representative JSLE experts. I: International experts to propose a provisional minimal dataset using clinical / laboratory variables which are already contained within current national and international collaborative databases. Consensus methodology to be used to agree the minimal dataset, informed by published literature and in-depth analysis of disease activity data collected by the UK JSLE Cohort Study. C: Not applicable O: An internationally agreed minimal core dataset with potential to improve collaboration and enable the analysis of the largest possible number of JSLE patients to improve understanding of the disease. Such data to be included as targets within a future 'treat to target' trial in JSLE.
TSG: JSLE **Question to be addressed:** ***What is the impact of treating to target in JSLE (combining work on core data set/disease activity measure/evolving JSLE and biomarkers) to improve disease related outcomes in children and young people with JSLE?***
Strategy/Comment: Treat to target (combining work on core data set/disease activity measure/evolving JSLE and biomarkers)
P: Children and young people with a new diagnosis of JSLE. I: Treating towards pre-defined disease activity targets (as defined above), according to a pre-determined treatment algorithm. C: Routine clinical care. O: Time to low disease activity / inactive disease / remission (disease activity measures) and outcomes at defined time-points (e.g. 6 or 12 months post disease onset or flare), steroid use, quality of life, patient reported outcome measures and patient reported experience measures (PREMS)
Global Themes – Shared with other TSGs
Question to be addressed which is also shared with all other TSGs: ***To identify, describe and understand the barriers and facilitators faced by young people, parents / carers, and the spectrum of healthcare professionals (HCPs) involved in the care of patients with connective tissue disorders at diagnosis and during transition to adult healthcare.***
Strategy/Comment: Transitional care within CTDs is a multifaceted, multi-professional process aiming to empower YP to take on responsibility for their health, optimize outcomes and mitigate long-term comorbidities. To date, there are

no studies of transitional care in CTDs despite this representing a critical pivotal time.
P: Young people (YP) with CTDs between the ages of 14-25, their parent/guardian and healthcare professional involved in their care. I: literature review, surveys of YP with CTDs / HCP's involved in their care, and in-depth semi-structured interviews. C: Comparison of the experiences of the different groups (YP of different ages, parents, HCP's). O: Strategies to improve access to specialist care at these crucial times. Key recommendations will emerge for a national collaborative strategy to improve access to specialist care and ultimately clinical outcomes for YP with CTDs.
Question to be addressed: ***To ensure that all patients with connective tissue disorders in the UK with a biologic agent are given the opportunity to contribute to the long-term collection of safety and efficacy data. The same methodology could be used for all other non-JIA indications***
Strategy/Comment
P: Patients with CTD on any biologics throughout the UK. I: Participation in an observational study that could be linked to existing biologic registries, or bespoke C: Patients with CTD on other disease modifying treatment (e.g. MMF, azathioprine etc). O: Description of use, real world safety and efficacy of biologics in CTDs.

7. CSG Clinical Research Strategy – Summary of Development

- The evolution of this Strategy reflects an exciting time in Paediatric Rheumatology in the UK and much has been achieved already by a small specialty with large clinical burdens. It has been the fruit of the expertise and strong collaborative ethos of the CSG, integrated closely into the established clinical research community of UK Paediatric Rheumatology, supported by the unique partnership that the CSG forged between the expertise and extensive resources provided by the NIHR CRN: Children and Arthritis Research UK**.**
- This report has outlined the on-going work of the NIHR CRN: Children /Arthritis Research UK Paediatric Rheumatology CSG since its inaugural meeting 28th January 2008 in developing its Clinical Research Strategy, according to the Arthritis Research UK 's Clinical Trial Initiative.
- It has outlined the methodology used to develop this evolving strategy, ensuring on going open and inclusive participation of all stakeholders in the process. In particular, it has outlined the work of its Topic Specific Groups in developing and setting key priorities.
- The CSG will continue to seek consultation and comment from all relevant stakeholders. In addition it will review its processes and procedures in a timely manner to ensure it continues to reflect the clinical priorities of the Paediatric Rheumatology in a comprehensive and inclusive way.
- In keeping with its remit to develop a comprehensive portfolio of key research priorities for clinical trials and related studies covering the entire spectrum of major disease areas in paediatric rheumatology in the UK, this revised strategy document embraces the key priority areas.
- In keeping with its remit to define priorities across the entire spectrum of paediatric rheumatology, the CSG clearly noted that the topic-specific groups are not ranked in any way, and specialty areas are not competing against one another in this document.
- The CSG offers a real opportunity for the development of a comprehensive, nationally agreed and scientifically robust research strategy for clinical trials and related studies in paediatric rheumatology. It is anticipated that the CSG in this way will continue to contribute to major advances in the treatment of rheumatological and musculoskeletal diseases affecting children.

CSG Approval of its Clinical Research Strategy

The CSG considers all feedback from its consultation processes in great detail and comments and suggestions continue to be incorporated and adapted with time, making this a current working document.

The CSG committee has approved this latest version on 6th July 2015.

Review of CSG's Clinical Research Strategy

- The CSG recognises that priorities will develop and evolve over time, and looks to respond continually to the growing clinical demands and developments of the research community nationally and internationally to constantly review and revise this strategy in a timely manner
- All stakeholders may contribute to this process.
- This published strategy (dated 1st July 2015) will form the working basis of its current pro-active activity for the rest of 2015, 2016 and 2017.
- Where an Expression of Interest is submitted to the CSG that does not match current priorities as outlined in its Research Strategy, the CSG will consider the importance of topic and whether it needs included in subsequent updates of this process.
- Formal review of the Clinical Research Strategy will take place early in 2017.

Many thanks to everyone who has work tirelessly and contributed in so many ways to the development of this Clinical Research Strategy.

Professor Michael W Beresford
Chair, NIHR CRN: Children / Arthritis Research UK Paediatric Rheumatology CSG

On behalf of the entire CSG (see Appendix)

8. Appendix: CSG Membership (July 2015)

Title	First Name	Last Name	Job Title	Address
Professor	Michael	Beresford	Professor of Child Health, Honorary Consultant Paediatric Rheumatologist	Institute of Women's & Children's Health, Alder Hey Children's NHS Foundation Trust
Dr	Eileen	Baildam	Consultant Paediatric Rhuematologist	Alder Hey Children's NHS Foundation Trust
Professor	A. V.	Ramanan	Lead Consultant in Paediatric Rheumatology Honorary Reader	University of Bristol, Bristol Royal Hospital for Children & Royal National Hospital for Rheumatic Diseases, Bath
Mrs	Sharon	Douglas	Consumer Representative	Consumer Representative
Dr	Jacqui	Clinch	Consultant Paediatric Rheumatology	Bristol Royal Hospital for Children, Bristol
Prof	Nick	Bishop	Professor of Paediatric Bone Disease	Academic Unit of Child Health, Sheffield Children's NHS Foundation Trust
Dr	Madeline	Rooney	Senior Lecturer in Rheumatology & Consultant Rheumatologist	Queen's University Belfast, Musgrave Park Hospital, Belfast
Prof	Wendy	Thomson	Professor in Complex Disease Genetics	Musculoskeletal Research Group, Stopford Building, University of Manchester
Mr	Simon	Stones	Consumer Representative	Consumer Representative
Dr	Ethan	Sen	Specialist Registrar in Paediatric Rheumatology	Bristol Royal Hospital for Children, Bristol
Dr	Clare	Pain	Consultant Paediatric Rheumatologist	Dept of Rheumatology, Alder Hey Children's Hospital
Dr	Kate	Armon	Consultant Paediatrician	Norfolk & Norwich University Hospital Jenny Lind Children's Department
Ms	Elaine	Haggart	Highly Specialised Paediatric Physiotherapist	Great Ormond Street Hospital London WC1N 3JH
Dr	Hannah	Batchelor	Formulations Research Fellow	
Mrs	Catherine	Wright	Consumer Representative	Consumer Representative
Mrs	Debbie	Janson	Consumer Representative	Consumer Representative
Dr	John	Ioannou	Reader and Honorary Consultant in Adolescent and Adult Rheumatology	UCLH/ Great Ormond Street Hospital

Dr	Dan	Hawley	Consultant Paediatric and Adolescent Rheumatologist	Department of Paediatric Rheumatology, Sheffield Children's Hospital
Dr	Kiran	Nistala	Wellcome Trust Clinician Scientist/ Honorary Consultant in Paediatric Rheumatology	UCL Centre for Rheumatology
Dr	Janet	McDonagh	Clinical Senior Lecturer in Paediatric and Adolescent Rheumatology	Centre for Musculoskeletal Research, University of Manchester; Manchester Children's Hospital
Dr	Despina	Eleftheriou	Senior Lecturer in Paediatric Rheumatology /Consultant Paediatrician	Institute of Child Health, University College London
Dr	Eve	Smith	Clinical Research Fellow	Institute of Women's & Children's Health, Alder Hey Children's NHS Foundation Trust
Ms	Claire	Duong	Clinical Nurse Specialist CYP	Paediatric Research Unit, Newcastle Upon Tyne Hospitals