

# **Arthritis Research Campaign (arc) & UK Medicines for Children Research Network**

## **MCRN/arc Rheumatology Clinical Study Group**

### **1. OVERVIEW OF INITIATIVE**

#### **1.1 The Vision**

The vision is of **arc** in partnership with the UK Medicines for Children Research Network (MCRN), other funders (such as MRC) and industry developing a comprehensive research programme in paediatric rheumatology. This will permit the testing of both new and existing interventions, based on a nationally agreed and scientifically robust research agenda, across the major rheumatological diseases affecting children. In achieving this, there will be a transformation of clinical practice which will drive both knowledge advance and quality of care.

#### **1.2 Overview of Proposal**

A comprehensive programme of clinical trials and clinical studies will be developed to cover the major disease areas in paediatric rheumatology with the aim of a rapid and effective evaluation of the role of both new and existing interventions. The strategy is designed to fit in with the topic specific component of UK Clinical Research Network aimed at children: Medicines for Children.

The aim will be to develop a scientifically robust research agenda, which will be delivered efficiently and effectively by the MCRN Local Research Networks (LRNs) with the active collaboration of industrial partners.

**arc's** role will be:

1. In partnership with MCRN, to support the establishment of an MCRN/**arc** Rheumatology Clinical Study Group to drive the research agenda within the field of paediatric rheumatology
2. To provide robust scientific evaluation of emerging research agendas in paediatric rheumatology
3. To support the conduct of pilot and other feasibility studies prior to undertaking full scale studies
4. To support the research costs of such full scale studies in partnership with other funders including NIHR, MRC and industry.

In addition **arc** will establish resource for clinical trial methodological support to enable this enhanced programme of research to run successfully

### **2. BACKGROUND**

#### **2.1 Clinical Research and Clinical Practice**

Interventions in clinical practice are based on physician choice built on experience, bias and data from clinical trials. The clinical trials agenda is typically set by industry and regulators and less frequently by clinical investigators. Whereas this approach is essential in progressing the licensing of new agents, key questions remain unaddressed about therapeutic and prevention intervention strategies, particularly in childhood disease. Thus head to head comparisons of new agents, novel indications for existing agents or

combinations of agents and use of patient stratification to determine therapeutic pathways are rare. There are many barriers to applying a research agenda to routine practice including financial, bureaucratic and the requirement for physicians to agree to work collaboratively.

## 2.2 Clinical Trials Initiative of arc – Historical Perspective

Since the late 1990's **arc** created a Clinical Trials Initiative to sponsor and support investigator-initiated clinical trials in rheumatology. This had some novel aspects compared to other research funding streams:

- i. The initiative was undertaken as a collaborative venture between the British Society of Rheumatology, the MRC (through the MRC Clinical Trials Unit) and the **arc** which was the overwhelmingly dominant funding body
- ii. The research agenda was based on extensive consultation with the clinical rheumatological community in regards to priority for randomised clinical trials. The formation of a large subcommittee reviewed proposals, judged those most deserving of further study and provided mentoring to produce robust trial designs with the aim that the trials the rheumatological community wanted to see funded could be worked up into a scientifically acceptable proposal, adhering to MRC standards
- iii. There was joint funding of a senior researcher post, based in the MRC Clinical Trials Unit, to provide methodological support and statistical advice.

The clinical trials subcommittee monitors the progress of supported trials as well as establishing a Data Monitoring and Ethics Committee for each trial.

Trials for this specific funding stream have been focussed on multicentre studies, requiring more than the standard 3 years project grant support and typically costing around £0.5 million, compared to the standard project grant of £150-200K

Since this programme commenced there have been 19 trials supported by this initiative at a total cost of £7.3m. Virtually all of these trials are still either at the analysis stage or are still ongoing. The cost of trials is obviously high and **arc** has been asked to fund the entire cost of the trial. Currently **arc** funds 1-2 new trials per year under this scheme.

Although this initiative has been very successful there have been a number of major problems identified:

- Recruitment has been challenging and has led to the abandonment of 2 trials and extensions granted to 2 more
- Current ethics and governance framework of trials has acted as a disincentive for local centres to recruit
- Absorbing the entire cost of trials limits the number of trials **arc** is able to fund

The establishment of the clinical trials initiative did not preclude small, predominantly single centre clinical trials being submitted to the standard project grant funding (or via a fellowship or educational programme). Since 2000, **arc** has funded 25 trials, at an average cost of around £100K (total cost £2.9M). Only one of these was for conventional pharmacological interventions with most being either for rehabilitation, educational or other approaches to management

Of note, there has been an increase in the regulatory burden for those conducting trials both as a consequence of EU regulations and the requirements to satisfy NHS trusts in regards to their research governance procedures

## 2.3 UK Clinical Research Network (CRN)

The Department of Health's document in 2006 "Best Research for Best Health" committed the government to a substantial boost to the support and funding of clinical research within the NHS. The key component of the strategy is the development of the UK Clinical Research Network (CRN) which comprises a managed set of Clinical Research Networks to facilitate the conduct of randomised trials and other well designed studies. There were initially six topic specific areas which included "Medicines for Children." The MCRN programme is now in operation. Acceptance of a trial into a CRN:

- Provides the NHS infrastructure to support clinical research
- Funds NHS support costs to facilitate the conduct of, and remove barriers to, research in the NHS (and equivalent organisations in Scotland, Wales and Northern Ireland).

The major relevance to **arc** is that the acceptance that the research portfolio will be driven by key funders (such as **arc**) with financial support from the National Institute for Health Research ([http://www.nihr.ac.uk/programmes\\_research\\_programmes.aspx](http://www.nihr.ac.uk/programmes_research_programmes.aspx)) through various funding streams such as the Research for Patient Benefit (<http://www.nihr-ccf.org.uk/site/programmes/rfpb/default.cfm>) projects, and HTA commissioned and response mode grants. In addition, studies adopted by MCRN will be supported by the MCRN LRNs which have been developed by MCRN as a means of delivering on a programme of clinical trials and other well-designed studies relevant to this topic in the NHS.

In summary, by **arc** supporting and developing a process whereby there is a national agreed strategy in cogent areas of interest, subject to robust peer review and open to national competition, eligibility criteria will be met such that MCRN will then be in a position to adopt the study portfolio and provide the support as listed above.

In partnership with MCRN, **arc** is therefore in a position to make a quantum shift in developing a clinical trials and clinical research programme, prioritised on robust scientific and public health grounds, but with substantial infrastructure support from the NHS.

## 2.4 Testing of Novel Agents: Role of Industry

Although target discovery is still one of the major goals of basic and translational research funded by **arc**, the development of new compounds, both small molecules and biologics, will come from industry. The recent Cooksey report ([http://www.hm-treasury.gov.uk/media/56F/62/pbr06\\_cooksey\\_final\\_report\\_636.pdf](http://www.hm-treasury.gov.uk/media/56F/62/pbr06_cooksey_final_report_636.pdf)) highlighted the difficulties industry faces in the UK environment in the testing of novel agents, particularly in Phase 1 and Phase 2 clinical trials. The capacity and organisation of the NHS and the links with clinical academics in theory should put the UK in a strong position to be the appropriate testing bed for new agents. This will be facilitated by the existence of a strong paediatric rheumatology clinical network capable of delivering a clinical trials programme in paediatric rheumatological diseases. **arc** will play a pivotal role in this by:

- i. Making a major contribution to the scientific agenda and
- ii. Providing resources for add-ons, such as pharmacogenetic and other studies, that will add to the knowledge base of specific interventions.

**arc**'s key mission is to undertake research that will lead to new therapies for patients with arthritis and related musculoskeletal conditions. It needs therefore to play a more central work in working with those who are developing such products

### **3. Establishing a Clinical Studies Group in Paediatric Rheumatology**

The cornerstone of the initiative is the establishment of an MCRN/**arc** Rheumatology Clinical Study Group (CSG). This will have a dual role of advising both the MCRN (and its Trials Adoption Committee) and **arc** in defining its research priorities in paediatric rheumatology and in developing a portfolio of clinical studies supported by **arc**. Its remit will be that of all MCRN CSGs to:

- be responsible for developing and overseeing its portfolio of studies
- propose and develop new trials and other well-designed studies
- consider trials proposed by others, and advise the MCRN Trial Adoption Committee
- provide specific advice to investigators
- ensure consumer involvement in all activities

(<http://ctuprod.liv.ac.uk/mcrnweb/images/stories/csg/mcrn%20csg%20remit%20document.pdf>)

MCRN, in partnership with **arc**, will oversee the selection and monitoring of the CSG.

The programme for the MCRN/**arc** Rheumatology CSG will have 3 stages:

#### **3.1 Establishment of an MCRN/**arc** Rheumatology Clinical Study Group**

The MCRN/**arc** Rheumatology CSG will be established by MCRN.

##### **Chair of MCRN/**arc** Rheumatology CSG**

A Chair will be appointed to head the CSG's activities. Responsibilities, duties and qualities of the Chair will be in keeping with other MCRN CSG Chairs (<http://ctuprod.liv.ac.uk/mcrnweb/images/stories/csg/mcrn%20csg%20remit%20document.pdf>).

Appointment will be following national advert and competitive interview with an interview panel including the Director of MCRN and Medical Director of **arc** (or appropriate representatives).

##### **Membership of the MCRN/**arc** Rheumatology CSG**

Membership of the MCRN/**arc** Rheumatology CSG will be fluid and inclusive.

Involvement of and representation by the major stakeholders in UK clinical and academic paediatric rheumatology is essential.

Of particular importance is the British Society for Paediatric and Adolescent Rheumatology (BSPAR). BSPAR is the specialist society within the Royal College of Paediatrics and Child Health representing all health care professionals involved in the care of children and adolescents with rheumatic disease in the UK. It has been successful in collaborative projects and research networks and is keen to develop further collaborative research. It is important that the BSPAR community is involved in and committed to the CSG and that it is seen to be inclusive. To promote this, the Chair will need to communicate effectively with BSPAR and it is likely that the Chair will be co-opted to the BSPAR executive.

At the same time, other important stakeholders will have the opportunity to be represented in the CSG. These may include representatives of major established paediatric rheumatology research networks, researchers with robust innovative ideas wanting support and representatives of the major clinical centres where patient recruitment occurs.

Members' duties, qualities and their appointment process to the CSG will be as outlined for all MCRN CSGs.

<http://ctuprod.liv.ac.uk/mcrnweb/images/stories/csg/mcrn%20csg%20remit%20document.pdf>

### **Resource to support the MCRN/arc Rheumatology CSG**

The arc will provide support to the CSG Chair of: one Programmed Activity of time per week; travel and other costs associated with CSG meetings by an annual grant of around £10K to the MCRN; an additional contribution to the MCRN CSG Administrator's salary, equivalent to 10% of the total costs per annum and whose remit is described in: (<http://ctuprod.liv.ac.uk/mcrnweb/images/stories/csg/mcrn%20csg%20remit%20document.pdf>).

Subject to review, appointment of the Chair of the CSG and maintenance of CSG status will be for a minimum period of 3 years, with a possible extension for a further 2 years.

### **Task and Remit of MCRN/arc Rheumatology CSG**

- The major remit of the CSG under the direction of the Chair will be that of all MCRN CSGs (see section 3 above)
- It will review the portfolio of trials in paediatric rheumatology supported by **arc**, NIHR and other funders and agree a priority list of major clinical research goals. The CSG will advertise for submissions of protocols needed to satisfy the goals, to be done in collaboration with the CSG. These protocols where relevant will also include the design of pilot and feasibility studies to provide proof of concept for definitive studies in terms of recruitment, data acquisition.
- The CSG will be encouraged to consider the research 'add-ons' outside, for example, of NHS or industrial interest, such as pharmacogenetic and qualitative studies.
- The CSG will also be asked to review proposals that may be received by MCRN or **arc** from outside the CSG to assess how they will fit in the portfolio or assist with their development
- The CSG will be expected to work in close collaboration with other MCRN CSGs and **arc**-associated topic specific research networks in all areas of mutual interest

### **Outputs of the MCRN/arc Rheumatology CSG**

As well as the documentation and recommendations expected of all MCRN CSGs, the CSG will produce an annual report to **arc** and MCRN. Each proposed study will need to provide strong scientific and clinical need/public health justification with additional justification for the pilot and feasibility aspects that were being requested. Pilot studies could include establishment of cohorts, evaluation of assessment procedures, development of endpoints and intermediate biomarkers.

Pilot studies could be for novel therapies and might be part of a Phase 1 or Phase 2 development programme. The CSG should have entered into collaborative links with industry which will protect the independent nature of **arc**'s contribution to the research. Funding will then be on a joint basis particularly if there were distinct differences in objectives between the partners.

### **Subgroups of the CSG**

Depending on the nature of the programme and the wishes of the CSG, it may be appropriate to establish subgroups with specific targets of interest such as specific disorders (eg JIA, JSLE, JDM, childhood scleroderma, etc..) while recognising the disease specific research networks already established within paediatric rheumatology and BSPAR. It is likely that any subgroups will need additional funding to that described above. It will be part of the peer review process of the output of the CSG that appropriate priorities and weighting is given to the divergent subgroup interests. The Chair of the CSG will be expected to take an active role in supporting any sub-groups within the area.

## **3.2 Selection, review and conduct of pilot studies**

The overall portfolio of trials and other well-designed studies, in terms of their priority and feasibility, together with the specific proposals for pilot studies, will then be subject to peer review and competitive funding application to **arc** or other funding bodies. The portfolio of studies should be mutually consistent in terms of potential patient recruitment and scientific strategy. Once accepted for funding by **arc** the pilot studies will be adopted by MCRN and recruitment will take place. **arc** will support any of the research add ons. The goal is that by the end of these studies (which might not be necessary for each of the proposed studies) all the necessary aspects will be covered that will enable the production of a protocol for definitive study that will reach MRC standards.

### 3.3 Submission of and Support of Definitive Trials

At the end of the pilot stage, the CSG will reach a decision whether to go for a full study which typically will be a clinical trial but could in some circumstances be an observational study. Working up the design of the study will take advantage of an enhanced Clinical Trials Support resource that is to be established by **arc** (see below). Full definitive proposals will be subject to competitive funding application and external peer review followed by their automatic adoption by MCRN.

- Discussions with MCRN will permit an accurate estimate of costings of the 'base study', though any research add-ons will be costed separately
- MCRN will advise on the LRN provision that will deliver the recruitment and data gathering.
- It is accepted for rare disorders that the trial activity might take place within certain specified centres
- Where appropriate collaboration with industry will be needed in relation to provision of the interventions (and matched placebos where relevant) and that regulatory requirements were being adhered to – this will be done in collaboration with the MCRN Industrial liaison officer
- Following successful peer review and adoption, MCRN will provide access to the NHS resource necessary to deliver and **arc** will provide the additional research costs
- As with current **arc** funded trials there will need to be properly formulated Trial Steering Groups and Data Monitoring Boards with the support of **arc**

### 4. Clinical Trials Support Unit

- Expertise is required in terms of trial design, data management, steering trials through the ethics and governance process, and coordinating trials. It is of prime importance that the CSG in Paediatric Rheumatology has access to the expertise and resource of a Clinical Trials Support Unit to help in this process
- The UK MCRN Clinical Trials Unit (MCRN CTU) based in Liverpool has been established to conduct and provide support for clinical trials undertaken within the MCRN and is the only CTU in the UK, out with neonatology and childhood malignant disease which is developing specific expertise in paediatrics.
- To further this initiative, the **arc** will develop close links with the MCRN CTU. **arc** will monitor this work closely and consider whether there is a need to a specific resource to support trials in paediatric rheumatology within the MCRN CTU.

## **Chair of MCRN/arc Rheumatology Clinical Study Group**

### *Further Particulars*

The UK Arthritis Research Campaign (arc) is planning to make a major investment in supporting clinical trial and related research. It seeks to appoint an individual with a track record in research leadership to direct the development of nationally agreed research programmes in clinical trial and related areas of research in paediatric rheumatology.

The UK Medicines for Children Research Network (MCRN) has been established to facilitate the conduct of randomised trials and other well-designed studies of agents and therapies for children, including those for prevention, diagnosis and treatment. MCRN Clinical Studies Groups (CSGs), under the leadership of a Chair, have a remit to advise investigators, propose and develop new trials, recommend studies to the MCRN Trials Adoption Committee and ensure consumer involvement in all activity.

MCRN are to establish a new **MCRN/arc Rheumatology** CSG and in partnership with arc, they looking to appoint a Chair of this CSG.

Applicants should submit a CV together with a 1000 word statement on their background in directing collaborative research in paediatric rheumatology and their potential vision as to how they will develop the proposals set out for paediatric rheumatology.