A new paradigm for musculoskeletal clinical trials in the UK: the Arthritis Research Campaign (ARC) Clinical Studies Groups initiative

A. Silman

In October 2007, the UK Arthritis Research Campaign (ARC) launched a new approach for the support of clinical trials and related research in the UK. The initiative depends on a partnership between ARC, the UK Clinical Research Network (UKCRN) and the pharmaceutical and related industry. The aim is to develop nationally agreed strategic plans for intervention research for the major musculoskeletal disorders. These will range from testing experimental therapies to novel approaches/ways of using existing interventions, taking advantage of the opportunities afforded for the enhanced support for clinical trials promised by the establishment of local research networks within the National Institute for Health Research (NIHR) Comprehensive Clinical Research Network (CCRN). The initiative encourages greater collaboration with industry with a move to enhance industrial support for research strategies prioritized by the key stakeholders of health care professionals and patients.

Background

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 often but less frequently by clinical investigators. Whereas this approach is essential in progressing the licensing of new agents, several key questions remain unaddressed about therapeutic and prevention intervention strategies. 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 indeed several barriers to applying a research agenda to routine practice including financial and bureaucratic requirements and the requirement for physicians to agree to work collaboratively.

ARC clinical trials initiative

In the late 1990s, ARC created a specific initiative to sponsor and support investigator-initiated clinical trials in rheumatology, with the first grant being awarded in June 2000. From ARC’s perspective there were some novel aspects compared with its other research funding streams.

- The initiative was undertaken as a collaborative venture between the British Society for Rheumatology and the Medical Research Council (MRC) [through the MRC (CTU) Clinical Trials Unit] though ARC was the overwhelmingly dominant body in regard to funding.
- The research agenda was based on extensive consultation with the clinical rheumatological community in regard to priority for questions to be addressed in randomized clinical trials. A mentoring process was developed, especially for those with limited clinical trials experience 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 sound/high-quality proposal, adhering to MRC standards.

Since this programme commenced there have been 19 trials supported by this initiative at a total cost of £7.3 million. Virtually all of these trials are either at the analysis stage or are still ongoing. The cost of trials is high and ARC typically funded the entire cost of the trial although some service support costs were met.

Although this initiative has been very successful in engaging with the rheumatological community and has stimulated investigator-initiated clinical trials that would otherwise not have been conducted, there have been a number of major problems:

- recruitment has been challenging and indeed has led to the abandonment of two trials and extensions granted to two more;
- in this regard, the current ethics and governance framework surrounding trials has acted as a disincentive for local centres to recruit;
- absorbing the entire cost of trials limited the number of trials ARC is able to fund; and
- difficulty in accessing the support available from the NHS to support research.

In addition, the initiative could be criticized for developing a portfolio of trials that has, as its main focus, aimed to provide an evidence base for current clinical practice. As a consequence, the programme has not been at the forefront of testing novel therapies or novel indications of new therapies.

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 also funded 25 trials, at an average cost of ~£100 K (total cost £2.9 million), with only one for conventional pharmacological interventions and most being either for rehabilitation, educational or other approaches to management.

NIHR Comprehensive Clinical Research Network

The Department of Health’s document in 2006 ‘Best Research for Best Health’ [1] 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 (UKCRN), which comprises a managed set of CRNs to facilitate the conduct of randomized trials and other well-designed studies. There were initially six topic-specific areas, including Medicines for Children, followed by a Primary Care Research Network, but this concept has now been rolled out into a Comprehensive Local CRN (LCRN), covering those disease areas not covered by the original six topics. Adoption of a project by CCRN brings considerable benefits to the investigators, in that it:

- provides the NHS infrastructure to support the research;
- funds NHS support costs to facilitate the conduct of research in the NHS, for example, in terms of recruitment of patients, monitoring treatment response and adverse events, investigations and pharmacy costs.

Processes are under way to develop parallel systems in Scotland, Northern Ireland and Wales. To access this vital source of resource and support it is necessary that a proposed study is ‘adopted’ by UKCRN. National research funders, such as ARC, which develop a process whereby there is a nationally agreed strategy in areas of relevance, which would drive both knowledge advance and, as a by-product, quality of care.

In achieving this, there would be a transformation of clinical practice in areas of relevance, which would drive both knowledge advance and, as a by-product, quality of care.

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 [2] highlighted the difficulties the industry faces in the UK environment in the testing of novel agents, particularly in Phase 1 and Phase 2 clinical trials. The capacity and organization 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 would be facilitated by the existence of strong clinical networks capable of delivering a clinical trials programme and experimental medicine facilities that are funded by UKCRN partners. Industry can apply for studies to be adopted by UKCRN. The alternative route is that by engaging with the clinical research community through a national funder such as ARC, the aim should be to align industry’s research strategies with that determined by the research community. This would as a benefit lead to adoption via the automatic process outlined earlier.

Overview of the initiative

The vision

The vision is that ARC, in partnership with the UKCRN, industry and other funders (such as MRC), develops a comprehensive programme that would permit the testing of both new and existing interventions, based on a nationally agreed and scientifically robust research agenda, across the major disease areas of the charity’s interests. In achieving this, there would be a transformation of clinical practice in areas of relevance, which would drive both knowledge advance and, as a by-product, quality of care.

Depending on the disease area the interventions will include pharmaceutical, surgical, psychological, and educational and rehabilitation approaches.

Clinical Studies Groups

Seven major topic areas have been identified, each of which will develop and deliver on their own strategy. These are:

- Adult inflammatory arthritis
- SpAs
- Auto-immune rheumatic disorders
- OA and related disorders
- Metabolic bone disease
- Musculoskeletal Pain disorders
- Paediatric rheumatological disorders

For each area, a Clinical Studies Group (CSG) is being established. Chairs of each of these groups were recruited by open competition in conjunction with UKCRN. A list of appointees and their contact e-mail addresses are available on ARC research website (www.arc-research.org.uk). Depending on the nature of the clinical area, it will be appropriate for the CSG to establish subgroups with specific targets of interest such as specific disorders (e.g. SLE, scleroderma, polymyositis within the Autoimmune Rheumatic Diseases CSG), by patient subgroup (early arthritis within the Inflammatory Arthritis CSG) or by nature of intervention (e.g. surgery, rehabilitation within the Osteoarthritis CSG). Some of these subgroups will be ‘standing’, i.e. have a continuing role during the duration of the initiative, whereas others will be ad hoc and be established to perform a specific task.

Development of research strategy

The major role of the CSGs is to develop a strategy in their area of interest, which should be modified and updated according to changing circumstances. Chairs have been tasked to ensure that all relevant interests are considered in the development of research strategy and will form advisory groups to assist them. More importantly, CSG chairs will be consulting widely and will aim to include all professional groups and, as a matter of policy, include the patient perspective.

The first stage in the development of the group strategy would be a detailed consideration of the current key issues within a specific area. Inputs to this stage would include some or all of the items listed in Table 1.

In reaching a strategy in any specific disease or disease subgroup area, the CSG would need to consider amongst other aspects the impact of the problem, the feasibility of investigation, the availability of patients, investigator interest, health economic issues, the nature of studies being conducted elsewhere and the timeliness of obtaining a robust result.

In considering any specific investigation, the CSG will have to address the question: ‘In this disease area or subgroup, is this the best/most important question on this therapeutic approach?’ It is an essential part of the initiative that the CSG can provide evidence of widespread consultation in reaching their conclusions though the exact mechanism will be left for the CSG to decide. The outline strategy would be subject to international review to provide an independent assessment of the priority listings, for example, though the CSGs would not be bound, after considering the review to alter their proposals either in whole or in part.

Implementing the research strategy

Role of the Comprehensive Local Research Networks. As studies approved by ARC receive automatic adoption by the CCRN, it will be necessary to develop the proposals alongside the activities of the networks. Thus, investigators would be encouraged to have an early dialogue at the design stage with CCRN to discuss issues such as recruitment and monitoring. This close collaboration with the UKCRN is illustrated by the

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<td>• Formal literature reviews and meta-analyses</td>
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<td>• Results of Cochrane reviews</td>
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<td>• Use of Database of Uncertainties in Treatments (DUETS) [3]</td>
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<td>• Expert working groups</td>
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model of partnership that ARC has formed with the Medicines for Children Research Network (MCRN) in forming the unique MCRN/ARC Paediatric Rheumatology CSG. This will significantly facilitate the development of a comprehensive, integrated and long-lasting research programme for paediatric rheumatology in the UK.

CTU. It is increasingly important that successful clinical trials require methodological input into issues such as trial design, power calculations, clinical record and database design as well as conduct, and ultimately analysis and reporting. In addition, the ethical and regulatory environment requires expertise in steering proposals through the regulatory hoops. Trials accepted within the portfolios of the CSGs would be linked to expert CTUs to free the investigators to concentrate on the clinical and scientific aspects.

Establishment of pilot and feasibility studies. Many investigations will require pilot and feasibility studies to assess aspects such as recruitment, retention and outcome assessment, toxicity monitoring and other issues. There will be a rapid process for submitting, reviewing and funding such key components with the CCRN being involved at all stages.

Scientific review of proposals. Following agreement of strategic goals the CSGs would need to consult widely to reach a consensus on who will take the lead for the different components identified. Protocols either for full or pilot studies will be subject to stringent peer review to ensure that, for example, for formal trials, they conform to MRC guidelines for clinical trials. The key aim would be for the review process to be facilitative helping the investigators to succeed.

Other benefits to the scientific community

There are a large number of other types of investigations that benefit from the collection of clinical case material and associated samples from actively treated patients. Many such studies will be directed towards the better management of patients via understanding their diagnosis, prognosis and treatment through study designs other than randomized clinical trials. The CSGs will be encouraged either to incorporate these questions such that they can be addressed within the clinical trial programme that they support or are developed as separate components, which by virtue of being designed for patient benefit would be eligible for adoption by UKCRN.

In addition, the opportunity afforded by any of the clinical studies outlined earlier would also permit the collection of data and materials, for example, serum, DNA and other tissues that could be used to address research questions about the disease of interest. Investigators wishing to access such materials will be encouraged to work with the CSGs in ensuring that the maximum scientific benefit should accrue from the recruitment of patients for the relevant studies. By linking such studies to the opportunities afforded by recruitment and clinical data collection supported by UKCRN, the resulting costs of supporting the research component to funders such as ARC is reduced, increasing significantly the quantum of such research it funds. In this regard, it would be expected that one consequence of this activity will be the establishment of national banks of clinical and biological materials available to the entire community.

Priority setting and funding

ARC has committed to spending up to £5 million a year on this initiative once it is fully established. This compares with the £2 million spent on all similar types of activities under its current schemes. In addition, the cost to ARC of any single study should be reduced given the resources available from adoption by CCRN and the co-funding where relevant from industry. Although in time it is possible that funding constraints will inform the priority setting both within CSGs and between CSGs, the key issues early on will be the availability of patients and the ambitions and industry of the clinical research community.

Rheumatology key messages

- Future musculoskeletal clinical trials in the UK will aim to be based on a national strategic consensus in the relevant area.
- The goal is that strategy should both inform and be informed by the industry’s strategies in relation to novel therapeutic areas.

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References

3 Database of Uncertainties about the Effects of Treatments (DUETS) www.duets.nhs.uk (3 March 2008, date last accessed).