REVIEW

Getting involved in clinical trials research in the UK: how can Clinical Research Networks help?

Mark A Hull,¹ Yan Yiannakou,² Jonathan Gower,³ Stephen D Ryder,⁴ Stuart L Bloom,⁵ Colin R Rees⁶

¹Lead for Gastrointestinal Research, West Yorkshire Comprehensive Local Research Network, Leeds Institute of Molecular Medicine, University of Leeds, St James's University Hospital, Leeds, UK

²Lead for Gastrointestinal Research, County Durham and Tees Valley Comprehensive Local Research Network, County Durham and Darlington NHS Foundation Trust, Durham, UK

³Comprehensive Clinical Research Network, National Institute for Health Research Clinical Research Network Coordinating Centre, Leeds, UK

⁴Hepatology National Specialty Group, Comprehensive Clinical Research Network, Nottingham University Hospitals NHS Trust, Nottingham, UK

⁵Gastrointestinal National Specialty Group, Comprehensive Clinical Research Network, University College Hospital, London, UK

⁶Chair, Northern Region Endoscopy Group, Department of Gastroenterology, South Tyneside Hospital, Newcastle, UK

Correspondence to

Professor M A Hull, Leeds Institute of Molecular Medicine, Wellcome Trust Brenner Building, St James's University Hospital, Leeds LS9 7TF, UK; M.A.Hull@leeds.ac.uk

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The Clinical Research Networks of the National Institute of Health Research have transformed clinical research in the UK, leading to a doubling in the number of patients involved in clinical research studies over the past 3 years. This has been achieved by streamlining the trials approvals process, by providing local infrastructure such as research nurse support for clinical trials recruitment and through recognition of the time and funding necessary for clinicians to contribute to clinical research. Here, we describe the structure and roles of the Comprehensive Clinical Research Networks in gastrointestinal disease and hepatology, particularly in England. We will explain how the networks have already accelerated clinical research in gastrointestinal and liver disease, as well as provide a simple guide about how individual clinicians can contribute to ongoing studies via the networks.

What are Clinical Research Networks and what are the main roles and objectives?

The National Health Service (NHS) should be an ideal environment for clinical trials research but in recent years it has underperformed in comparison with clinical research activity in health systems in other countries. The National Institute of Health Research (NIHR) was formed in 2006¹ in order to create an environment for world class health research. Following the success of the original topic specific Research Networks such as the Cancer and Stroke Networks, a Comprehensive Clinical Research Network (CCRN) was created in England covering 24 medical specialties, including gastroenterology and hepatology as separate specialties. Separate Clinical Research Networks (CRNs) exist in Scotland (Scottish Clinical Research Network), Wales (Clinical Research Collaboration Cymru)

and Northern Ireland (Northern Ireland Clinical Research Network). Although the structure and aims of the individual CRNs in the devolved nations are similar, the following description is directly relevant only to the CCRN in England.

The stated aims of the CCRN are to²

- ensure patients and healthcare professionals from all parts of the country are able to participate in and benefit from clinical research
- integrate health research and patient care
- improve the quality, speed and coordination of clinical research
- increase recruitment to studies in the NIHR portfolio (with the initial stated aim to double recruitment in the first 5 year period)
- increase collaboration with industry partners and ensure that the NHS can meet the health research needs of industry.

What is a Comprehensive Local Research Network and what does it do?

The CCRN in England consists of 25 Comprehensive Local Research Networks (CLRNs), each representing a population of approximately 2 million (figure 1). CLRNs are important because they are the main source of local infrastructure support.

CLRNs provide service support costs (as opposed to the direct costs of doing the research) of NIHR approved clinical research studies, which are included in the NIHR CRN portfolio (see below). These include the provision of research nurses and other research staff support (including consultant time) required for patient identification, recruitment, data entry and follow-up, as well as funding for extra NHS costs linked to a given study (eg, extra time taken for endoscopy) and involvement of other local NHS services,

Figure 1 Regional structure of the Comprehensive Clinical Research Network (CCRN) as 25 Comprehensive Local Research Networks. Permission from the National Institute for Health Research CCRN.

including radiology, histopathology and pharmacy. CLRNs do not provide direct research costs (eg, equipment, drug costs or extra research endoscopic procedures). These costs are usually met by research grant funding from the NIHR or an eligible NIHR partner organisation (see below).

Funding for CLRNs from the Department of Health has three components: a management component required to support centralised administrative costs, a per capita element based on the size of the CLRN population and an activity based element based on the number of patients recruited to NIHR CRN portfolio studies from that particular CLRN. This activity based funding element is based on the complexity of the design of the study, to which recruitment has occurred within a given CLRN, distinguishing between, for example, simple observational and more complex, time consuming intervention studies.

A CLRN can name a designated local lead and form a Local Specialty Group (LSG) in any specialty area where there is local expertise, interest and potential for research activity. Currently, 23 of the 25 CLRNs in England have a designated lead for gastrointestinal disease and 20 of the 25 CLRNs have a designated lead for hepatology. Some CLRNs currently have a joint

lead for both gastrointestinal disease and hepatology. A list of designated CLRN leads and their contact details is available on the British Society of Gastroenterology (BSG) website (<http://www.bsg.org.uk/research/general/using-the-comprehensive-clinical-research-network.html>) and the CCRN website (http://www.crncc.nihr.ac.uk/about_us/ccrn/specialty).

There are local differences in LSG structure and activity but most LSGs are built around representatives from acute NHS Trusts in a given CLRN. For example, the West Yorkshire gastrointestinal disease LSG consists of clinicians from the five acute Trusts in the region, along with representatives from pharmacy, radiology and primary care endoscopy.

The role of a LSG is to coordinate activity across local Trusts such that research activity is coordinated and research infrastructure is used efficiently. For example, involvement of more than one research site within a CLRN in a NIHR portfolio study can maximise local accrual and lead to increased efficiency via shared use of resources such as a research nurse. This facilitates recruitment to clinical trials, which was previously confined mainly to recognised teaching centres, in all NHS organisations that provide care for patients, with appropriate resources being made available to such centres.

National Specialty Groups

CLRN local leads for gastrointestinal disease and hepatology meet, together with CRN Coordinating Centre representatives, as a National Specialty Group (NSG) several times per year. NSGs take a national view on study feasibility issues, recruitment targets and resolve potential blocks to study recruitment. NSGs are also an opportunity for CLRN leads to share best practice in their CLRNs. A crucial role is to act as an adoption panel in order to advise the CRN about adoption of commercially funded and sponsored studies to the NIHR CRN portfolio. There is cross representation of the NSGs with the BSG Research Committee in order to help inform and educate BSG members about clinical trials activity and opportunities, in parallel with dissemination of information locally by LSGs. The gastrointestinal disease and hepatology NSGs have also played a role in determining clinical research priorities for NIHR funding via funding schemes such as the Health Technology Assessment programme administered by the NIHR Evaluation, Trials and Studies Coordinating Centre.

What type of research is supported by the CRN?

CLRNs may only support research studies which are registered on the NIHR CRN portfolio.³ There are several routes available for securing adoption of a particular study to the portfolio.

(a) Automatic adoption of a particular study to the portfolio results if the predominant source of funding is from a NIHR partner organisation. All eligible organisations provide research funding that:

- is a result of open, national competition
- has undergone high quality peer review
- supports research of clear value to the NHS and
- is responsive to Department of Health and NHS priorities and needs.

A full list of NIHR partner organisations for gastroenterology and hepatology is available on the NIHR website at http://www.crncc.nihr.ac.uk/about_us/processes/portfolio/p_eligibility/p_auto_elig/.

(b) Commercially funded studies (including investigator led, commercially funded studies and studies funded by non-

Figure 2 Activity in gastroenterology and hepatology studies on the UK Clinical Research Network (CRN) portfolio. (A) Total number of participants recruited to studies in the gastroenterology and hepatology portfolios. (B) Number of observational and interventional studies open to recruitment in the UKCRN gastroenterology and hepatology portfolios. Light grey, observational studies; black, interventional studies; dark grey, studies with both interventional and observational components.

UK sources (such as the EU) can also be adopted onto the portfolio following review by the NSG adoption panel.

Progress of the Clinical Research Networks to date

There has been a steady increase in study activity in both gastrointestinal disease and hepatology since the establishment of the CCRN and specialty groups (figure 2). The number of open studies and recruitment to gastrointestinal and liver studies has doubled over three years (figure 2).

Case studies: how the CRNs are working in practice

PBC Genetics Study

The PBC Genetics Study is a national initiative to establish a DNA collection containing several thousand samples, intended to support high throughput genetic studies of primary biliary cirrhosis (PBC). It has been a UKCRN portfolio study since September 2008. Samples from the UK PBC DNA collection were recently used for the Wellcome Trust Case Control Consortium (WTCCC3) genome wide association study of PBC,⁴ which generated enormous statistical power because of the large sample size derived from more than 140 NHS Trusts in the UK (figure 3). Development of this large collection of samples was made possible by networking between centres through the liver NSG and local CLRN funded support.

Barrett's Oesophagus: Surveillance Versus no Surveillance

BOSS (Barrett's Oesophagus: Surveillance Versus no Surveillance) is a large, multicentre, randomised trial which is funded by the NIHR Health Technology

Assessment Programme and has been co-adopted by the gastrointestinal CCRN and National Cancer Research Network (NCRN). The potential for relatively high recruitment to this interventional trial has prompted significant support from CLRN to clinicians, giving access to funding for recruitment to the trial even if they have previously had little research infrastructure. As of October 2011, there were 110 sites open in the study. Gastrointestinal CCRN input has contributed to the enormous success of BOSS, highlighted by the fact that recruitment was ahead of schedule at recruitment closure in October 2011 (figure 4).

"BOSS has demonstrated that the UK gastroenterology community is able to deliver a large trial which will address a fundamental question regarding the management of Barrett's oesophagus.

The success of the trial is entirely due to the fantastic support of the CLRN, the National Cancer Research Network and the Gastroenterology Specialty Group in particular"

Professor Hugh Barr, BOSS Trial Chief Investigator

Increasing regional clinical trials activity

The County Durham and Tees Valley CLRN covers three acute Trusts serving a population of 1.2 million. Gastroenterology research in this region in 2007/8 was virtually non-existent, with no infrastructure and only around 10 patients recruited to what would now be NIHR clinical trial portfolio studies. CLRN infrastructure has allowed a rapid expansion in activity with trial accrual for 2010/11 likely to exceed 700 in 12 portfolio studies.

Initially, part-time research nurse funding allowed recruitment to multicentre studies such as BOSS and a number of simple observational studies. High recruitment to these studies generated further resource so that, for 2010/11, each Trust now has a full-time research nurse. There are a total of six PAs of consultant sessional support across the three Trusts and clinical research has become embedded as a core activity. Several clinicians are now developing personal academic portfolios following successful applications for NIHR grant funding with the help of the local Research Design Service, Clinical Trials Unit and Northern Region Endoscopy Group.

"Despite my location in a district general hospital, I have a funded research session, work with a CLRN funded research nurse and I am local PI for six multicentre portfolio studies. A key to this success has been close collaboration with colleagues at the Northern Region Endoscopy Group (NREG), support from the local CLRN LSG lead and strong links with the Durham University Clinical Trials Unit"

Dr Anjan Dhar, Consultant Gastroenterologist, CDDfT.

Regional networking and collaboration with like minded clinicians can provide a fertile environment

Figure 3 Participant accrual for the primary biliary cirrhosis (PBC) Genetics Study up to March 2011. Red lines indicate the number of cases recruited from a single liver transplant (LT) centre (Addenbrooke's); all UK LT centres combined; all liver centres in England; and all liver centres in the UK. Blue points indicate when sufficient cases had been recruited to provide 80% power to identify the labelled locus at a genome wide level of significance.

Recruitment up to end July 2011

Figure 4 Recruitment to the Barrett's Oesophagus: Surveillance Versus no Surveillance (BOSS) trial. At the end of July 2011, 2937 patients had been recruited.

for developing research ideas, as well as optimising trial recruitment. The Northern Regional Endoscopy Group has been successful in harnessing local enthusiasm for endoscopy research and driving CLRN funded activity. Development of similar local networks should be encouraged elsewhere.

How to get started in clinical trials research?

The NIHR CRN portfolio is easily accessible at <http://public.ukcrn.org.uk/search/> and gives a good idea of what interventional or observational studies are currently open for recruitment. Investigators interested in contributing to one or more of the multicentre studies that are on the gastrointestinal or hepatology sections of the NIHR CRN portfolio should contact either the relevant CLRN gastrointestinal or hepatology lead, or the named trial contact in the portfolio trial entry.

Potential investigators should contact their CLRN lead to get details of the next LSG meeting in order to learn more about local research activity. The BSG publishes a Clinical Trials Update three times a year, which provides a summary of current trials with contact details for the trial manager for those investigators who wish to learn more about a trial.

In order to contribute to a clinical trial, Good Clinical Practice certification within the past 2 years is mandatory.⁵ Your CLRN lead or Trust R&D office will be able to arrange this free of charge, either as online distance learning or as a dedicated 'face to face' 1 day meeting. The time taken to gain Good Clinical Practice

accreditation can be counted as non-clinical continuing professional development.

Conclusion

Most clinicians understand the importance of clinical research and want to contribute to multicentre trials but are discouraged by perceptions of layers of bureaucracy and the lack of time available to concentrate on research.⁶ CLRNs now provide local support to help get Trust R&D approval for a study, to use research nurse time for patient recruitment and follow-up, and to fund protected time for portfolio trials activity. No gastroenterology unit should now be too small to contribute to clinical trials research, particularly when research nurse time can be spread across different Trusts within a CLRN. Access to these resources should be discussed with the relevant CLRN lead in the first instance.

Opportunities now exist for Gastroenterologists and Hepatologists to become involved in research even when they have a limited track record and have historically had little, if any, research infrastructure. Resources and support mechanisms are now in place via the CRNs to help clinicians to recruit to multicentre clinical trials. Widespread engagement of Gastroenterologists and Hepatologists with this process is important to ensure that patients across the country can contribute to clinical research, that critical research questions are answered and that existing gastrointestinal and liver clinical trials recruit to target.

The successful CRN systems that have been adopted in the UK may be adopted by other national health systems in the future, depending on the existence of a compatible health service infrastructure.

Interested clinicians should contact the lead for gastrointestinal disease or liver disease in their CLRN in order to join the LSG and access support for trials activity.

Although significant improvements have been made to the clinical research infrastructure in the UK, challenges remain with ensuring uniform standards for the rapid approval of studies and ensuring that resources are targeted to, and get through to, priorities in front-line services. Progress is being made and there is a commitment to overcoming the remaining hurdles so that researchers can derive maximum benefits from the radically different ways in which research is now supported in the NHS.

Summary box

- ▶ The UK Clinical Research Network (UKCRN) structure facilitates clinician involvement in clinical research studies adopted to the UKCRN portfolio.
- ▶ Comprehensive Local Research Networks can provide a variety of funding (including consultant PA support and research nurse salary) to allow recruitment to UKCRN portfolio studies.

Commitment to and involvement in clinical research in gastrointestinal disease and/or liver disease is variable across the CLRNs. An important task will be to prioritise gastrointestinal disease and liver disease in all CLRNs leading to broader national coverage for clinical studies on the respective UKCRN portfolios.

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