Research-intensive cancer care in the NHS in the UK

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In the late 1990s, in response to poor national cancer survival figures, government monies were invested to enhance recruitment to clinical cancer research. Commencing with England in 2001 and then rolling out across all four countries, a network of clinical cancer research infrastructure was created, the new staff being linked to existing clinical care structures including multi-disciplinary teams. In parallel, a UK-wide co-ordination of cancer research funders driven by the ‘virtual’ National Cancer Research Institute, combined to create a ‘whole-system approach’ linking research funders, researchers and NHS clinicians all working to the same ends. Over the next 10 years, recruitment to clinical trials and other well-designed studies, increased 4-fold, reaching 17% of the incident cancer population, the highest national rate worldwide. The additional resources led to more studies opened, and more patients recruited across the country, for all types of cancers and irrespective of additional clinical research staff in some hospitals. In 2006, a co-ordinated decision was made to increasingly focus on randomized trials, leading to increased recruitment, without any fall-off in accrual to non-randomized and observational studies. The National Cancer Research Network has supported large successful trials which are changing clinical practice in many cancers.

introduction

Towards the end of the last millennium, there was a growing realisation that the survival of patients diagnosed with cancer in the UK was consistently and significantly poorer than much of the rest of the developed world [1, 2]. For example, despite being one of the earliest countries in Western Europe to introduce comprehensive screening for breast cancer, the 5- and 10-year survival rates were amongst the lowest in Europe.

After a decade when the UK’s National Health Service (NHS) priorities perhaps focussed more on the process of care delivery than assured excellence of outcomes, there was recognition that something additional was required to improve the survival of UK cancer patients. The first significant development was the publication of the Calman/Hine report in 1995 [3], the associated service redesign to restructure the patient pathways/service provision. This led to the creation of 34 ‘cancer service networks’ across England, together with three in Scotland and one each in Wales (subdivided into three sub-networks) and one in Northern Ireland. Many UK leading cancer clinicians were involved. Delivery of cancer clinical care was rapidly revamped into this new network structure, mostly based on a concept of tertiary care Cancer Centres, and secondary-care Cancer Units. Multi-disciplinary team meetings (MDTs) were created within these networks for all the common cancers, such that (almost) every patient diagnosed with a common cancer in the NHS would be discussed by relevant specialists before treatment plans were finalised. Cancer Centres were predominantly based around large radiotherapy centres and/or University cancer departments, whereas the Cancer Units were district general hospitals, often but not exclusively served by non-surgical oncologists visiting from the Centre, working with local surgeons, pathologists, physicians and radiologists.

Once these networks were created, further data suggested that there was still a gap between UK and other European cancer survival statistics. The UK cancer community was research active, but much of the recruitment to clinical trials occurred in academic centres. It was hypothesized that, if more patients could have access to late phase clinical trials, not only would their outcomes improve as they gained access to novel therapies, but the inculcation of a research culture across all hospitals delivering cancer care would also lead to a general improvement in the standard of care for all cancer patients (see Chapters 1, 3 [4, 5] and references [6, 7]).

National Cancer Research Network – the approach

Thus began a unique experiment in health service research – to establish an NHS infrastructure for clinical research based on the clinical service networks and to evaluate its impact on the scale, quality, speed, participation and integration of clinical research and ultimately on its impact on healthcare outcomes. The creation of a broad-based research infrastructure should allow patients across the whole of England to have access to an agreed portfolio of quality clinical studies in cancer.

Following an open, peer-reviewed competition, the National Cancer Research Network (NCRN) was established in April 2001 led by colleagues in both the University of Leeds and the
Medical Research Council Clinical Trials Unit in London. Government money, around £250 000 per year per million population, was invested evenly across the whole country, in contrast to the more traditional programme- or project-based research funding model whereby resources would be focussed at sites leading the research. Resources were allocated along the same geographical lines as the service cancer networks, and each network had a research network manager with clinical support that was separate from, but encouraged to work closely with, similar leadership in the service delivery network. There was a co-ordinating centre based in Leeds with input from the MRC in London, in order to performance-manage the access to cancer trials and to encourage best practice. However, each network was permitted to work in whatever way suited the local body-politic. The research networks provided NHS infrastructure support for the trials recruitment and conduct, notably research nurses and trials practitioners from life sciences backgrounds and support to diagnostic and pharmacy departments.

Around the same time, a separate but equally prominent change occurred in the UK cancer research funders. The National Cancer Research Institute (NCRI) was created in 2000 as an ‘institute without walls’. It brought together all those organisations that funded more than £1 million per year of cancer research, in order to collaborate and create synergy rather than duplication of research. Joint initiatives were developed in previously under-researched areas like prostate cancer, prevention of cancer and supportive and palliative care. Between the NCRN and the NCRI, a number of new clinical studies groups were created, some formed from pre-existing disease-based advisory groups, with other new group focussing on non-disease specific topics like translational research and complementary medicine. Together, these clinical studies groups were tasked with the oversight and development of portfolios of research across all cancers. This has led to an ever-growing portfolio of studies into which the networks recruit patients. The interactions of the NCRN and NCRI promoted a ‘whole system approach’ balancing the portfolio with the capacity of the research networks and Clinical Trials Units.

NCRN – results

The central purposes of the NCRN have always been to bring benefits to patients by increasing participation in clinical research and providing an excellent evidence base for the development and improvement of healthcare. The evaluation of the organization’s performance moved through phases

- impact on recruitment to its research portfolio
- the growth of the portfolio through the NCRI Clinical Studies Groups
- the delivery of the portfolio to time and target
- the contribution to improved care and outcomes.

The first three outcomes were first reported up to 2007 [8] and are updated here to 2010. Studies of the development of the evidence base for cancer care and the impact of the NCRN on overall healthcare outcomes are ongoing and are reported here only with preliminary findings.

At the start of the NCRN, there were no centrally collected data on the total UK recruitment to cancer trials.

Comprehensive searching of trial portfolios and discussion with research funders and active researchers suggested that before 2000 around 3.75% of new cancer patients were being enrolled into trials and other well-designed studies each year. In order to encourage engagement of local oncologists, support departments and hospital R&D departments, an initial target for NCRN was simply to double this total recruitment within 5 years. Eligibility for inclusion in the national (NCRN) portfolio required compliance with criteria defining peer review research quality and NHS relevance.

As can be seen in Figure 1a, patient recruitment quickly increased such that the target was reached well before the end of the first 5 years of the NCRN [8]. This figure shows the growth in recruitment which was under 5% of new cancer patients in the first year of operation of the NCRN (2001/2) increased to well over 10% of all new patients after 3 years of operation. Continued growth has now taken this to approach 20%.

Figure 1a also shows steady growth in the portfolio with increasing turnover of studies. The proportion of studies completed to time and target also rising from 39% to 74% [8]. Although around 85% of studies remain drug-based, the rise in the number of studies (Figure 1) resulted in an absolute increase in non-drug studies as well. Figure 1b shows the...
Changes in clinical practice are mostly driven by RCT, whether by their results or by their influence in defining treatments and standards through structured protocol. For this reason, following the initial enthusiastic expansion of research activity during the first 5 years of the NCNR, the decision was made in 2006 to focus on increasing recruitment to randomized trials. Figure 1b confirms that the patients and clinicians continued to support clinical cancer research, and interestingly, overall recruitment continues to rise as well, perhaps in part because of some observational studies in the portfolio that can be supported at the same time as offering patients the opportunity to enrol in randomized trials.

Many important trials in cancer are sponsored and funded by pharmaceutical companies. Some, but not all, such studies are in narrowly defined groups of patients, and thus perhaps not as important in changing the overall standard of care as larger, more inclusive academic studies. Therefore, early on in the life of the NCNR, it was felt that in order to ensure adequate focus was given to extending the research culture across the country, such commercially sponsored trials were not part of the NCNR portfolio, though there was no discouragement to clinicians supporting such studies. However, once the first phase of the experiment was deemed a success, commercially sponsored studies were included, provided they also met certain quality and compatibility standards and senior NCNR staff were appointed to promote this important aspect of clinical cancer research. Following their inclusion, the number and overall recruitment into commercially-sponsored studies has also increased, and not to the detriment of support for academic studies.

In parallel to the development of networks to support patient recruitment into trials, which has been internationally recognized [9], a number of other initiatives were developed whose precise impact may be harder to measure but may be no less important to the success of the NCNR. Firstly, under the auspices of the NCRI, those UK-based clinical trials units specializing in cancer studies were invited to be accredited as cancer trials units, and to work together more closely. This has led to closer working in a number of areas, including communication with networks and research sites, and work is under way to standardise follow-up schedules and Case Report Forms for studies in some common cancers. Secondly, networks and clinical studies groups were encouraged to develop greater patient and carer engagement in the research process, supported by staff and funds via the NCNR coordinating centre (see Chapter 9 [10]). This has led to closer working between researchers, clinicians recruiting to clinical trials, clinical trials units and patients, such that the NCNR patient and public involvement (PPI) is at the leading edge of UK clinical research. Thirdly, in a desire to ensure greater safety for patients in trials of chemotherapy, a working party of oncology pharmacists and clinicians now scrutinizes all protocols submitted to two of the main research funders (the independent charity Cancer Research UK and the government-funded Health Technology Assessment committee) in order to standardize how drugs are prescribed, dispensed and dose-adjusted, both within and between protocols. Finally, as the new resources invested employed many staff not previously engaged in clinical cancer research, there was a need to provide a comprehensive training package for these staff. Rather than leave all the training to local initiatives, the NCNR set up a national training approach, and extended access to the courses to both staff working in cancer trials units and new lay people working with the NCNR. This had the double advantage of not only reducing the risk of heterogeneity in quality between courses delivered to different audiences, but encouraged greater mixing between different groups of people involved in delivering the NCNR vision of greater access to clinical cancer research leading to better outcomes for patients.

The four UK Departments of Health and Cancer Research UK also fund the Experimental Cancer Medicine (ECMC) Network. This was established in April 2007, and replaced the earlier National Translational Cancer Research Network (NTRAC) which had been established in 2003, initially in only English centres. The ECMC network comprises 19 centres across the UK which perform early phase trials and translational research, aiming to drive the development of new therapies and biomarkers to bring benefit to cancer patients. The ECMC research portfolio feeds in to the pipeline of new ideas to be tested in the UK NCNRNs in the late phase setting.

The initial NCNR investment came from the English Department of Health, and formed an early example of a broader-based clinical research infrastructure. More recently, the National Institute for Health Research (NIHR) has been established and has radically reformed and strengthened many aspects of investment in clinical research in the NHS in England, including research networks in different diseases and specialism biomedical research centres and units (see Chapter 6 [11]).

Health care structures and budgets are devolved in the UK between the four nations, but a clinical research network was implemented in Northern Ireland and in Wales a similar initiative had already begun in 1998. In Scotland the Scottish Cancer Therapy Network (SCTN) had been established in 1993 with a broader remit in quality improvement through audit as well as support for clinical trials. When its funding was reviewed 4 years later, it was recognized that SCTN’s help with the administration and coordination of large multi-centre
studies had already achieved a marked increase in trials recruitment. Thus, when the Acute Services Review (1998) instigated changes in clinical delivery and the formation of Managed Clinical Networks for cancer care, the landscape was ripe for a further evolution in the clinical trials infrastructure and the research support activity evolved into the Scottish Cancer Research Network formed of three regional networks which have much in common with those elsewhere in the UK and from an early stage have worked to create a pan-UK system.

Similarly based on the service cancer networks, parallel investment in a clinical cancer research infrastructure has led to similar increases in recruitment. It is interesting to note that in the 2009–2010 period, in which the recruitment in England to cancer trials was the highest yet, and corresponds to the equivalent of one patient enrolling into a national portfolio study for every six diagnosed with cancer, additional resources to support cancer trials were invested in many of the English networks from the new NIHR Comprehensive Clinical Research Network. Increases in investment in the three devolved nations were smaller, and their recruitment in 2009–2010 increased to a lesser extent than in England, suggesting that the rise in recruitment in England reflects in part the greater access to resources in the presence of continued commitment amongst staff.

**impact of NCRN over and above pre-existing resources**

When the NCRN was established in 2001, there were varying levels of pre-existing clinical cancer research investment across England. Research support staff were funded from varying sources, including NHS Research and Development funding (known at that time as the ‘Culyer stream’), local charities, national charities (such as Cancer Research UK) and other sources including in the most research-active institutions, commercial trial income. In order to assess the impact of the additional NCRN resources, the 34 local research networks were grouped into five ‘Clusters’ based on these pre-existing resources. Cluster A networks had minimal pre-NCRN resource, and over 90% of the available clinical research infrastructure was funded by NCRN; conversely Cluster E networks had extensive other investment, so NCRN resources comprised less than 25% of the total available resource to support NCRN portfolio studies. It can be seen from Figure 2a and 2b that irrespective of the pre-existing level of investment, the additional resources coming via NCRN resulted in more patients being able to enrol into NCRN studies. Notably, in Cluster E the new NCRN resources were a smaller proportion of the overall total resources to support clinical research and their baseline was, as expected, higher. However, their increase in recruitment was still 4-fold. This strongly supports the view
Table 1. Examples of practice-changing randomized trials that have been supported by the NCRN

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>UK recruitment</th>
<th>Reference</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZURE</td>
<td>Breast cancer</td>
<td>2710/3360</td>
<td>NEJM accepted</td>
<td>Likely to reverse the current trend to give adjuvant bisphosphonates to all early breast cancer patients</td>
</tr>
<tr>
<td>CLASSIC</td>
<td>Colorectal cancer</td>
<td>794</td>
<td>Lancet 2005, JCO 2007</td>
<td>Demonstrated the safety and efficacy of laparoscopic surgery for colorectal cancer, which led to its widespread adoption in the UK</td>
</tr>
<tr>
<td>COMICE</td>
<td>Breast cancer</td>
<td>1623</td>
<td>Lancet 2010</td>
<td>Demonstrated that there was no advantage in routine use of MRI in early breast cancer diagnosis, potentially saving health care system resources</td>
</tr>
<tr>
<td>GEMCAP</td>
<td>Pancreatic cancer</td>
<td>533</td>
<td>JCO 2009</td>
<td>Established this combination as the usual standard UK treatment for advanced pancreatic cancer</td>
</tr>
<tr>
<td>MS01</td>
<td>Mesothelioma</td>
<td>401</td>
<td>Lancet 2008</td>
<td>Eliminated some standard chemotherapy drugs as being ineffective for this difficult to treat cancer, focusing research attention on the development of new approaches</td>
</tr>
<tr>
<td>RT01</td>
<td>Prostate cancer</td>
<td>862</td>
<td>Lancet Oncology 2007</td>
<td>Introduced and developed standardised approaches to conformal prostate radiation in the UK</td>
</tr>
<tr>
<td>ICON1/ACTION</td>
<td>Ovarian cancer</td>
<td>194/925</td>
<td>JNCI 2003</td>
<td>Supports use of adjuvant chemotherapy for early ovarian cancer. Long term follow up suggests that benefit after 10 years is mainly in high risk early stage disease.</td>
</tr>
<tr>
<td>ALMANAC</td>
<td>Breast cancer</td>
<td>1031</td>
<td>JNCI 2006</td>
<td>Supported the widespread and controlled introduction of sentinel node biopsy for early breast cancer patients, reducing NHS costs AND patient morbidity and length of hospital stay</td>
</tr>
<tr>
<td>HERA</td>
<td>Breast cancer</td>
<td>519/5102</td>
<td>NEJM 2005, Lancet 2006</td>
<td>Registration study for adjuvant trastuzumab in Europe and other parts of the world: transformed standard of care and has led to more cured breast cancer cases</td>
</tr>
<tr>
<td>MAGIC</td>
<td>Upper GI</td>
<td>503</td>
<td>NEJM 2006</td>
<td>Changed standard of care - operable lower oesophago-gastric cancer now gets chemotherapy as standard of care</td>
</tr>
<tr>
<td>OEO2</td>
<td>Upper GI</td>
<td>802</td>
<td>Lancet 2002, JCO 2009</td>
<td>Changed standard of care - operable oesophageal cancer now gets pre-operative chemotherapy as standard of care</td>
</tr>
<tr>
<td>QUASAR1</td>
<td>Colorectal cancer</td>
<td>3239</td>
<td>Lancet 2007</td>
<td>Supported a small but detectable benefit from adjuvant chemotherapy in stage II (moderate risk) colorectal cancer</td>
</tr>
<tr>
<td>START</td>
<td>Breast cancer</td>
<td>2215</td>
<td>Lancet 2008</td>
<td>Changing standard of care to reduced number of radiotherapy fractions- major savings for health care systems and easier for patients</td>
</tr>
<tr>
<td>TACT</td>
<td>Breast cancer</td>
<td>4124/4162</td>
<td>Lancet 2009</td>
<td>Reversed some of the ever increasing use of adjuvant taxanes in early breast cancer, with financial and toxicity savings for health care systems and patients</td>
</tr>
<tr>
<td>Neo-TANGO</td>
<td>Breast cancer</td>
<td>831</td>
<td>ASCO 2009</td>
<td>Demonstrated a benefit for the reverse sequence of taxanes &amp; anthracyclines. This has been incorporated into many current trial designs and is leading to changes in clinical practice</td>
</tr>
<tr>
<td>COIN</td>
<td>Colorectal cancer</td>
<td></td>
<td>Lancet 2011, Lancet Oncology 2011</td>
<td>Demonstrated that even with molecular selection, addition of antibody therapy does not necessarily add benefit to combination chemotherapy. Also showed that most patients do not require continuous treatment but can have treatment breaks.</td>
</tr>
<tr>
<td>SIGNIFICANT</td>
<td>All cancers</td>
<td>1565</td>
<td>NEJM 2005</td>
<td>Demonstrated benefit for the use of prophylactic antibiotics in chemotherapy - has led to changes in practice</td>
</tr>
<tr>
<td>CR07</td>
<td>Colorectal cancer</td>
<td>1350</td>
<td>Lancet 2009</td>
<td>Demonstrated the superior benefit from short-course pre-operative radiotherapy over selective post-op. Also clarified the importance of optimal surgical resection. Both findings will change standard practice.</td>
</tr>
</tbody>
</table>
that the increase in recruitment was related not only to resources but also to the structure, processes and clear aims of the NCRN, to its active management and to the commitment of staff inside and outside the NCRN itself. Figure 2b suggests that the higher the level of pre-existing resource, the more the less common cancers benefit from the additional NCRN staff, without prejudice to the common cancers (data not shown).

The 23 clinical studies groups managed within the NCRN cover all the common cancer sites, as well as groupings of less common diseases and some cross-cutting themes like radiotherapy, translational research, supportive care etc. Analysing the impact of the NCRN investment it is clear that all diseases gained in terms of additional recruitment, but for some the impact was critical for answering pertinent clinical questions, and resulted from an expansion in the number of networks (and thus sites) recruiting to this part of the portfolio. Figure 3a demonstrates this for a ‘less common cancer’, head and neck, where it can be seen that during the 10 years of the NCRN, there has been a massive extension of the geographical access to studies. From 2 networks in 2001, this rose to 32 networks by the end of decade, and was associated with increased uptake of commercially sponsored trials (data not shown). In contrast, Figure 3b shows the situation for prostate cancer, considered a common cancer. Pre-NCRN 27 networks were enrolling patients, but during the decade of the NCRN this increased to 32, and was associated with a 6-fold rise in the annual recruitment to portfolio studies. The improvement in recruitment into prostate cancer trials, as well as the increase in the number of trials, is also likely to be due to the NCRI initiative into prostate cancer research. This demonstrates the benefits of ‘whole system working’, in which research funders, the academics designing and running trials, and the networks supporting their recruitment all working together can enhance research.

There are a number of factors which have underpinned the success of the NCRN. First, the creation of NHS infrastructure released the commitment and energy of cancer patients and healthcare professionals to deliver research. Clinical engagement and leadership was readily apparent across the country. However, it is also clear that there was a close correlation between the increase in available research staff, funded by the new investment, and the increase in overall recruitment (Figure 4).

**NCRN – conclusions**

Ten years into the experiment, it is pertinent to ask the question as to whether the NCRN has delivered the survival improvement needed by patients. Early indications suggest that the enhanced recruitment has led to trials completing earlier [8], and evidence that their results are being implemented into practice is accumulating. We are currently exploring survival patterns in relation to increases in recruitment.

Data both for the whole network, and the cluster analysis, strongly supports the notion that not only does one need committed local staff, but that the level of additional investment links to the increases in recruitment that can then be achieved.

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**Table 1. (Continued)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>UK recruitment</th>
<th>Reference</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOCUS</td>
<td>Colorectal</td>
<td>2135</td>
<td>Lancet 2007</td>
<td>Demonstrated that sequential treatments may be equally beneficial and better tolerated in comparison to combination chemotherapy from the outset. Provided important framework for testing new approaches.</td>
</tr>
<tr>
<td>ASTEC</td>
<td>Endometrial cancer</td>
<td>1404</td>
<td>Lancet 2009</td>
<td>The two negative findings will simplify therapy and new standard practice: no advantage for systematic lymphadenectomy for endometrial cancer; and no advantage for adjuvant external beam radiation for high risk early stage endometrial cancer</td>
</tr>
<tr>
<td>ICON7</td>
<td>Ovarian cancer</td>
<td>375/1528</td>
<td>ASCO 2011</td>
<td>Demonstrated advantage for the use of Bevacizumab – will be used to help get regulatory approval for this drug in ovarian cancer</td>
</tr>
</tbody>
</table>

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**Figure 4.** NCRN studies between 2001 and 2010: total patients recruited and NIHR-funded staff (wte) supporting recruitment.
when appropriately managed. Furthermore, the increase in recruitment to randomized trials after 2006 in response to the change in emphasis, not only demonstrates the flexibility of this managed approach to research infrastructure, but also how as networks mature, they need to be able to respond.

The success of the NCRN, closely followed by a series of other networks (see Chapter 6 [11]), contributed to the wholesale revolution in the way that the NHS in England invests in clinical research and provided evidence that the NHS could support and deliver a world class clinical research portfolio in the UK. Early indications suggest that this is proving to be an effective way to increase recruitment to clinical studies across all of medicine, but as with the NCRN, it will be a few years yet before it can be concluded that this enhanced research activity has delivered the improvements in outcome that formed the hypothesis for the experiment.

acknowledgements

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disclosures

The authors have not declared any conflicts of interest.

references