The UK Model: The NIHR Cancer Research Network

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Outline

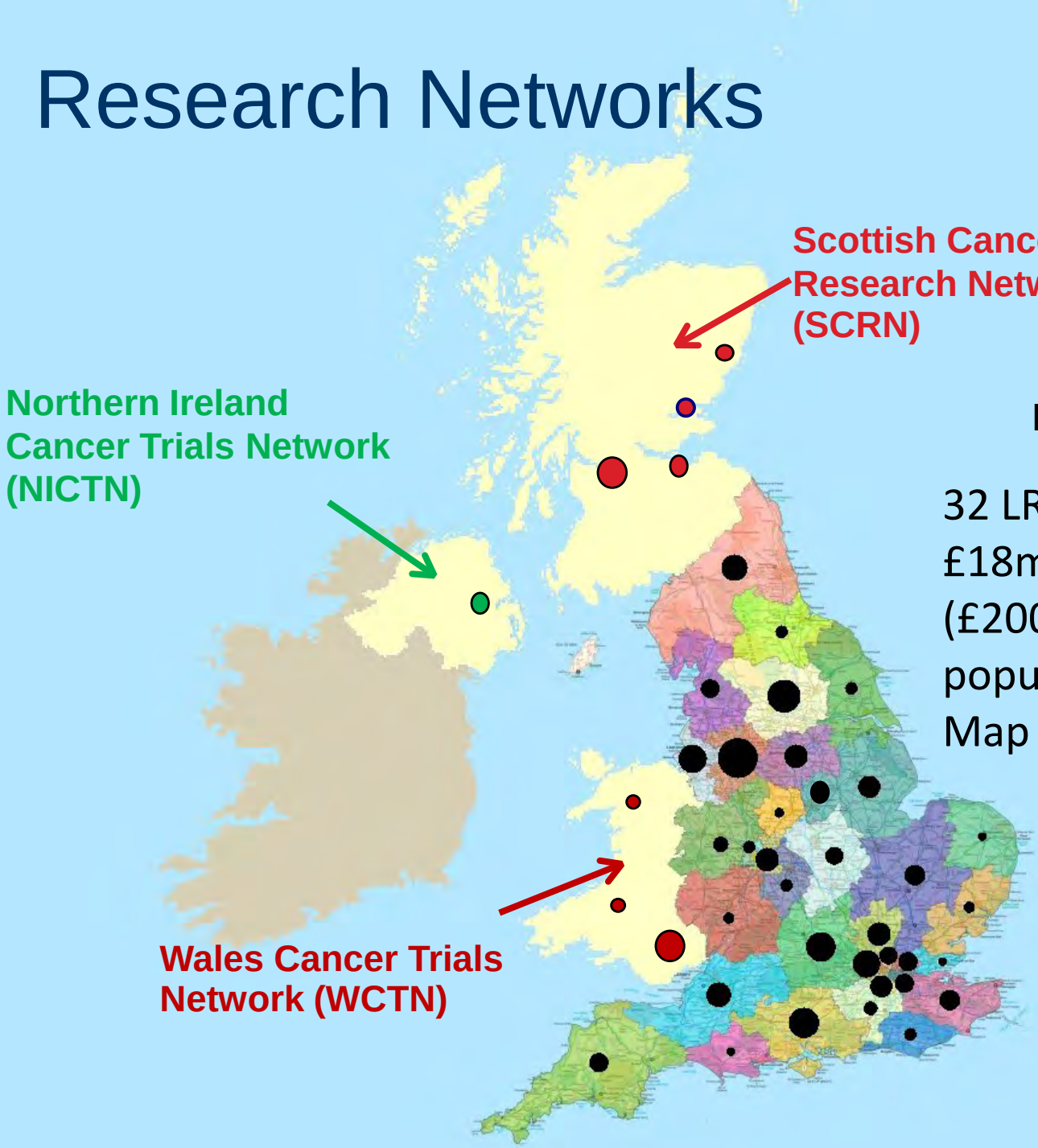
- The UK single national system for cooperative clinical trials (NCRN)
- What it has accomplished thus far
- Differences from NCI system
- Some relevant strengths and disadvantages
- Are any of the strengths transferable?

Glossary of tedious acronyms

- NCRN: *National Cancer Research Network* manages the research staff in 32 regions ('networks') tightly linked to the regional cancer treatment organisations in the English NHS
  - Also coordinates with counterparts in Scotland, Wales, N Ireland
  - Supports research nurses & data managers throughout the NHS
- NCRI: *National Cancer Research Institute*, the partnership of government & charity funders who jointly set policies & coordinate needed resources
- NIHR: The subsequently established agency of the English DoH that is most similar to NIH: Provides research funding programs, centre grants, training grants, funds for sessional support of clinicians . . . and
  - both population-based & activity-based research support to networks
- CRUK: *Cancer Research UK*, the largest UK cancer charity & largest cancer research funder in Europe
- MRC: *Medical Research Council*, a government agency now most focused on funding centres, biomarkers & translational research technology
- CSGs: *Clinical Studies Groups*, (single) UK-wide disease committees responsible for developing studies & overseeing their portfolios
- CTUs: *Clinical Trials Units*, equivalent to Coordinating + Data Centers in US Groups

NCRN
National Cancer Research Network

Research Networks



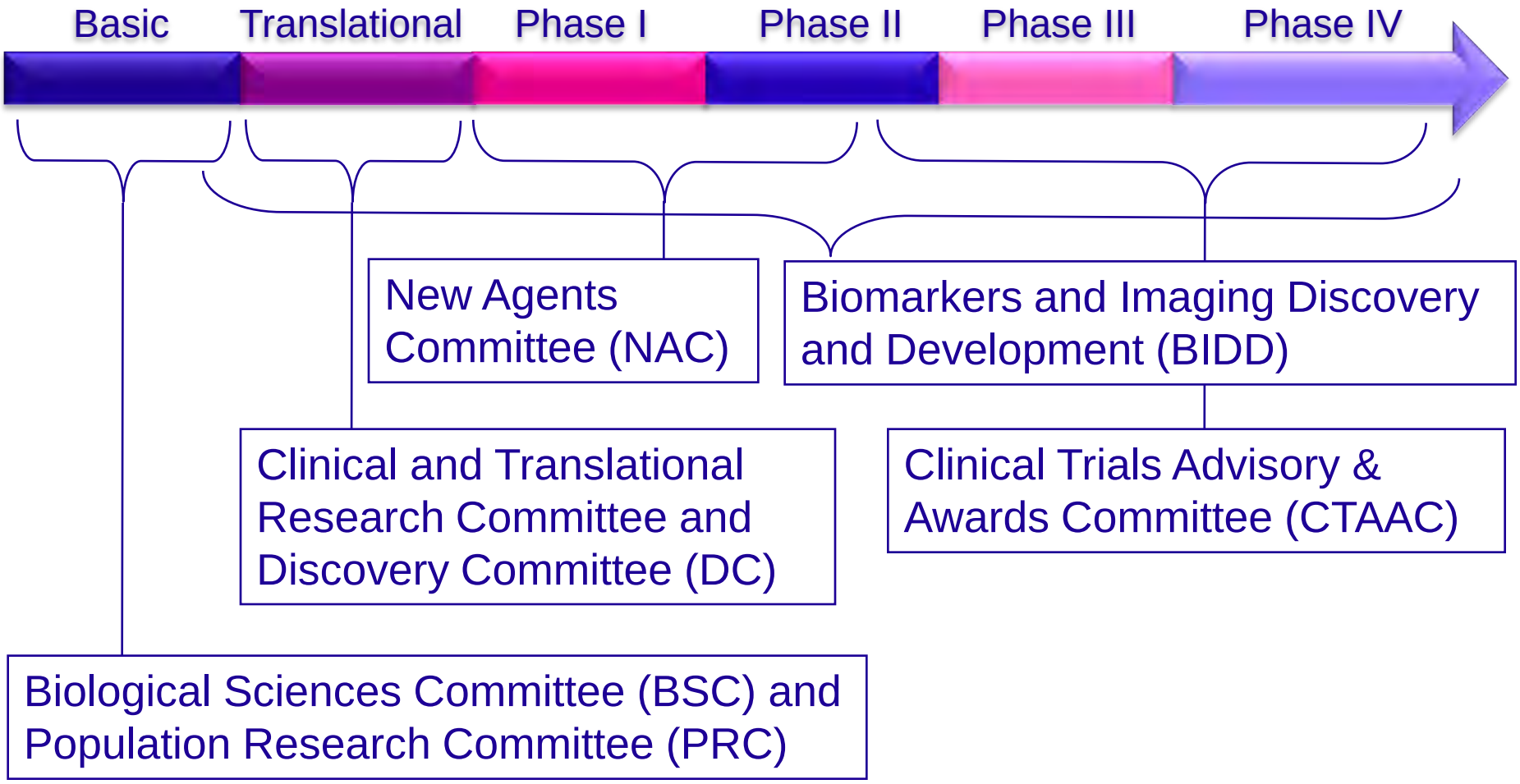
NCRN

32 LRNs
£18m core funding (£200k/1M population)
Map on to NHS

How are trials funded?

- All (nearly all) of the clinical costs for patients on trials is 'covered' by the NHS
- The network infrastructure is funded by NIHR (DoH in England)
  - Regionally based nurses and DMs
  - A small NCRN staff coordinating centre staff
- (Some) CTUs receive core funding via competitive peer review every 5 years
- The CSGs have a tiny budget, for meetings only
- Each trial applies for individual peer review funding to NIHR, CRUK or other funders
  - Covers the CTU central costs and sometimes stand out clinical costs

The CRUK research funding pipeline….



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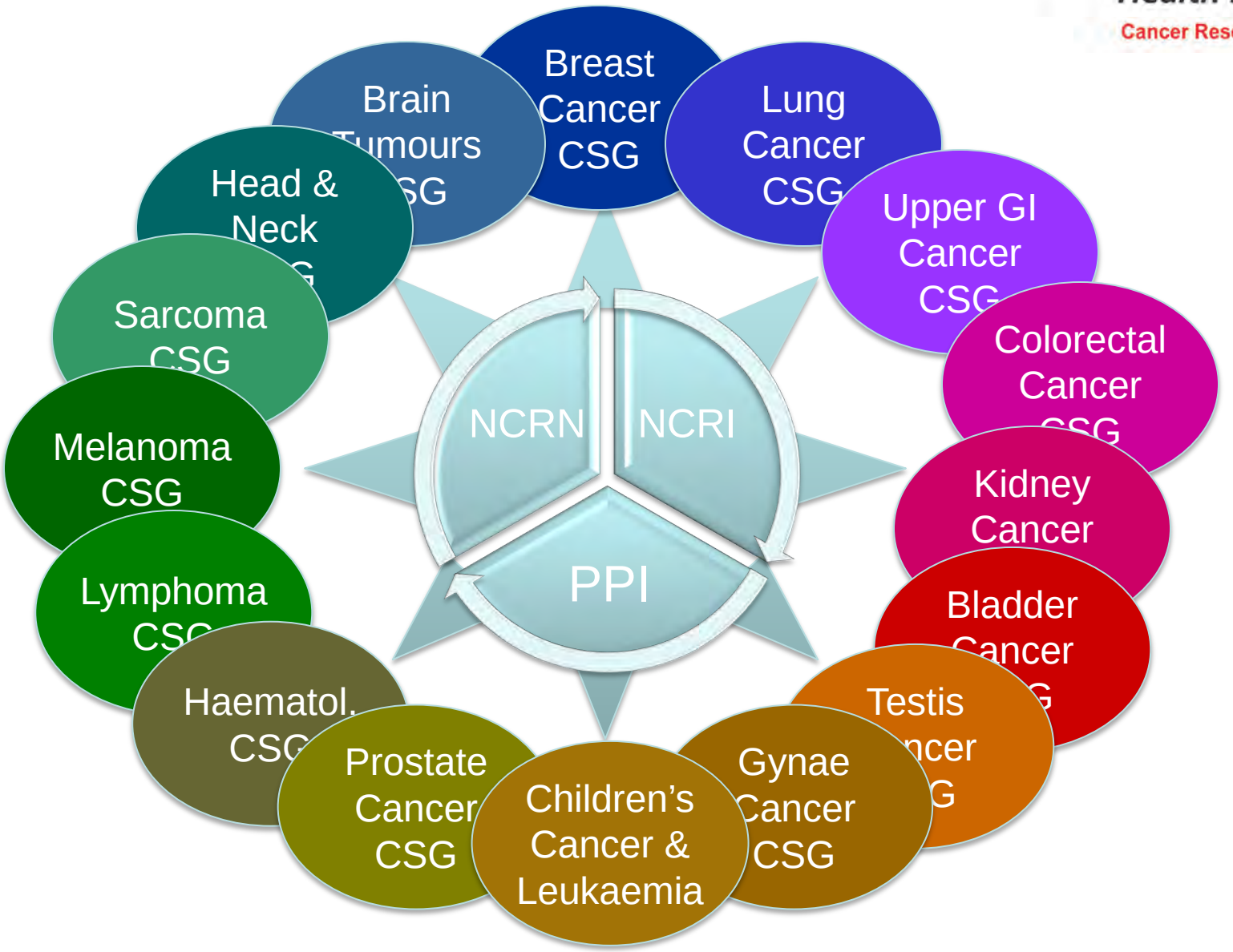
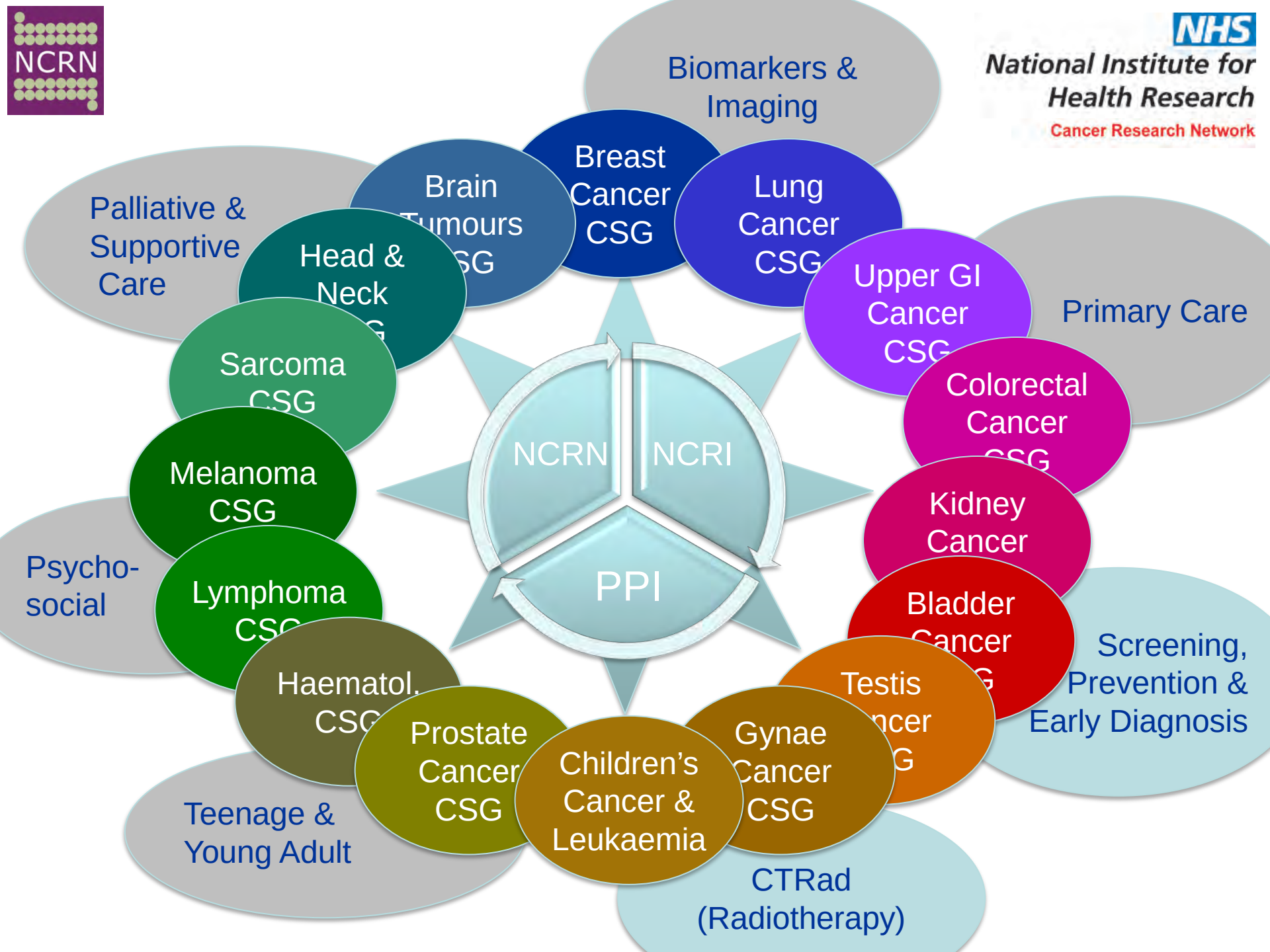
Clinical Studies Groups

- Provide the primary (but not only) route through which new proposals for clinical trials are developed in a specific disease area
- Membership rotational; competitive national appointment process for new Chairs and members
- Mainly clinical/scientific members; + patient and funding body reps
- Oversee existing studies, consider new research questions, develop new proposals, provide expert advice
- Interface with industry partners for consultation, feasibility

NCRN

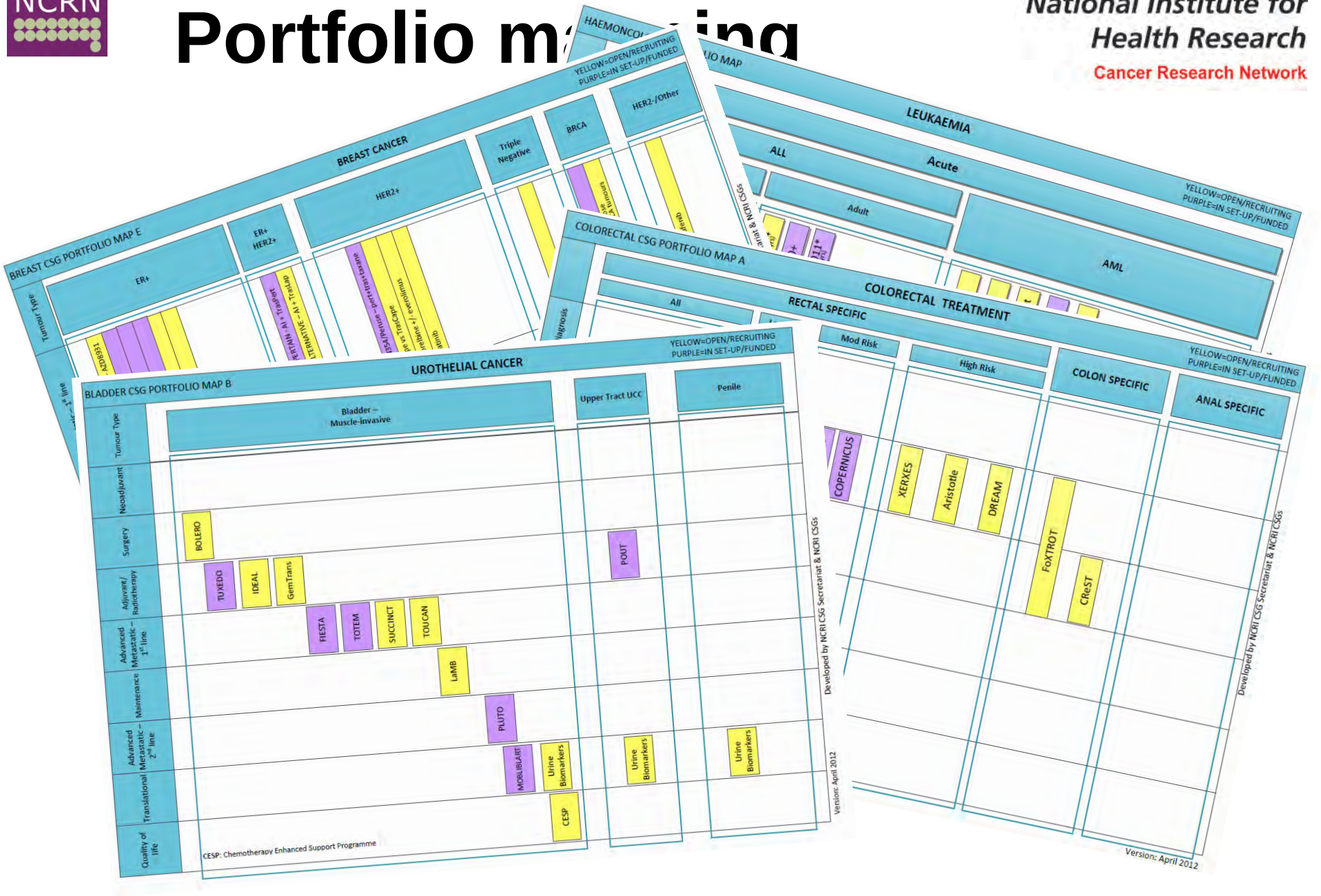
NHS
National Institute for Health Research
Cancer Research Network




NCRN
NHS
National Institute for Health Research
Cancer Research Network
Biomarkers & Imaging
Breast Cancer CSG
Lung Cancer CSG
Brain Tumours CSG
Head & Neck CSG
Palliative & Supportive Care
Upper GI Cancer CSG
Primary Care
Sarcoma CSG
Colorectal Cancer CSG
Melanoma CSG
Kidney Cancer
Psycho-social
Lymphoma CSG
Bladder Cancer CSG
Haematol. CSG
Testis Cancer CSG
Screening, Prevention & Early Diagnosis
Prostate Cancer CSG
Gynae Cancer CSG
Children's Cancer & Leukaemia
Teenage & Young Adult
CTRad (Radiotherapy)
NCRN
NCRI
PPI

Portfolio mapping

National Institute for Health Research
Cancer Research Network



CSG Progress Reviews

- All undergo external, but light touch, peer review every 3 years
- UK & International peer reviewers
- Consideration of membership, activity, scope, future plans & strategic direction
  - Review of research portfolio, but not current trials individually in depth
- Provides some guidance for incoming Chairs
- Most reviews continue to recommend tighter integration of translational research

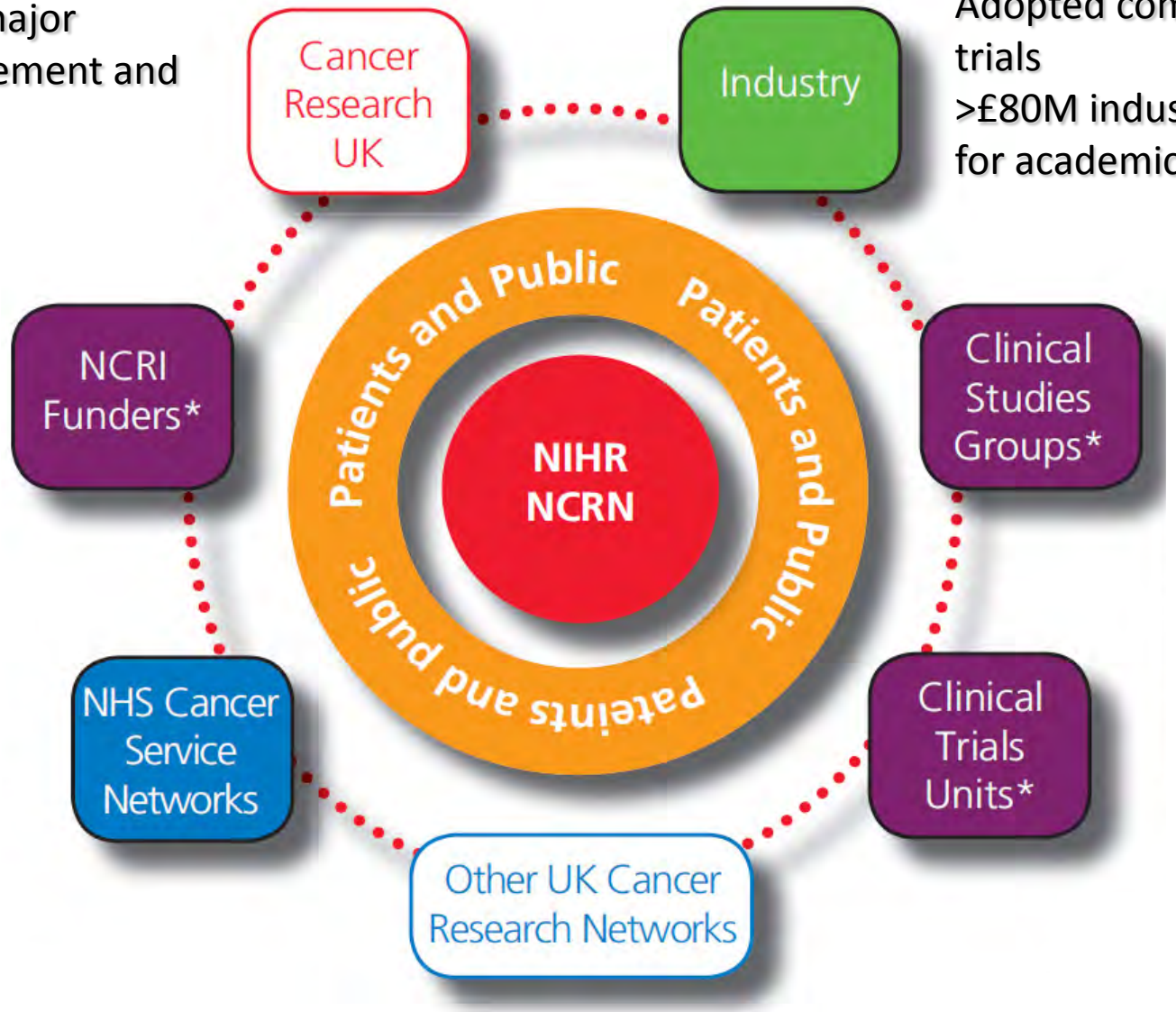
National Portfolio Database of Clinical Trials (650+)

NHS National Institute for Health Research

Whole system working

NCRI, NIHR & major funders' engagement and commitment

Adopted commercial trials
>£80M industry support for academic trials



Research part of Service Network agenda

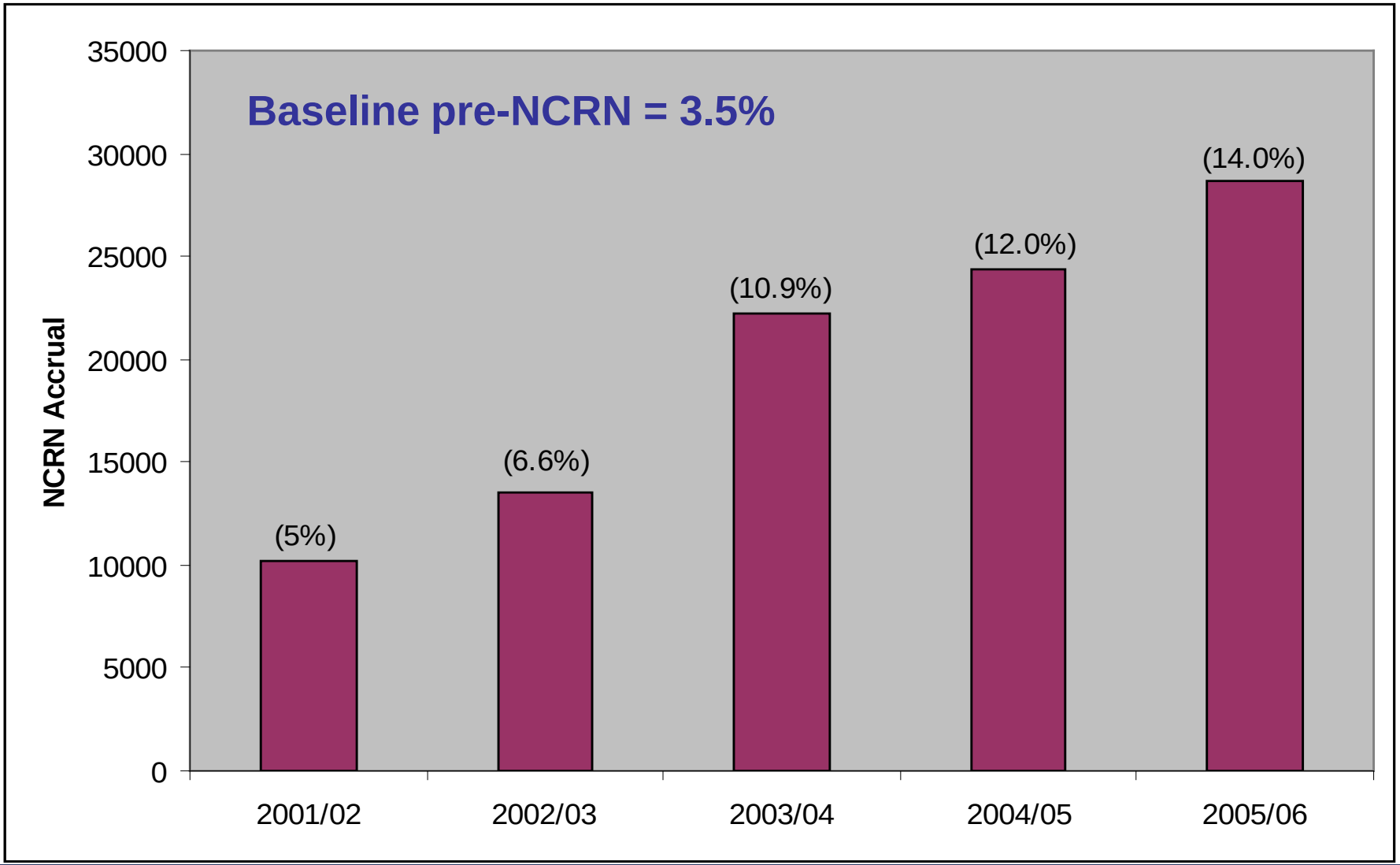
NCRN National Cancer Research Network

Original aims of the NCRN

- To benefit patients by improving the coordination, integration, quality, inclusiveness and speed of cancer research
- To develop a world class infrastructure
- To double the number of cancer patients entered into clinical trials and other well designed studies by April 2004
- Accrual is compared to annual incidence of all cancers (except non-melanoma skin cancer)

→ Doubling of accrual achieved in < 3 years

Accrual to NCRN Portfolio studies English Cancer Research Networks



NCRN

NHS National Institute for Health Research Cancer Research Network

CLINICAL RESEARCH BOOST

United Kingdom Becomes the Cancer Clinical Trials Recruitment Capital of the World

By Gunjan Sinha

The more cancer patients that doctors recruit into clinical trials, the faster they can test new therapies. Yet recruitment remains abysmally low—except within the United Kingdom. Last year 32,000 patients—the equivalent of 14% of Britain's annual cancer incidence—participated in cancer clinical trials.

"That's the highest rate of cancer clinical trial participation of any country in the world," said Richard Kaplan, M.D., associate director of Britain's National Cancer Research Network (NCRN). By contrast, less than 3% of all U.S. cancer patients participate in clinical trials, according to the National Cancer Institute.

Beginning in the early 1990s, the United Kingdom's Department of Health set out to overhaul cancer care. The National Health Service (NHS) not only established regional networks to ensure better access to care but also in 2000 set up NCRN to boost clinical research—and clinical trial participation jumped.

Can the United States boost its own clinical trial participation by following Britain's lead? Not quite, experts said, but the United States is working toward improving clinical research in other ways.

The Backdrop

Britain's cancer network was borne from research suggesting that U.K. patients received inferior cancer care. According to the Eurocare-3 study published in 2003, British patients were up to 30% less likely than their European counterparts to survive cancer. The study pooled data from 19 countries between 1990 and 1999.

The study only confirmed widespread fears. For decades, patients had complained that doctors were catching cancers too late to treat them effectively, partly because of the time between diagnoses and treatment at a specialized care facility was often longer than 1 month. To address the disparity, the NHS created a cancer care network during the late 1990s by dividing the country into regions and making hospitals and specialists responsible for cancer care within their designated region. Scotland and Wales followed suit. Each region set up a structured referral system, streamlining access to specialized cancer care, Kaplan explained.

But these regional cancer care clusters did not coordinate clinical research. That task was added in 2000 when a consortium of health care groups and funding agencies created the NCRN. As part of its overall cancer plan, the U.K. health department joined with other government agencies and large charities to pledge substantial funds to set up the research network's infrastructure. By 2004, the NHS had allocated an additional £570 million ($1.1 billion) each year to improve patient access to cancer care and boost clinical research.

At 14%, the United Kingdom has "the highest rate of cancer clinical trial participation of any country in the world."

Recruitment in Practice

About £5 million ($10 million) of that goes to the NCRN, which in turn distributes the additional funds to regional networks on the basis of population size and, increasingly, on performance. There are now 41 networks across the United Kingdom. Although these regional networks allocate funds to suit the network's needs, most have hired more staff such as dedicated research nurses and data managers to satisfy goals laid out in the department of health's cancer plan to increase clinical trial recruitment.

For time-strapped doctors, support staff have smoothed the traditionally kinked path from patient to clinical trials. Dedicated nurses interact with patients and clinicians to determine whether a patient is eligible for a particular trial. They also explain trial details to patients, handle informed consent, and ultimately register patients in any given trial. Data managers collect follow-up data and log information in databases.

NCRN's initial mandate was to double clinical trial participation from 3.5% in 3 years. The agency rocketed past it—14% of cancer patients now participate in clinical trials. Preliminary studies also show that care has improved. The rate of rectal surgery to remove diseased parts of the large bowel or rectum, for example, has fallen from 24.5% to 18% from 2001 to 2005—suggesting that physicians are detecting and or treating bowel cancer earlier.

Patient advocacy groups, such as CancerBaCUP, have also largely applauded the improvements but are calling for a second plan to address remaining shortfalls. "Whilst we are pleased at the progress, there are still unacceptable delays in waiting times for some diagnostic procedures, a shortage of suitable information for patients, and a lack of coordination of services," said Joanne Rule, chief executive of the U.K. cancer patient advocacy group. For example, patients in some regions still experience unacceptable delays in treatment, Rule said, because of an acute shortage of radiographers.

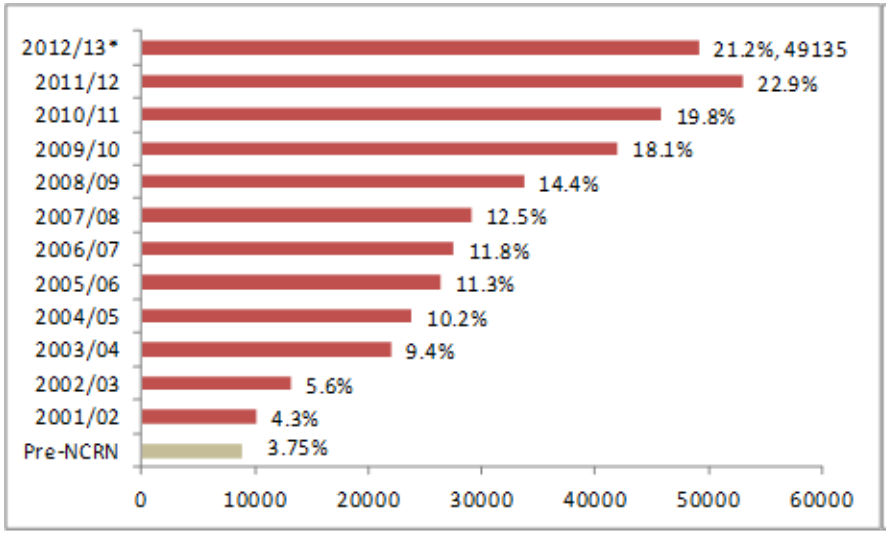
"There is also the ongoing issue of access to drugs and spending on cancer treatments still lagging behind [those of] other European countries."

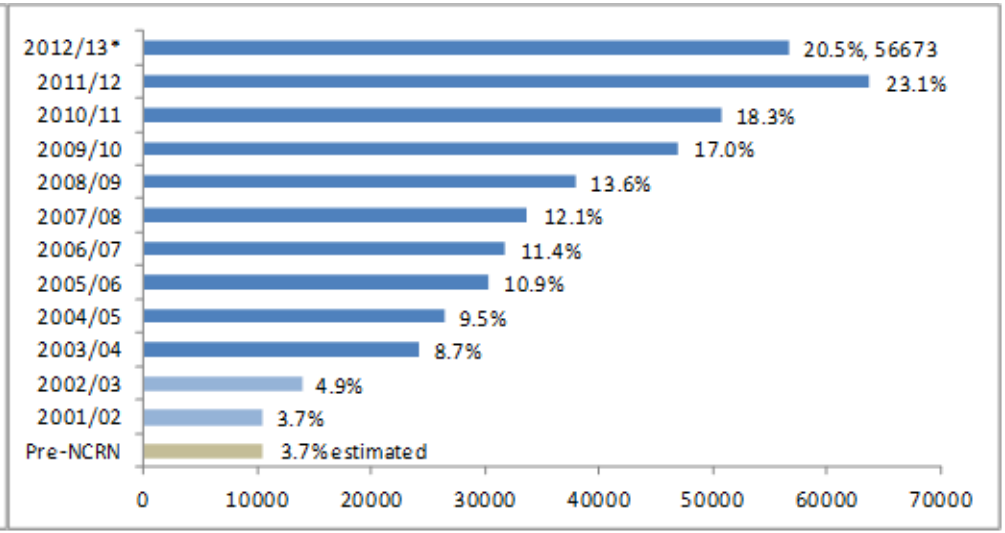
JNCI 99 (6) 420-421, 2007

NCRN

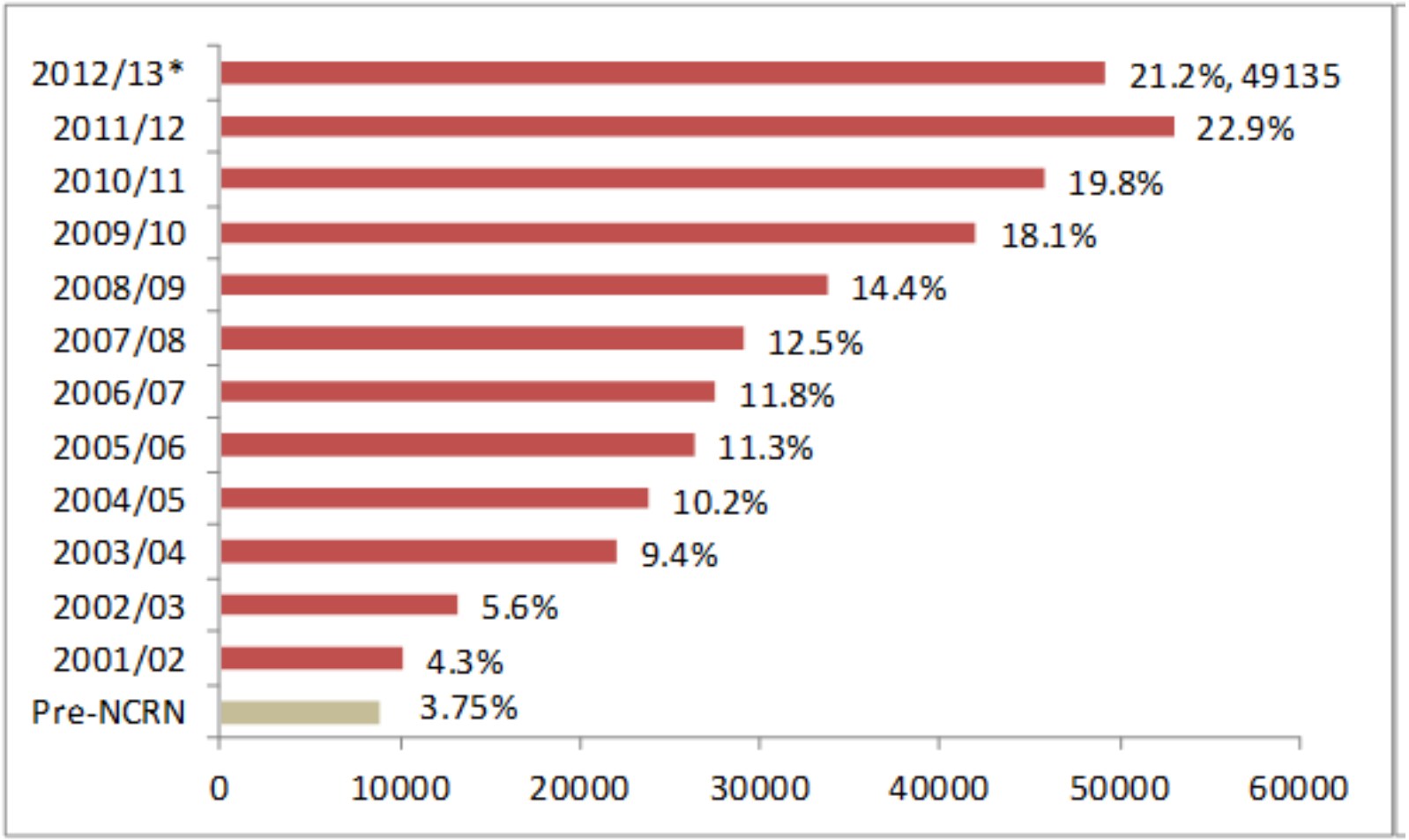
NHS
National Institute for Health Research
Cancer Research Network

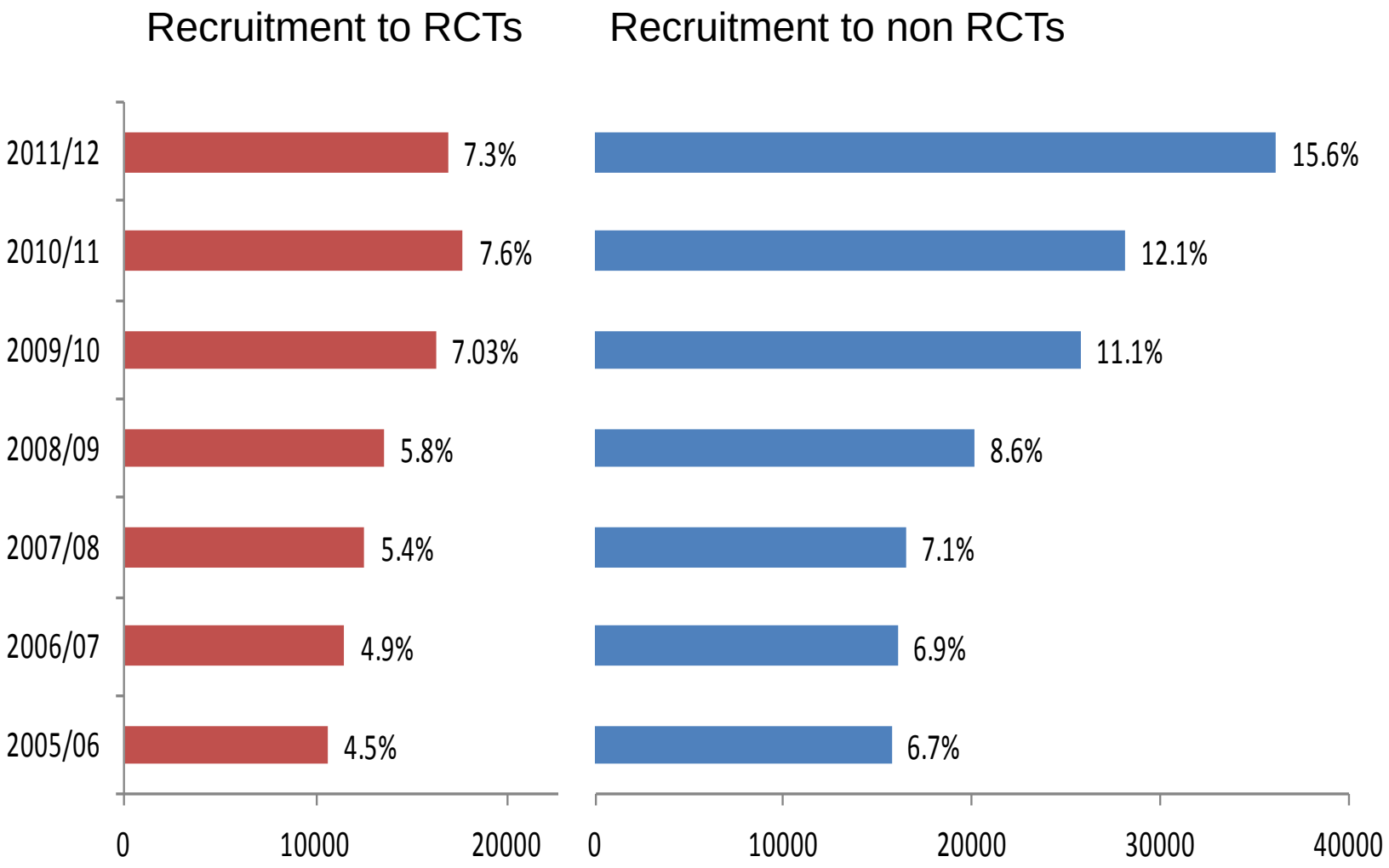
Cancer study enrolment England & UK as a whole



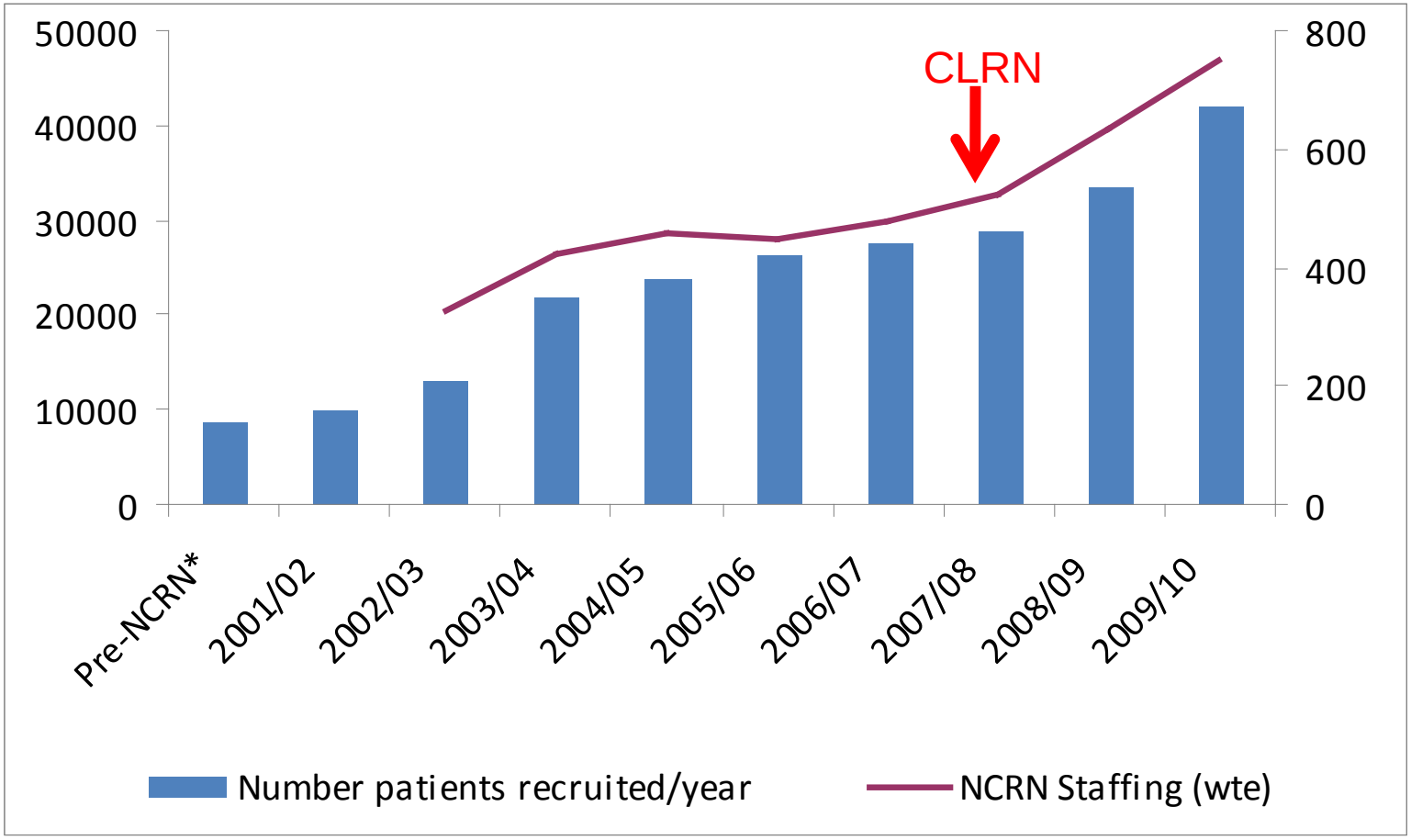


Cancer patient trial enrolment - England

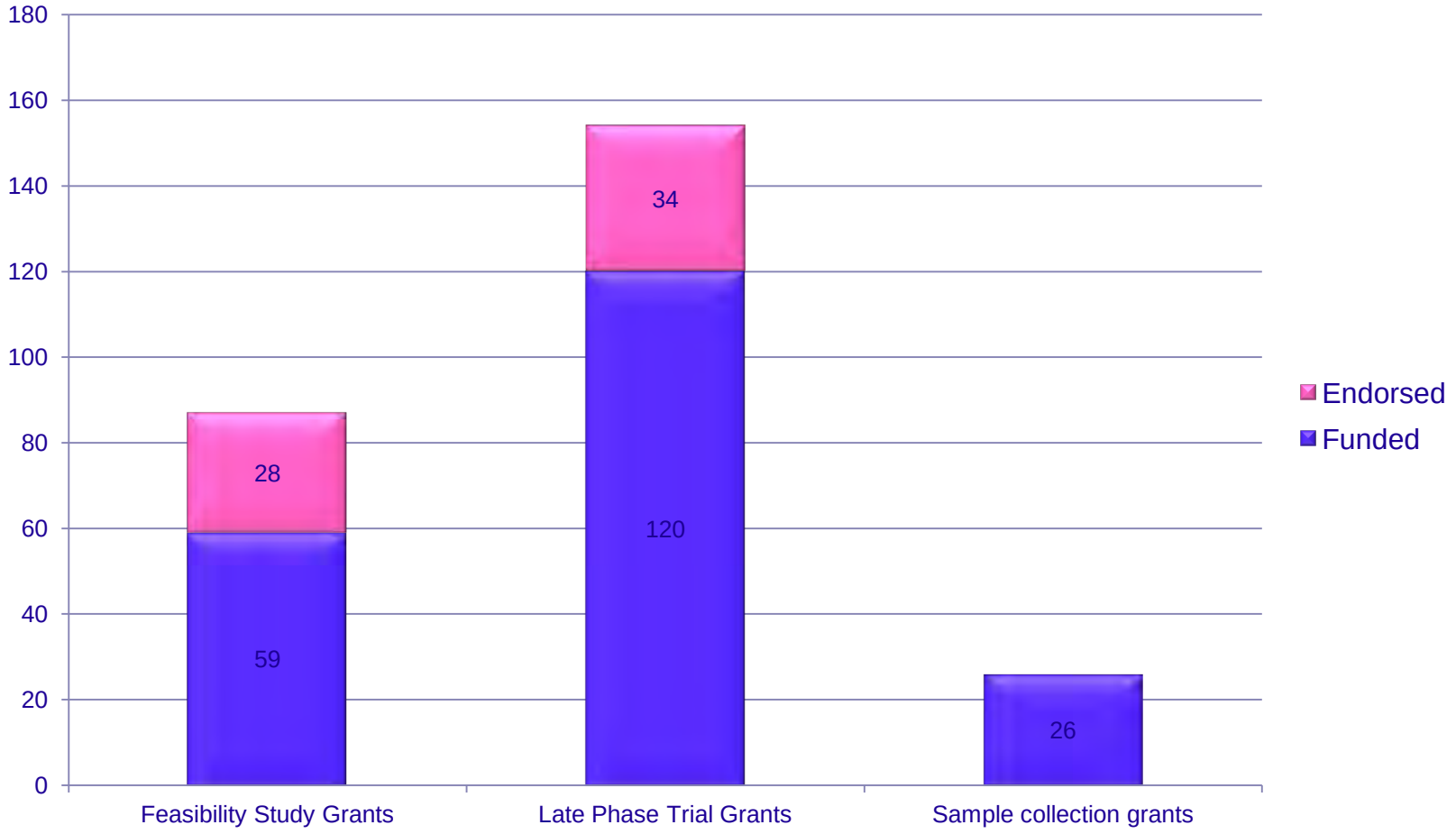



Recruitment to RCTs
Recruitment to non RCTs
2011/12
2010/11
2009/10
2008/09
2007/08
2006/07
2005/06
7.3%
7.6%
7.03%
5.8%
5.4%
4.9%
4.5%
15.6%
12.1%
11.1%
8.6%
7.1%
6.9%
6.7%
0
10000
20000
0
10000
20000
30000
40000

Sustained funding
Committed staff



Current CR-UK Portfolio – CTAAC studies



CTAAC Portfolio Summary (n=267). Data correct as of 28 June 2011

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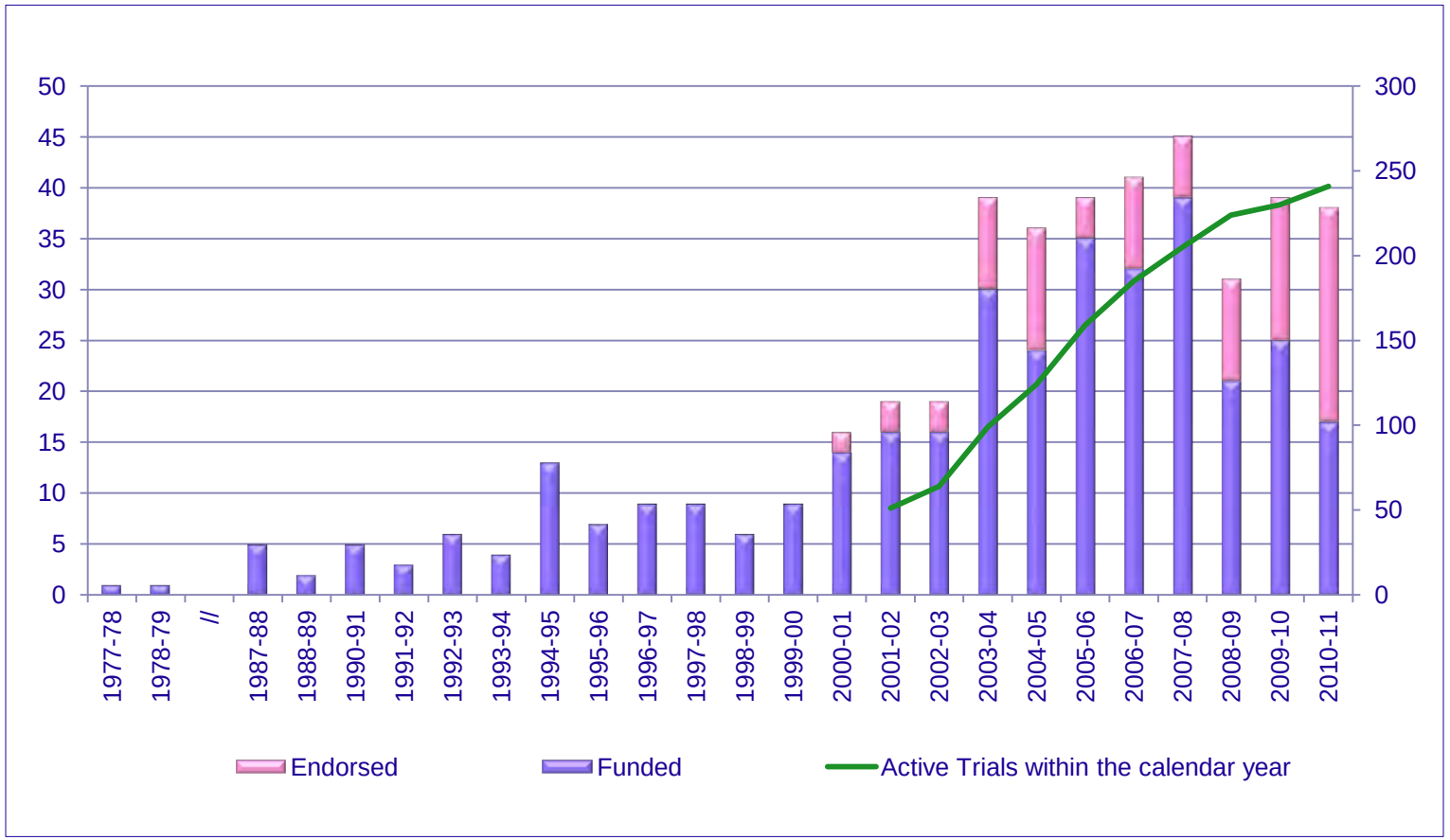
CTAAC clinical trials supported 1978 – 2011(total n=444)



Data correct as of 28 June 2011

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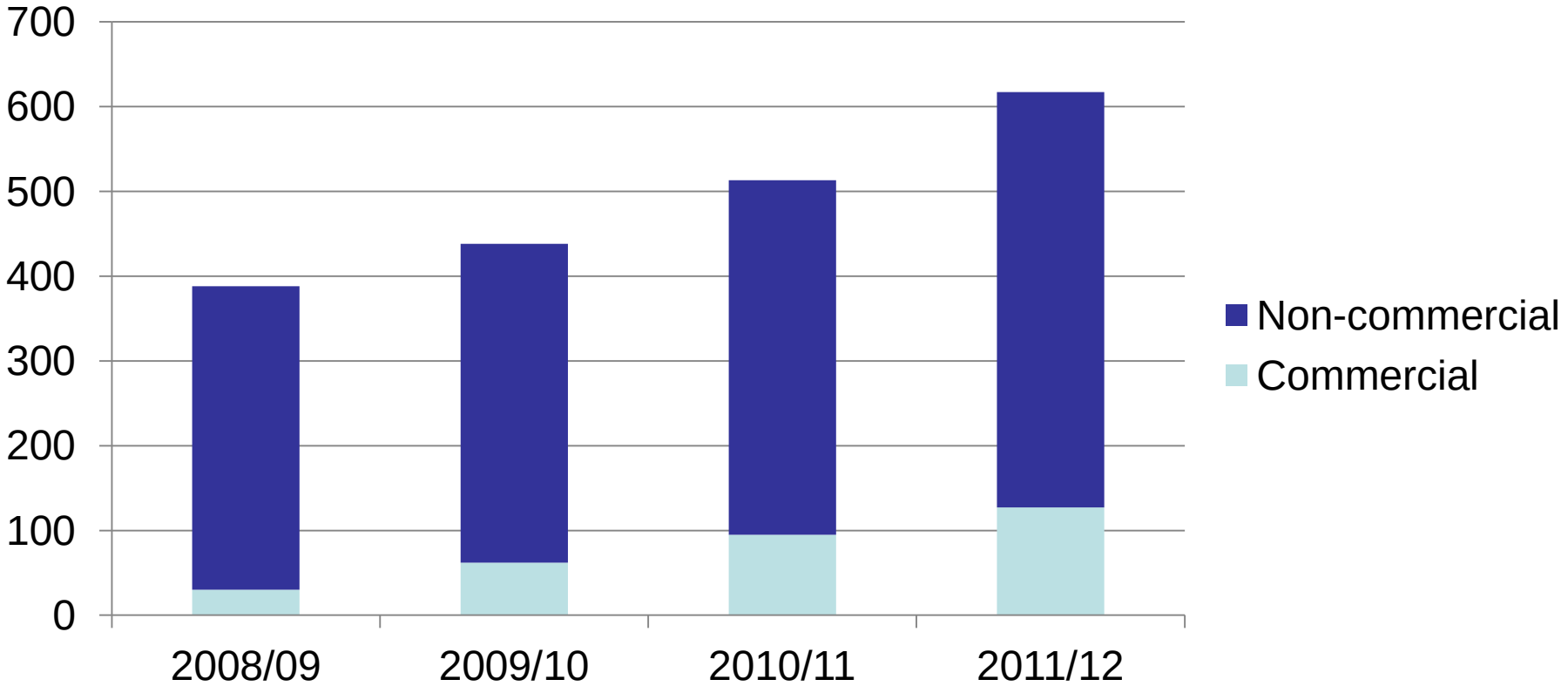
Number of cancer studies open to recruitment/year



CSG portfolios as of May 2012	Trials in Set-Up	Currently Open	Completed or suspended	Total
Site-specific CSGs:				
Bladder Cancer CSG	3	10	18	31
Brain Tumour CSG	0	16	10	26
Breast Cancer CSG	8	81	142	231
Colorectal Cancer CSG	6	46	68	120
Gynaecological Cancer CSG	7	26	52	85
Haematological Oncology CSG	8	61	48	117
Head and Neck Cancer CSG	7	17	30	54
Lung Cancer CSG	5	49	63	117
Lymphoma CSG	1	37	45	83
Melanoma CSG	2	15	27	44
Prostate Cancer CSG	4	30	48	82
Renal Cancer CSG	2	12	11	25
Sarcoma CSG	2	17	10	29
Testis Cancer CSG	1	5	13	19
Upper GI Cancer CSG	4	42	51	97
Cross-Cutting CSGs:				
Biomarkers & Imaging CSG	0	3	0	3
Children's Cancer & Leukaemia CSG	3	37	64	104
Complementary Therapies CSDG	1	2	12	15
Palliative Care CSG	1	32	40	73
Primary Care CSG	0	8	22	30
Psychosocial Oncology CSG	4	24	61	89
Teenage & Young Adult CSDG	0	2	2	4
Portfolio Totals	**61**	**488**	**768**	**1317**

How was NCRN successful?

- Accrual increased 4-5x in 10 years, reaching >20% against annual incidence
- Raw numbers now roughly twice US Cooperative Group system, with about 1/5 the population
- Both momentum and availability of increased research funding led to major increase in number of trials, as well as rate of completion
- Initial expansion of activity was greatest in DGHs (community hospitals) previously not research active
- The new resources (research nurse staff) seemed to be the most important driver of success
- However, limited NHS access to novel agents does make trials quite attractive to clinicians & patients in Britain

Why was NCRN successful?

- Size of UK favours nationwide collaboration
- NHS has accepted that clinical research should be an accepted element of what a health care system does
- Funders careful to prevent too many competing large scale trials; they coordinate to some extent
- Funders careful to assess that research questions are considered ‘important’ by external peer reviewers
  - Or by national agreement to support one trial instead of others

Why was NCRN successful? -2

- Each regional network (and each hospital within it) can select which trials it chooses to support
  . . . (subject to qualifications and resources)
- Networks have targets for trial participation and are reviewed annually
- 'League tables' are compiled and made public
- Smaller community hospitals tend to participate in non-interventional (*eg*., genetic) and non-randomised studies, and refer patients through defined care pathways to major cancer centres for more complex and IMP trials
- 90%+ of care is via the NHS and involves no fee-for-service

Why was NCRN successful? -3

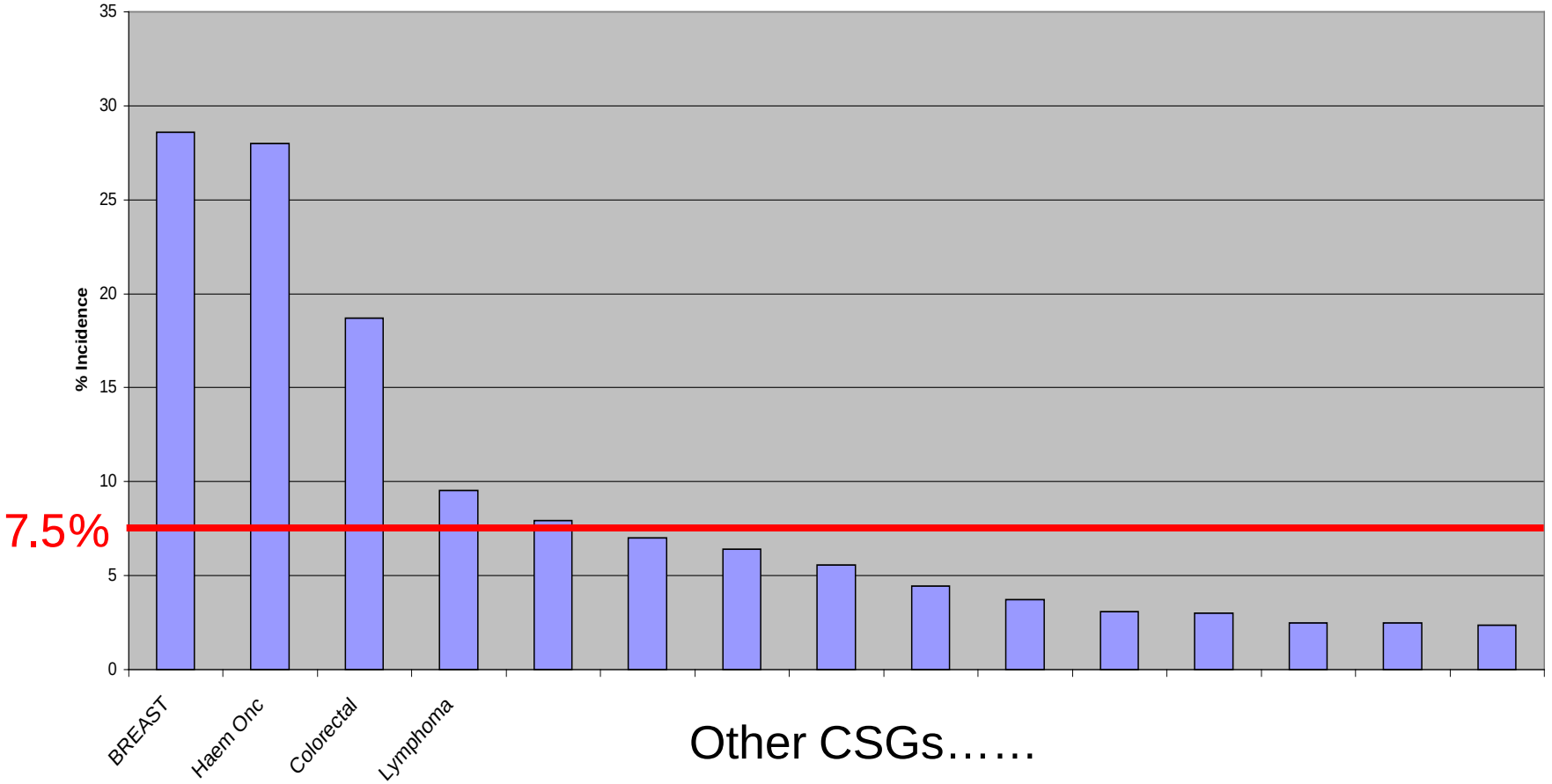
- Strategic alignment of charity & government funders →
- Cancer R&D infrastructure with a high degree of coordination →
- National forums for strategic planning
- . . . which involve the CSGs at every step

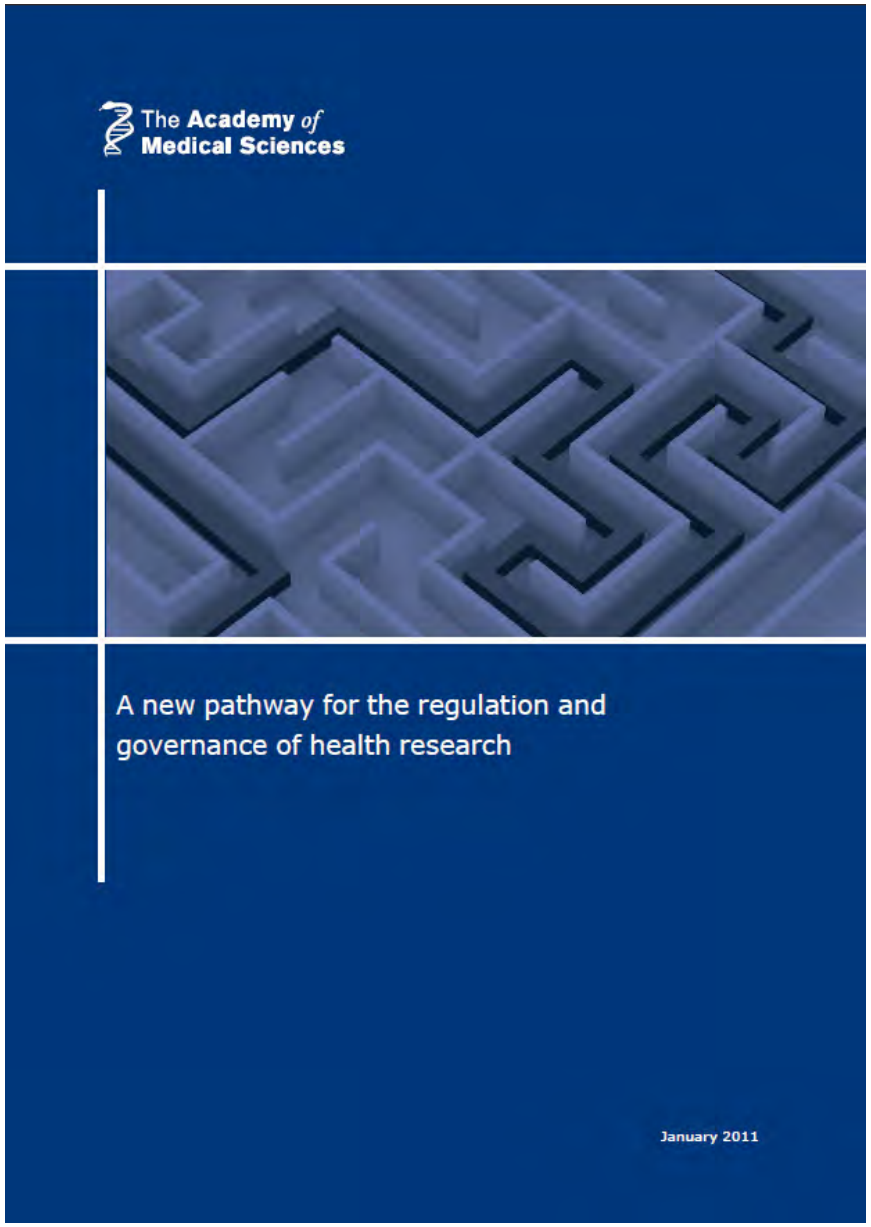
- Recently, an element of (regional) network funding has been explicitly linked to actual activity
- And individual trials will be required to meet time & target metrics

Challenges for NCRN

- Maintaining momentum in the face of nearing full capacity
  - Economy will not now support increase in overall allocation
- Increased burden of following patients on prior trials interfering with ability to take on new ones
- Some of the most important studies are the most work-intensive; local networks tending to activate the easier studies
- Studies in rarer disease types should be a UK strength but the metrics put them at a disadvantage
- Organisational changes as the DoH tries to fold NCRN into a larger comprehensive network for all diseases
- Complex system for approvals (delays in activation of trials)

Overall accrual against Incidence





Regulation and Governance

Building on UK strengths and recent investment

Government commission

Scope:

'Health research'.

Review the landscape and make recommendations to increase the speed of decision-making, reduce complexity and eliminate unnecessary bureaucracy and cost.

Process:

Academy working group.

Two calls for evidence – over 300 submissions.

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Key bottlenecks identified

- Delays and duplication in obtaining research permission from **NHS Trusts**.
- **Complexity and inconsistency across the regulatory pathway** e.g. access to patient data.
- A lack of proportionality in the **regulation of clinical trials**.
- A healthcare culture that fails to fully support the value and benefits of health research.

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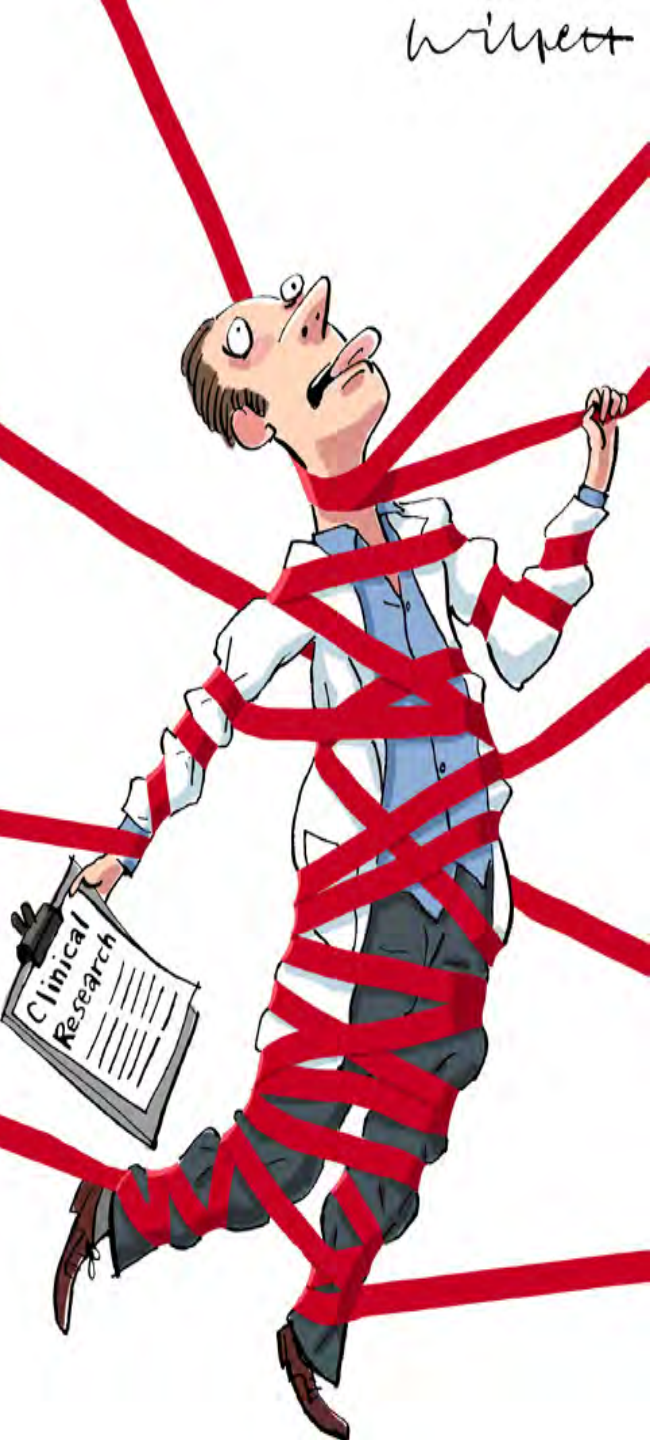

Main recommendations

The creation of a new **National Research Governance Service**.

As one core component within a new **Health Research Regulatory Agency** that would also undertake ethics and required specialist approvals.

Streamlining access to patient data while maintaining appropriate safeguards.

Revision of the European Clinical Trials Directive and a more proportionate approach by the MHRA to clinical trials regulation and monitoring.

Health research formally and irreversibly **embedded into NHS** leadership and governance processes.

⇒ Broad support from across the political parties and the commercial and non-commercial research community.

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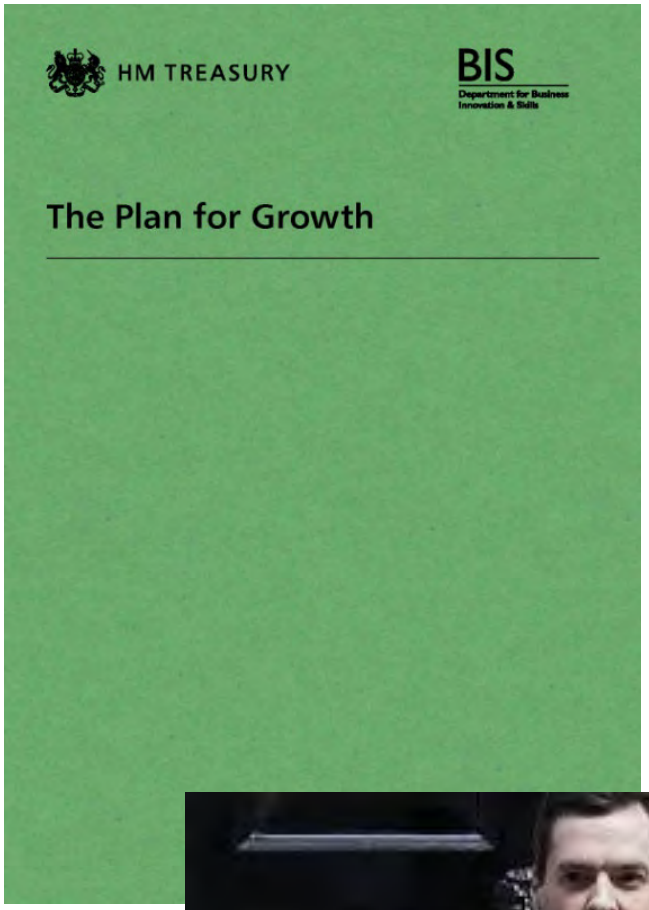

Government response

'In life sciences…we will radically reduce the time it takes to get approval for the clinical trials.'

George Osborne

- Focus on 'healthcare and life sciences' as a key sector for long-term growth.

- Commitment to take forward many of AMS key recommendations.

CANCER RESEARCH UK

NHS
National Institute for Health Research

Government Plan for Growth

- The Health Research Authority
  - Initially a Special Health Authority with the NRES as its core
  - Streamline regulation, create a unified approval process, and promote proportionate standards for compliance and inspection within a consistent national system of research governance
  - Legislation laid before Parliament in September 2011

- NIHR Research Support Services framework
  - Launched in May 2011
  - Framework of good practice and standard procedures for consistent local research management and greatly improve performance
  - Publish outcomes against public benchmarks, including a 70-day benchmark to recruit first patients for trials

Differences from the US

- Clinical trials considered a responsibility of every NHS Trust – and a significant component of costs accepted
- Research nurses & staff employed by NHS in each locality but have only trials responsibility, not routine care
- Performance targets in place for networks (largely informal)
- . . . met by local choices from a national portfolio
- Restrictions on access to drugs outside approved indications
- Little disincentive to refer patients for trials within regional networks
  - But far more reluctance of patients to travel
- Few oncologists who do not actively recruit to trials

Differences from the US - 2

- A single national committee overseeing the portfolio for each type of cancer
  - For rarer cancers there may be a single national trial
  - For more common cancers, still one committee oversees all trials
  - Very large trials feasible, incl. those requiring ambitious coordination (*eg*., FOCUS4 stratified trial in colorectal ca)
- Research (non-clinical) costs for each trial funded by individual peer review