

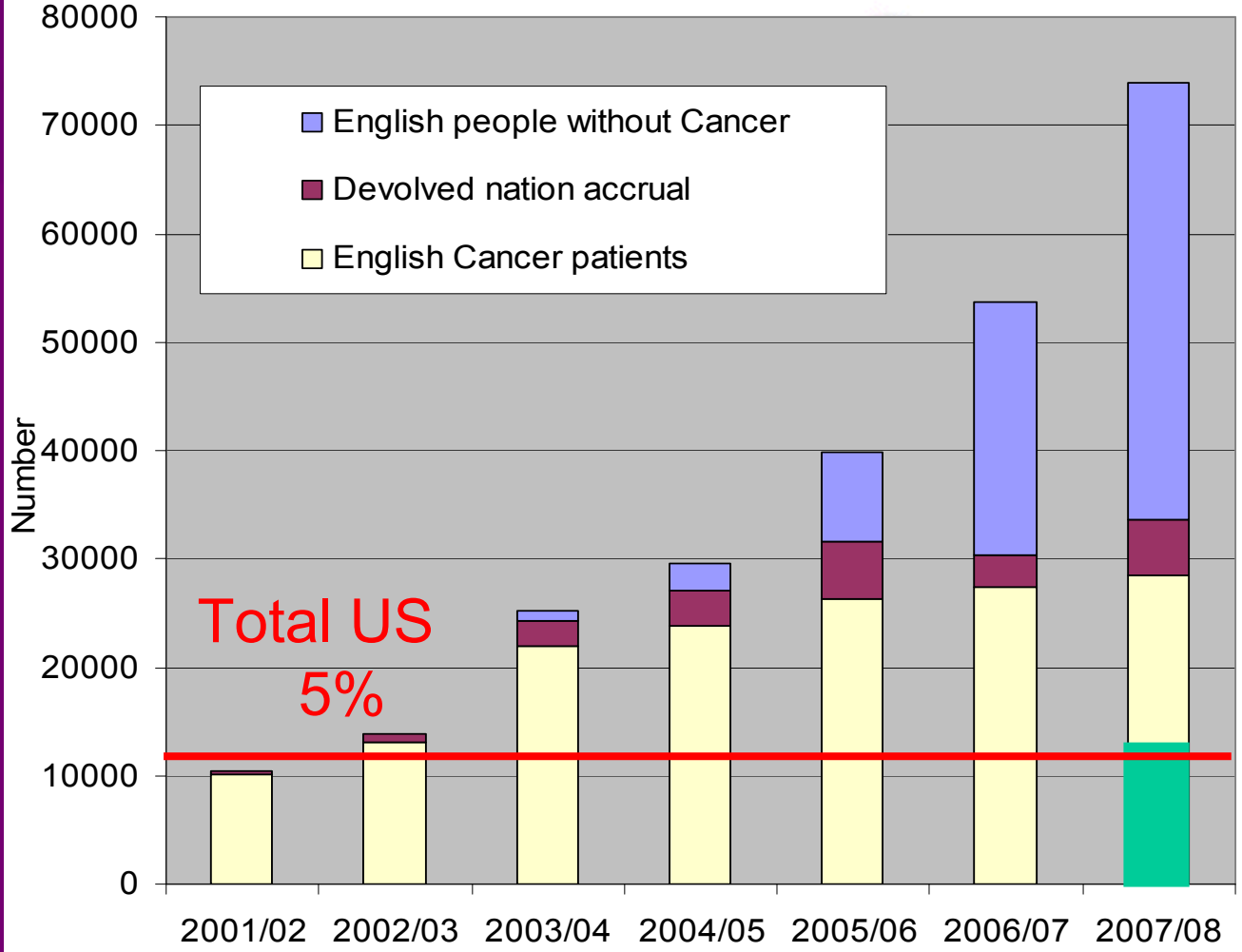
# Challenges & Strategic Directions in Cancer: learning from the NCRN Experience

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National Cancer Research Network  
&  
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# 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 was compared to annual incidence of all cancers (except non-melanoma skin cancer)
- Doubling of accrual achieved in < 3 years

# Total annual accrual to NIHR cancer trials



5.4% cancer patients into randomised trials

# NCRN's Initial Advantages

- Late phase oncology trials were typically collaborative and multi-centre and there were some standing structures to support them
- CRUK was already a huge and pro-active funder
- The NCRN as a managed research network was mapped directly onto the NHS cancer service networks across England

# How was NCRN successful?

- Accrual more than trebled in 5 years, reaching a peak of >13% against annual incidence
- Raw numbers now roughly equal to 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
- Expansion of activity was greatest in district 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

# US Reaction:

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## NEWS

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### CLINICAL RESEARCH BOOST

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

By Gunjan Sinha

**T**he 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

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

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

# UK Advantages – Oncology/NCRN

- Cancer trials infrastructure with a high degree of coordination but local priority setting
- Strategic alignment of charity & government funders
- DH and NCRN commitment to industry partnership
- National forums for strategic planning
- Highest rate of cancer trials accrual of any country
- A trials 'culture':  $\geq 13\%$  of cancer patients in trials
- Potential for nationwide clinically annotated specimen resource
- Potential for comprehensive epidemiological, demographic, outcomes, & resource utilisation data

# UK advantages for Pharma

- UK has a coordinated national research infrastructure (NIHR), with effective control over non-evidence-based drug usage (NHS)
  - *Can undertake studies that are difficult to do in more open pharmaceutical markets*
- Expanding clinical research funding mechanisms + commitment to working with industry
- A pool of some of the world's most experienced drug developers
- Major Pharma anxious to retain UK base & operations; especially committed to oncology

# Industry Trials in NCRN

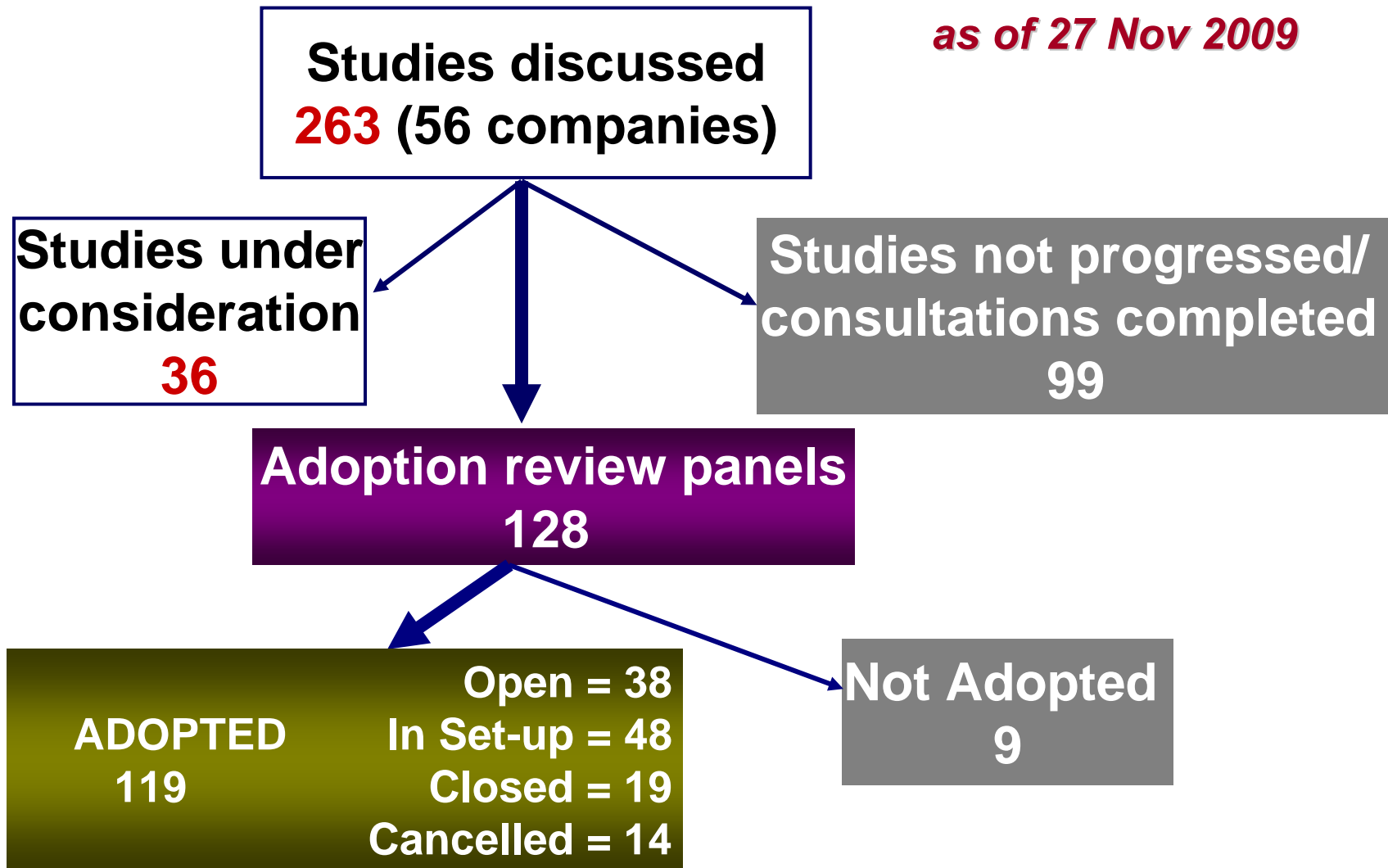
- Effective collaboration with the UK pharmaceutical, biotech & device industries is a founding principle of NIHR (now a parent organisation of NCRN)
- Trials need not come through or use the networks, but it is intended to be advantageous to do so
- NIHR working with DH and industry partners to improve the clinical research environment for industry in the UK – and in the process improve the research environment for all clinical research
  - Scale & scope of the initiative → momentum for progress
- Industry-led and investigator-led trials within the same overall portfolio

# NCRN offer to companies for commercial trials

- *Reliable UK feasibility & site selection*
  - Single point of contact for network sites
  - Rapid access to new sites and patient populations
  
- *Systems for expediting start-up*
  - Rapid site set up through streamlined RM&G (CSP)
  
- *Study delivery to promised targets:*
  - Shared performance goals
  - Network monitoring and performance management
  - Experienced and trained research staff
  - Small to large trials
  - NCRN 'badging' of trials

# NCRN Industry Adoption Activity National Institute for Health Research

*as of 27 Nov 2009*



# Organisational/structural challenges for NCRN

- Linking funding to performance, whilst maintaining trials access
  - Infrastructure allocation is on a regional population basis
- Maintain momentum in the face of nearing full capacity
  - Economy unlikely to 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 tend to activate easier studies

# Structural challenges for NCRN model

- Studies in 'rarer' types of cancer are at a disadvantage
- Studies that need to recruit from non-oncology clinics (or primary care) are challenging
  - Including many surgical trials
  - Screening / diagnosis / prevention trials
- Imaging resources, pathology, and (research) pharmacy are constraints
  - May need additional mechanisms of support

# Challenges for NCRN networks

- Integration of translational research
- Access to high priority new agents
- Links with industry
- Join up industry interactions at early-phase level (ECMC centres) with CSGs' planning of late-phase trials
- Augment funding pool from industry work and charity support
- Support for investigator time and effort
- Establish clinical research participation as a critical and recognised priority activity throughout every cancer service network

# Challenges for UK oncology

- Access to new agents
  - Cost-sharing – especially for potential indications & opportunities additional to primary registration strategy
  - ~ 125 current (academic) trials have industry support
  - Joint company/NCRN/ECMC workshops
- Integration of translational research into network trials
  - Specimen handling, tracking logistics/staffing – especially if needed prior to randomisation – can tend to inhibit recruitment
- International coordination in trials planning & design

# Industry goals / achievements

## Broad partnerships with companies:

- Portfolio-based, not individual studies
  - 2 Companies bring all UK Oncology studies to NCRN
  - New, far reaching, **5-year arrangement with AZ** for collaborative novel agent development → *~30 phase randomised II studies approved to go ahead*
- Peer-review:
  - CRUK provides fast-track review of investigator-initiated industry collaborative translational studies (IITs)
- Pharma/biotech collaborations on IITs in 2006-08:
  - *£41.9M direct research support (+ free drug)*
  - *Currently 54 RCTs*

# Collaborative Trials (Investigator-initiated)

- Though this category has been little emphasised by pharma, the UK infrastructure and funding of ECMC centres and NCRN networks makes this an area of great potential
  - Phase II and Phase IV studies
- Studies of these types could have even more financial impact for UK companies

- Collaborative investigator-initiated (or investigator-influenced) studies are perhaps the most natural and consequential sphere of partnership
  - Phase II + Phase IV > Phase III
- Emphasise potential shortening of total cycle time (the overall sequence from early trials → completion of Phase III)

# Challenges for oncology in general

- How can we speed up development and testing, shortening time to patient access?
  - ECMC links; novel trial designs; combination development;
- How do we assess activity in early phase trials to improve our success rate in novel agent development?
- How can we predict which patients will respond to a new agent/regimen?
  - Validation of predictive or prognostic markers, particularly across multiple trials

- Patients have varying prognoses as well as varying probabilities of being helped by a given treatment
- Trials that ignored molecular heterogeneity may have missed important therapeutic benefit in subgroups
- Clinical trials that incorporate molecular stratification and recognize specific sensitive subgroups are critical to future progress

# Public/Private partnerships to 'validate' biomarkers or surrogates

No single large industry – or academic – trial may be able to advance on its own:

- Risk stratification algorithms
- Intermediate endpoints and surrogates for clinical response
- Surrogates for patient benefit

However, public funders (NIHR, MRC, CRUK, NCRI)  
+ an industry consortium  
+ an organised trials infrastructure  
. . . could co-ordinate this kind of research



# International strategic planning

- Some developments lead rapidly to widespread alterations in standard practice (in developed economies)
- In other situations standard practices remain divergent between countries for some time
- Both circumstances are relevant to planning trials strategy on an international basis
  - Collaboration on large trials or coordination of research questions & endpoints
  - Filling in knowledge gaps where the appropriate trials fit well

# International strategic planning

- In many places inadequate attention is paid to trials under way elsewhere
- In any case, knowledge of trials in development is poor – often it's only after they have been finalised and can't be changed that others have access
  - unnecessary duplication
  - trials that are poorly aligned and therefore not genuinely complementary
- (Meta-analysis is not a good substitute for poor planning of joint or complementary trials)

# Barriers to collaborating on a single international trial

- Regulatory complexity
- Industry business arrangements
- Logistical complexity (e.g., pharmacovigilance)
- Disincentives for investigators
  - delays
  - funding
  - academic recognition
  - control

# International strategic planning

- For uncommon cancers, joint international trials may be required for any progress to be made
- Also, where huge trials are required (*e.g.*, breast adjuvant), some joint trials are worth the effort involved
- For most cancers, the majority of trials are feasible on a regional basis, but coordinated planning may be necessary to maximise the information gained and the number of questions answered

- Transatlantic and international collaboration is necessary to:
  - Improve reliability
  - Improve Speed
  - Maximise Opportunities
- **As much about planning as doing trials together**
- Some tumour types have mechanisms in place, many do not

# International Coordination: What is Needed

Routine, consistent, communication about the design of trials still in development:

- Aligned eligibility criteria
- Similar treatment regimens (or at least consistent planned differences)
- Similarly defined endpoints
- Common control arm(s)
- Complementary questions or arms
- Prospectively planned joint analyses
- Cross validation of biomarkers
- Occasionally, joint trials

# What is needed

- Routine, consistent, communication about the design of trials still in development
  - requires organised approach and up-to-date information resource
  - identified individual(s) charged with this role
  - cross-representation on major national steering/strategy groups
- Coordination of funding peer review decisions for joint international trials
- Staff resource with experience in international collaborations

# Future plans

- **Augmenting capacity**
  - increase number of experienced, proven sites
  - Investment of commercial income
- **Optimal portfolio management**
  - Sharing information on all trials
- **Overcoming NHS systems barriers to cross-network (and cross-Trust) referrals to studies, especially for less common tumours**
- **National IT systems that can link potential subjects to trials for which they are potentially eligible**

