

Pragmatic Trials: The Next 50 Years

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&

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Pragmatic Trials @ 50

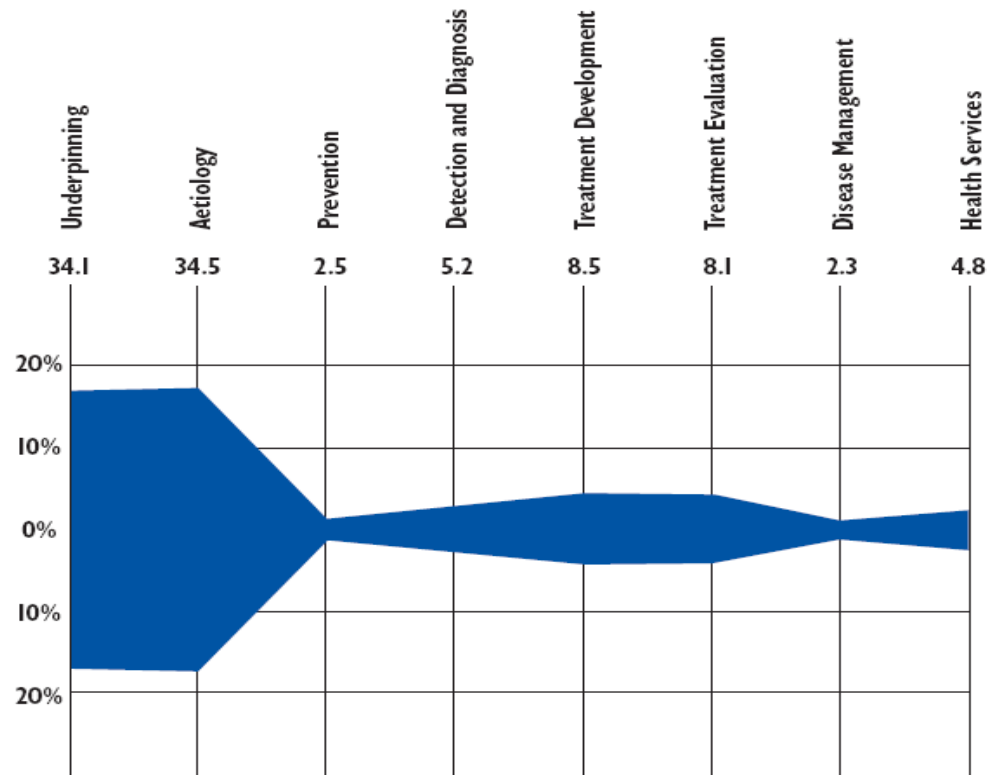
“Study the past if you would define the future” ~Confucius



Pragmatic Trials @ 50

- Past
- Present
- Future





Combined MRC and DH spend
Research spend 2004/2005 - UKCRC analysis

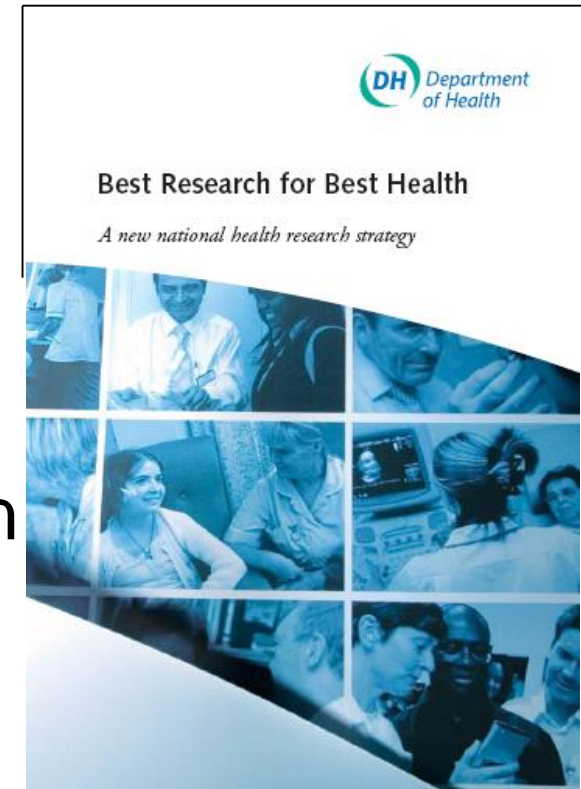
Key issues that needed addressing:

- Decline in clinical research community
- Decline in infrastructure for clinical research
- Complex regulatory environment
- Need to recognise Industry R&D needs in the UK
- Not yet realising the potential of a single National Health Service

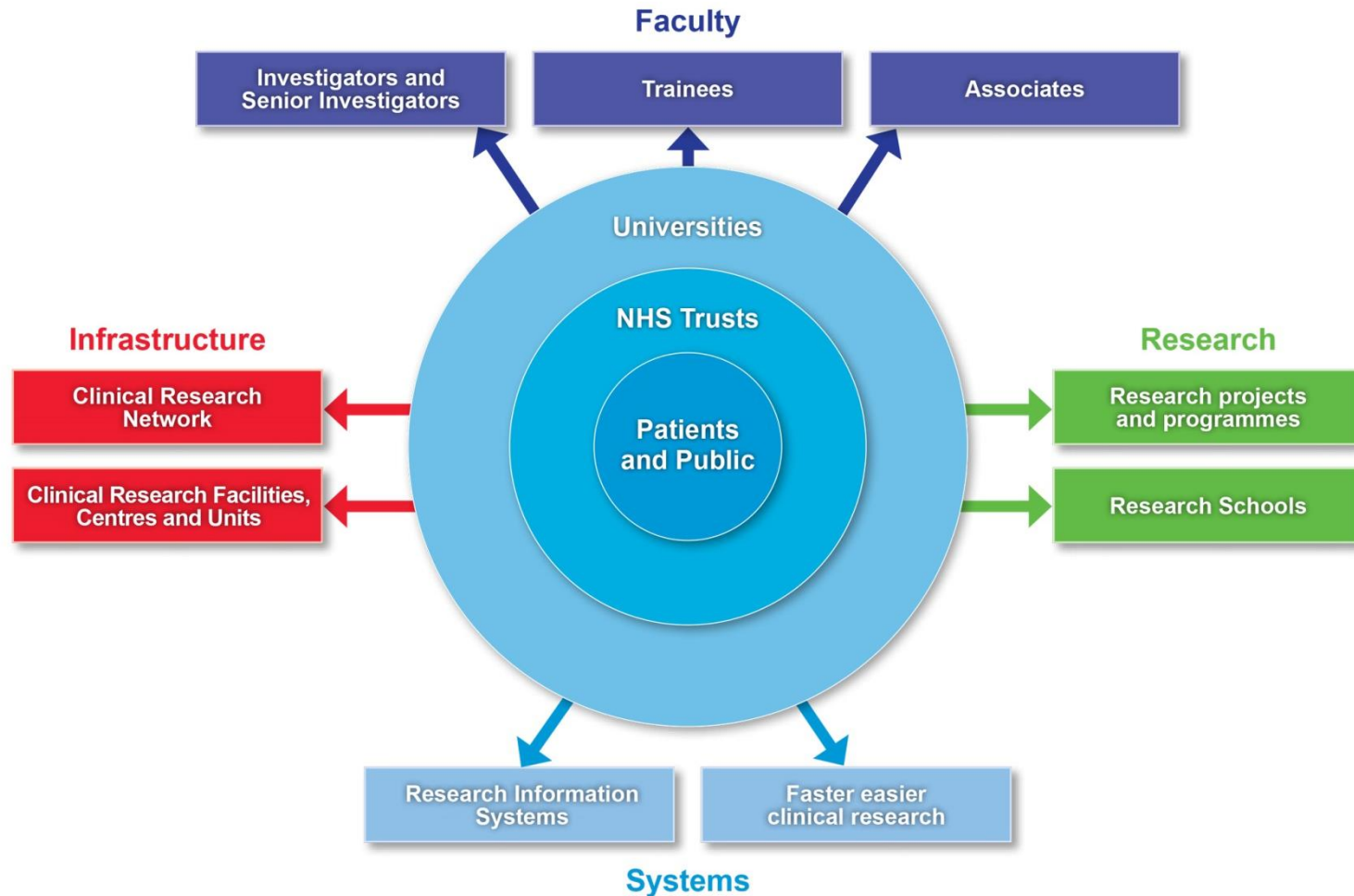


NHS R&D Strategy 2006

“To create a **health research system** in which the NHS supports **outstanding individuals**, working in **world-class facilities**, conducting **leading-edge research**, **focused on the needs of patients and the public**”



The NIHR health research system



NIHR-Supported Facilities

NIHR Biomedical Research Units



NIHR Health Protection Research Units



NIHR Biomedical Research Centres



NIHR Blood and Transplant Research Units



NIHR Healthcare Technology Co-operatives



NIHR Diagnostic Evidence Co-operatives



NIHR-supported Clinical Research Facilities



NIHR School for Public Health Research



NIHR School for Primary Care Research



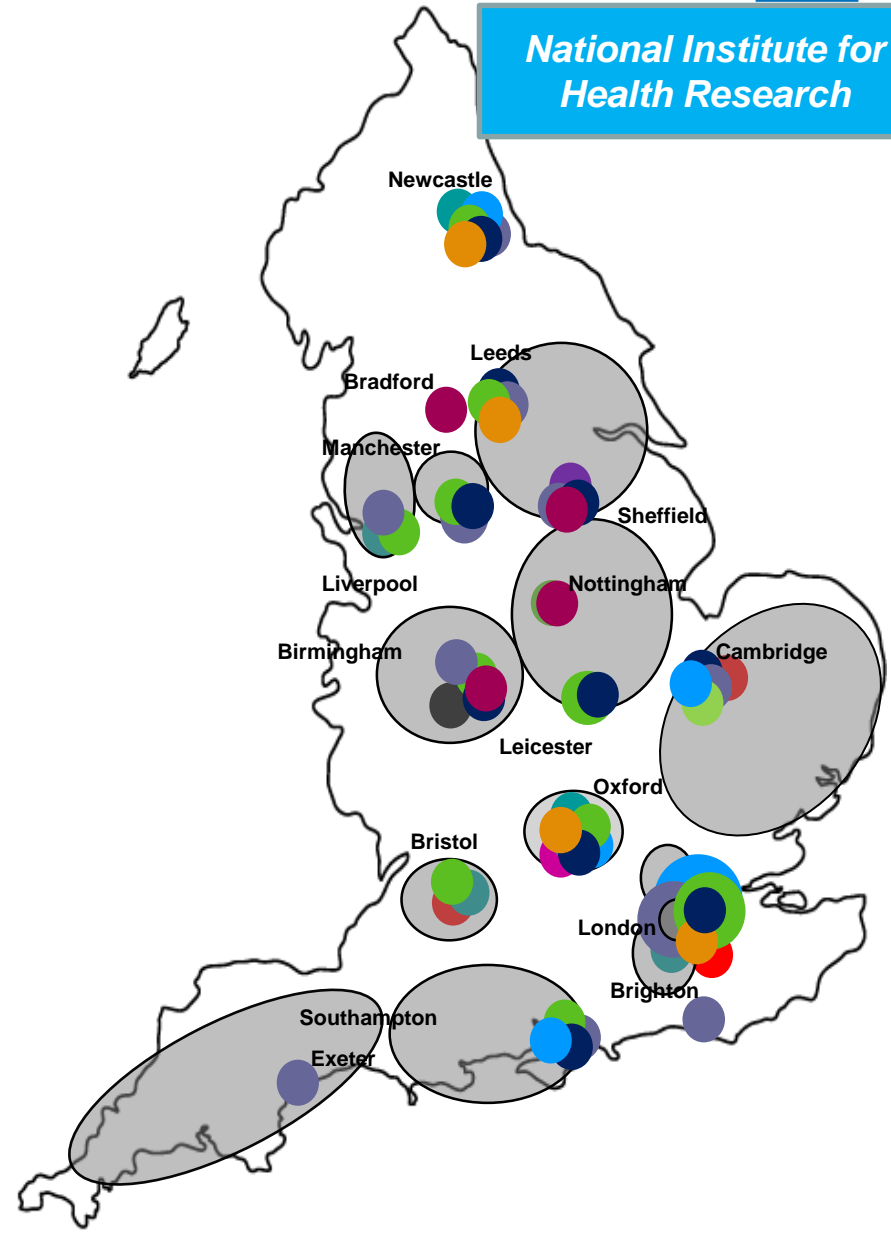
NIHR/CR-UK Experimental Cancer Medicine Centres



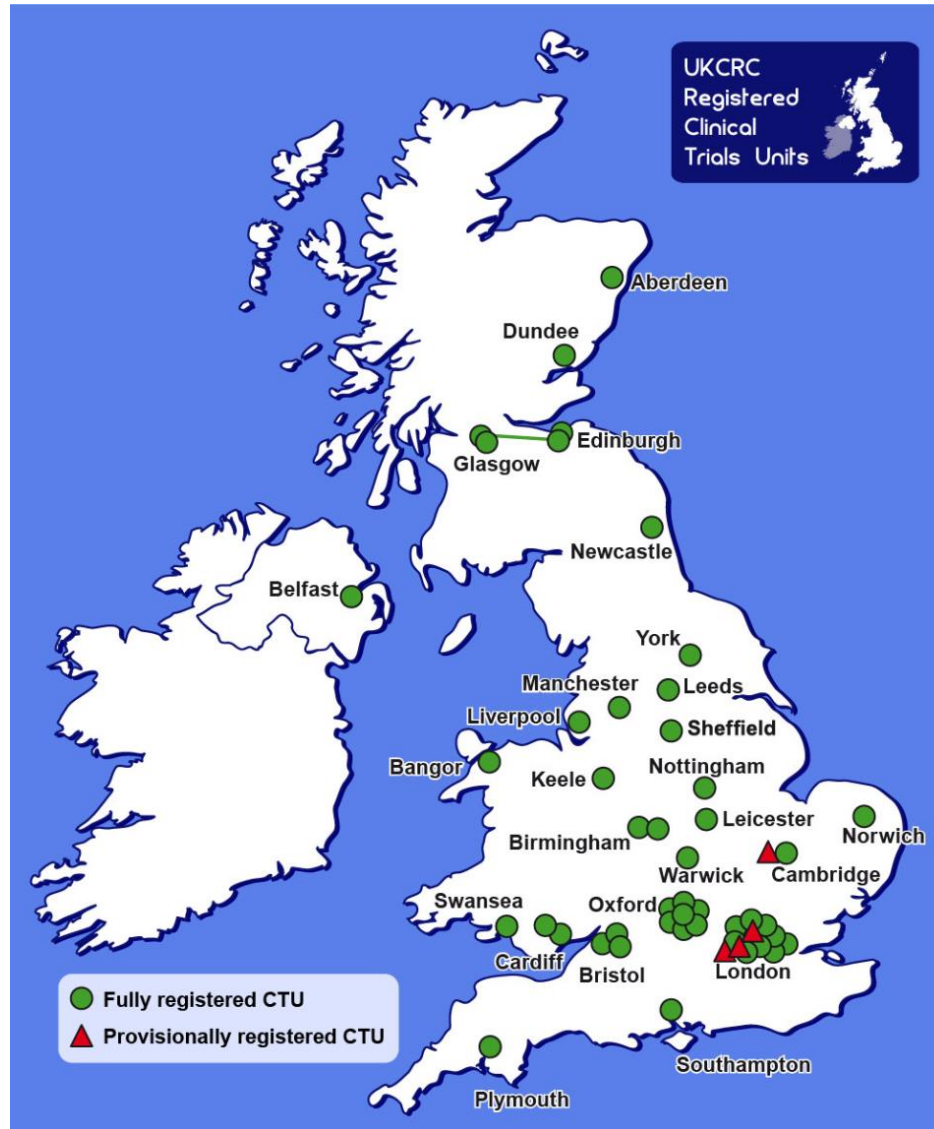
NIHR Surgical Reconstruction and Microbiology Research Centre



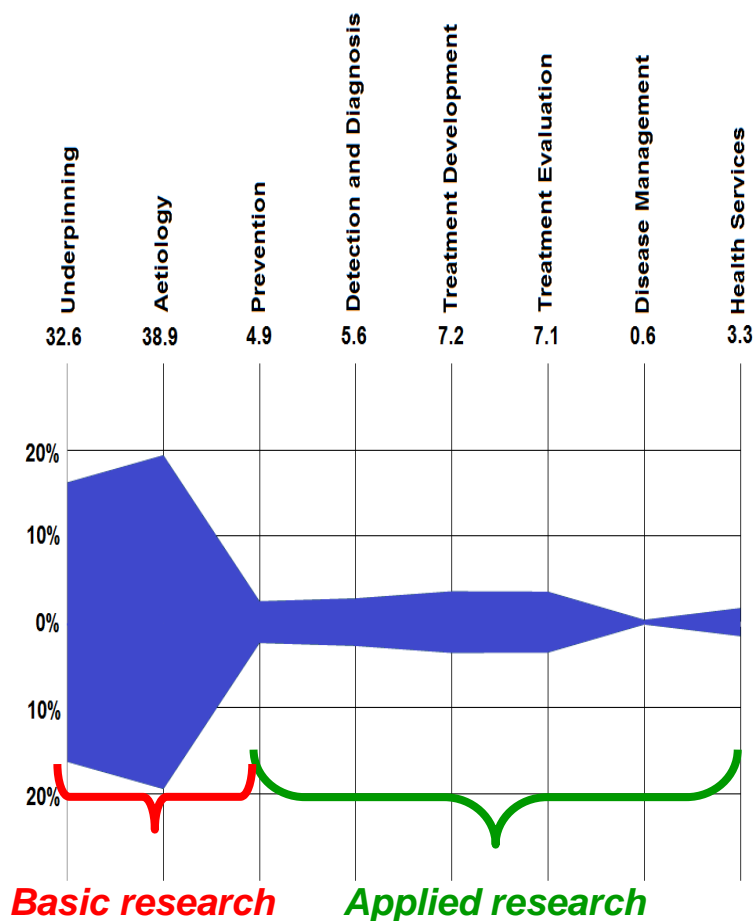
NIHR Collaborations for Leadership in Applied Health Research and Care



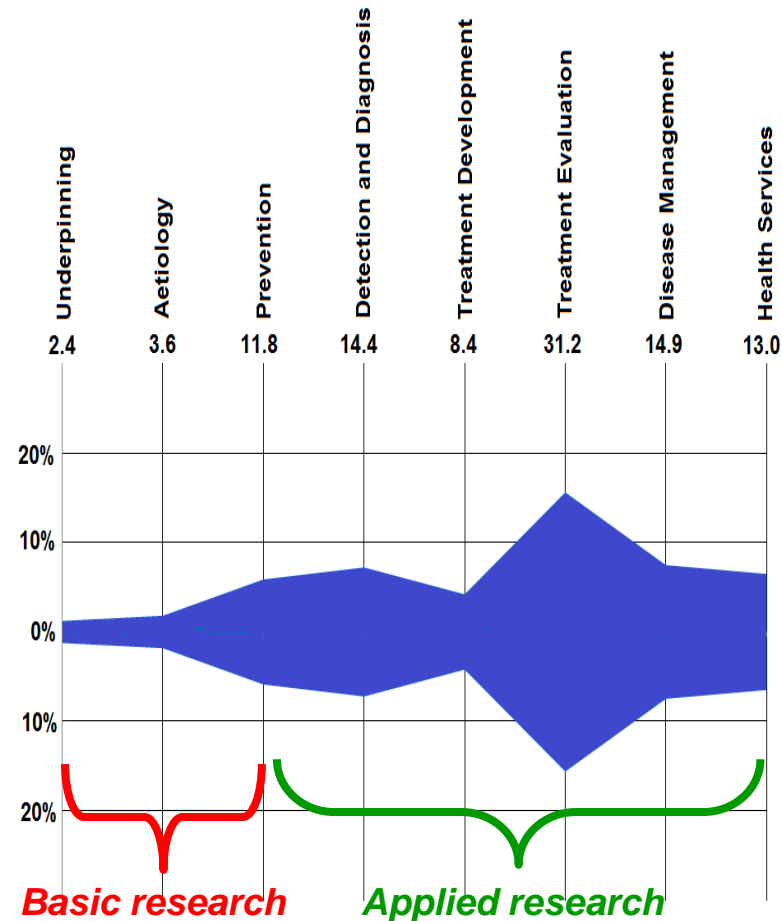
Clinical Trials Units



Spend by UK public funder



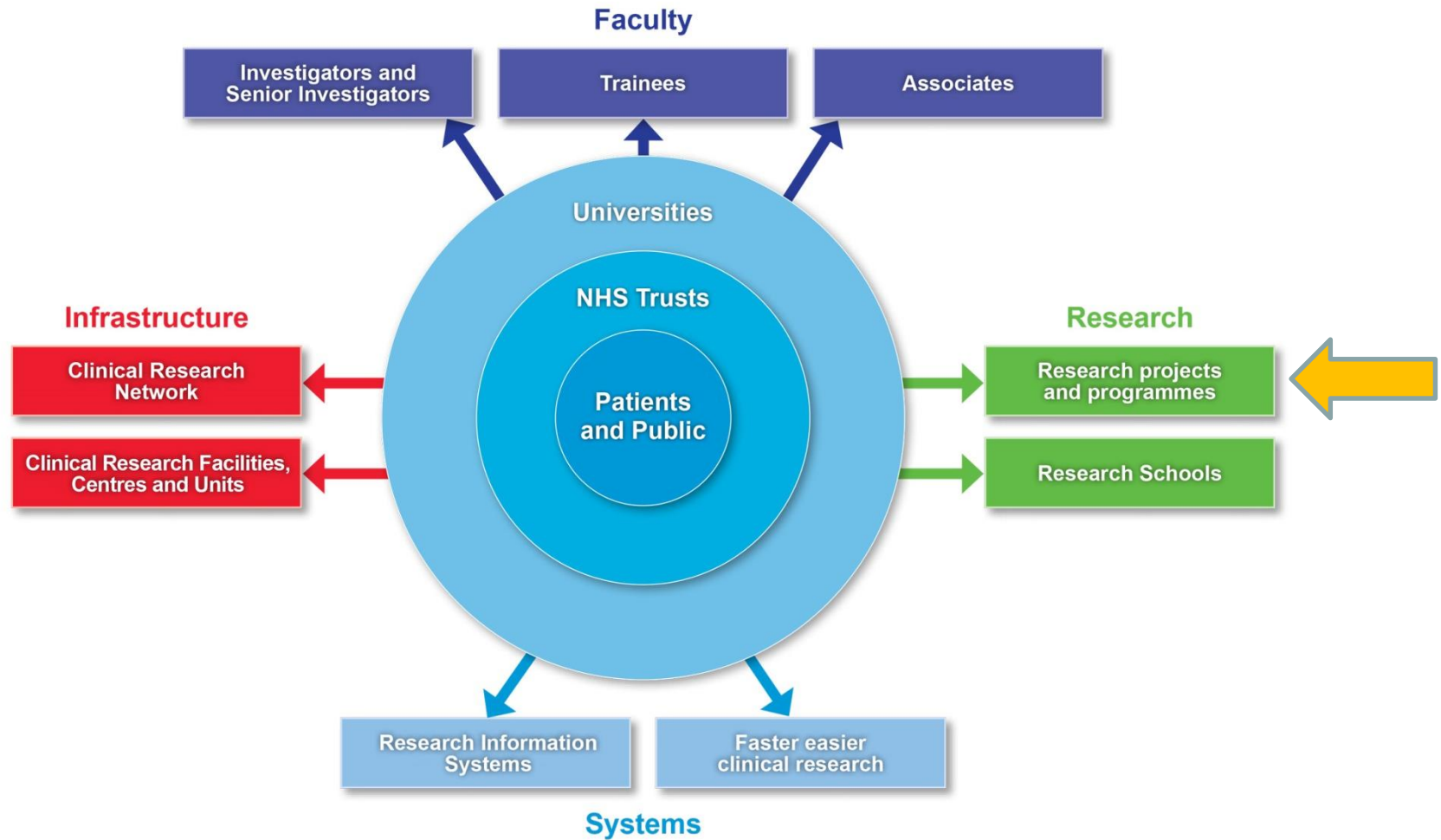
MRC



NIHR

Research spend 2013/2014

The NIHR health research system



Getting innovations into practice



National Institute for Health Research

Does it work?
Is it safe?
Can it be done in the NHS?

What if it is done in the NHS?

Should it be done in the NHS - appraisal

Horizon-scanning

EME

HTA

HS&DR

Basic biomedical research

Translational research

Safety and efficacy

Effectiveness and cost-effectiveness

General clinical use

MRC, Various funders

MRC
i4i

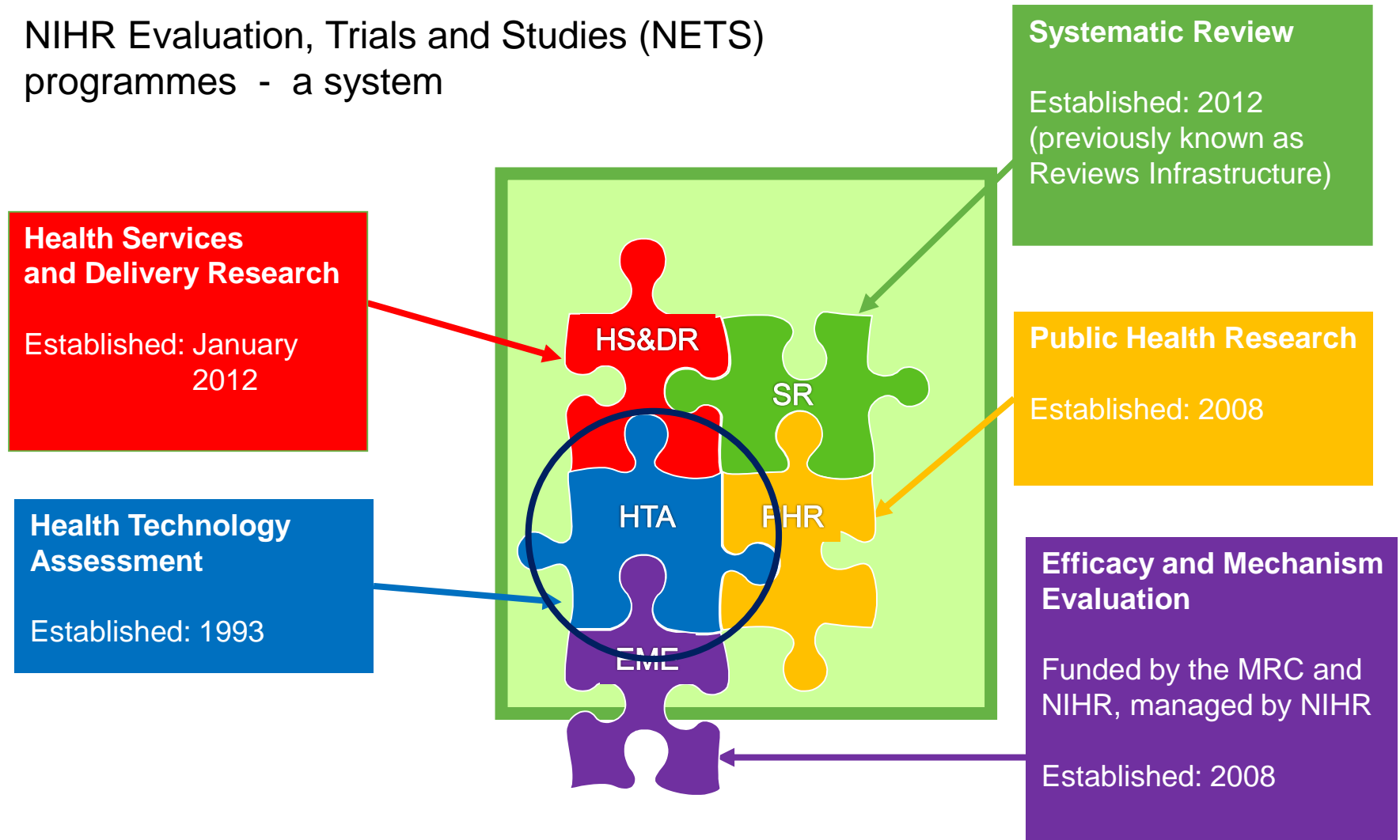


Appraisal (NICE)
Specialist commissioning



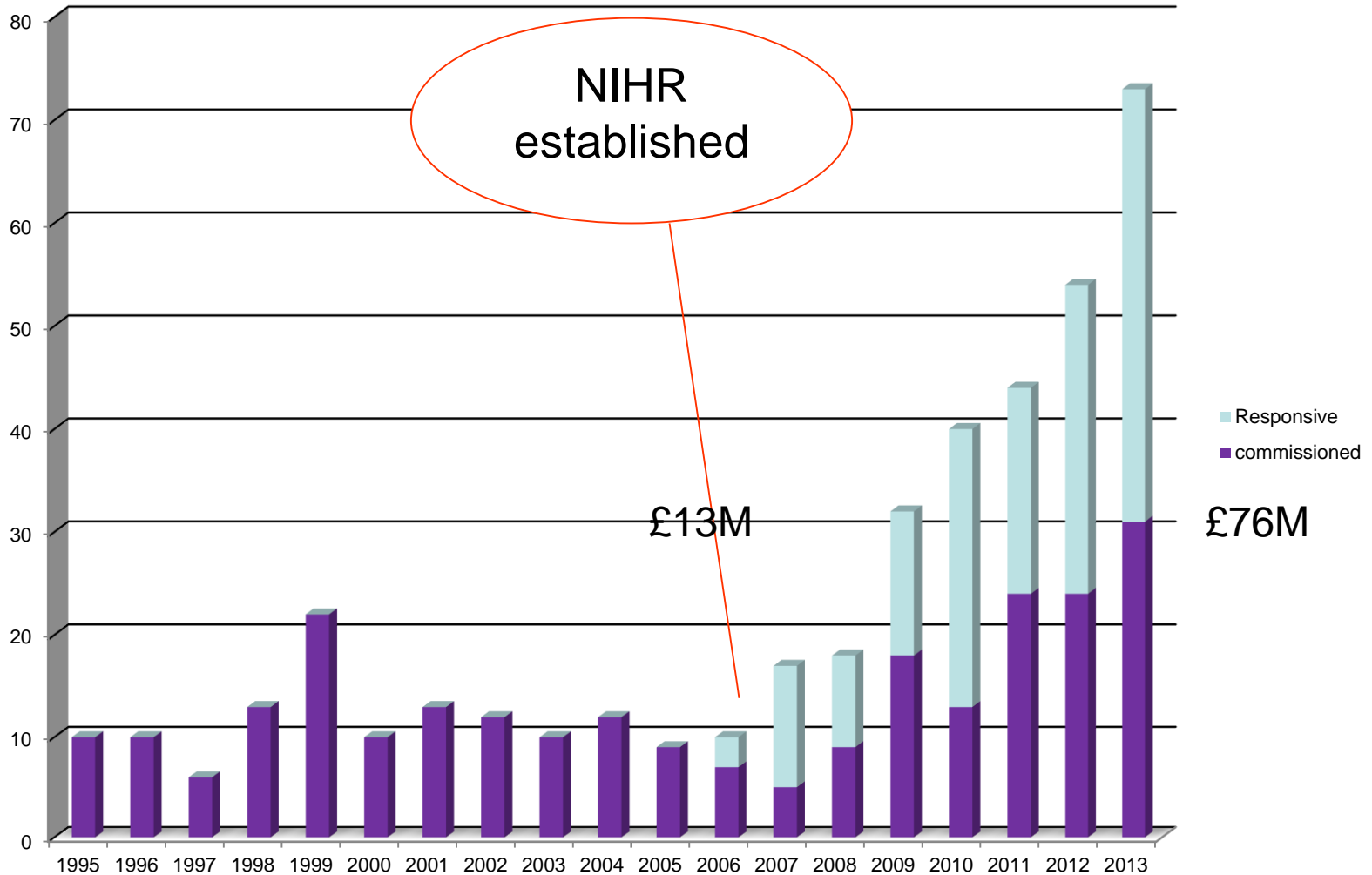
Some NIHR programmes

NIHR Evaluation, Trials and Studies (NETS)
programmes - a system





Clinical trials funded by NIHR HTA



Themed calls – across all NIHR National Institute for Health Research

The 2017 NIHR theme is **older people with complex health needs**. This call will build on the 2015 NIHR Themed Call in multimorbidities.

Year	Themed Call
2015	Prevention and treatment of obesity
2015	Multimorbidities in older people
2014	Mesothelioma
2014	Long-term conditions in children and young people
2013	Antimicrobial resistance *Ongoing highlight notice in this area
2013	Primary care interventions
2012	Applied health research in surgery
2012	Applied clinical research on very rare diseases
2011	Applied health research on dementia
2011	Pandemic flu (HTA Programme)
2009	Obesity (HTA and PHR Programmes)
2009	Diagnostic tests and test technologies (HTA Programme)
2008	Healthcare associated infection (HTA Programme)
2007	Emergency medicine, pre-hospital care and trauma (HTA Programme)
2005	Medicines for children (HTA Programme)

NIHR puts patients at the heart

“People-focused research in the NHS simply cannot be delivered without the involvement of patients and the public. No matter how complicated the research or how brilliant the researcher, patients and the public always offer unique, invaluable insight.”

*Professor Dame Sally C Davies FRS, FMS
Chief Medical Officer and Chief Scientific Adviser, Department of
Health*

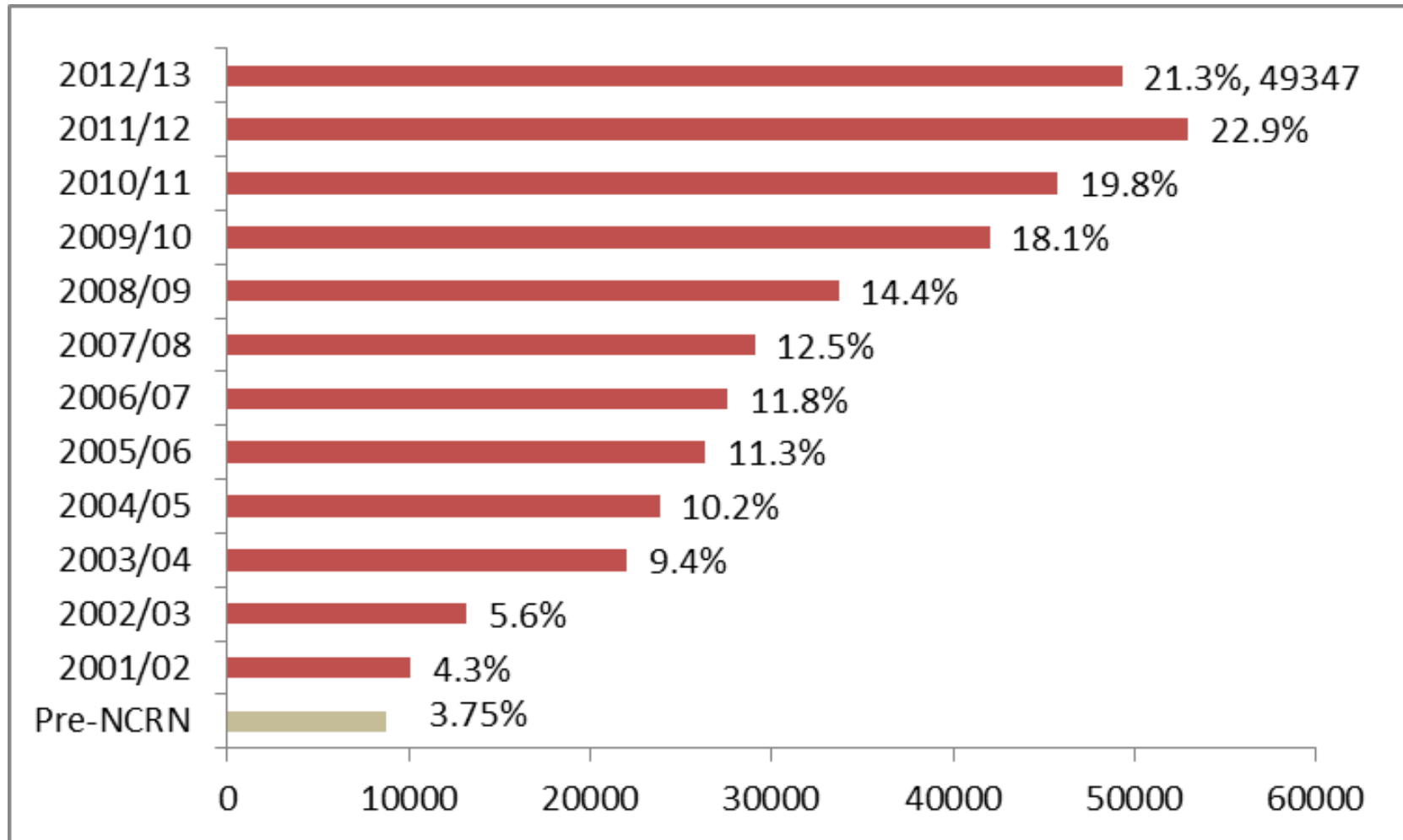
- **Over 1,000 members of the public**

were involved in 2013/14 on NIHR’s expert advisory groups reviewing funding applications and advising on research priorities.

- **3 million patients recruited**

into NIHR studies since 2008, accessing leading edge treatments and best care.

Cancer patient recruitment in England (as a % of cancer incidence)



Pragmatic Trials @ 50

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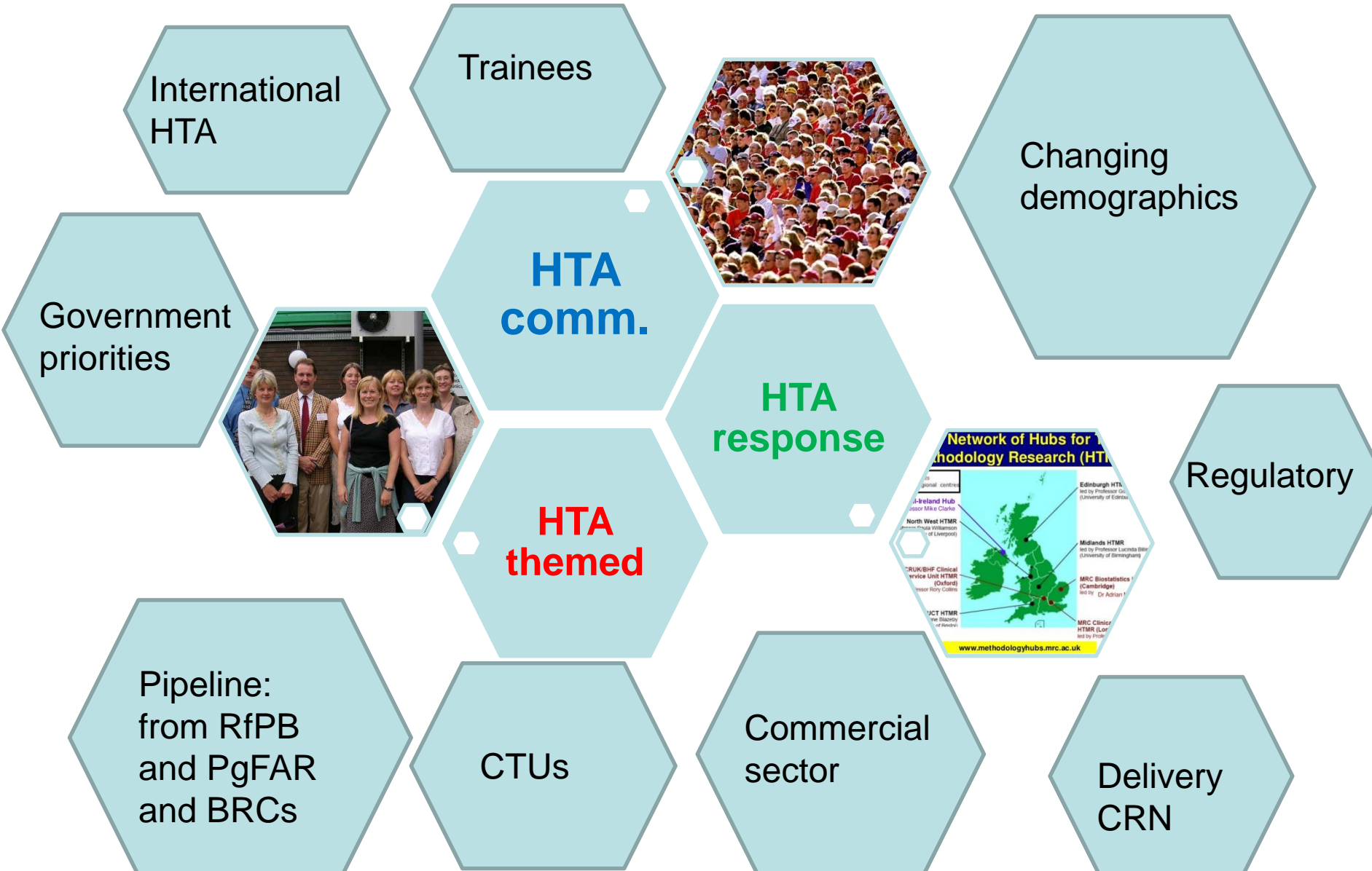
What is “health technology”?

- range of methods: systematic reviews, clinical trials, cohort studies, modelling studies
- to promote health, prevent and treat disease and improve rehabilitation and long term care including:
 - **Drugs:** eg antidepressants, contraceptives, antibiotics, repurposing
 - **Devices:** such as pacemakers, dialysis machines, hearing aids
 - **Procedures:** eg surgical techniques, acupuncture, counselling
 - **Settings** of care: such as general practice, hospitals, care homes
 - **Screening:** for cancer, sexually transmitted diseases, stroke

Tasks for the HTA Programme

- Identifying needs of NHS for research into technologies
 - What are the large and challenging problems?
 - Who else will examine them?
- Getting the right questions at the right time
- Commissioning/monitoring research
- Getting timely and useful results to decision-makers
 - To allow them to act on the answers
- The programme is:
 - **Needs- led** (relevance to the NHS)
 - **Science- added** (seeks to add value at every stage)

HTA sits in a complex adaptive system



Good research questions are:

- Important to the NHS and its patients
- Supported by current evidence
- High scientific quality
- Feasible (not all trials...)
- Timely, *i.e.* research will continue to be relevant following completion of study
- Clear and well-defined
- Represents value for money

A FEW HTA FACTS 2015/16

440	Live projects
250	Active trials
67	New projects
99	Final reports
131	Articles in peer reviewed journals
43,432	Participants were recruited
110,781	Participants in RCTs
1,801	Peer reviewers

Commissioned Primary Research examples

- **CESAR** (Peek et al, Lancet) – resolved question of whether ECMO is useful for severe but potentially reversible respiratory failure
- **SYCAMORE** (Ramanan et al, NEJM) – value of adalimumab for juvenile idiopathic arthritis uveitis
- **Bell's palsy study** (Sullivan et al NEJM) – value of early treatment with prednisolone (rather than acyclovir)
- **CBT for back pain** (Lamb et al, Lancet) – sustained value of group CBT for low back pain in primary care
- **SIGGAR** (Atkin et al, Lancet) – showed similar sensitivity of computerized tomographic colonography for colon cancer cf colonoscopy

Examples of responsive mode

IVAN (Chakravarthy et al, Lancet) – compared generic bevacizumab v ranibizumab **I**nhibit **V**EGF in **A**ge-related choroidal **N**eovascularisation

CRASH2 (Roberts et al, Lancet) – tranexamic acid vs placebo for trauma

Persephone (Earl et al, J Clin Oncol) – compared six months trastuzumab treatment with twelve months, in women with early stage breast cancer

PET-NECK (Mehenna et al NEJM) – compared PET-CT-guided watch-and-wait policy with current node dissection policy in head&neck SCC and advanced nodal metastases treated with radical radiotherapy.

Protect (Hamdy et al NEJM) - compared active monitoring, radical prostatectomy, and external-beam radiotherapy for the treatment of clinically localized prostate cancer.

Methodology strength in boards

NHS

*National Institute for
Health Research*



- Strong methodological legacy from Jon Nicholl
- Panel methodology teleconferences
- Board members – around 50% methodologists (statisticians, health economists, evidence synthesis experts, database experts)

Core outcome sets

The screenshot shows the homepage of the COMET Initiative website. At the top, there is a navigation menu with links for Home, About COMET, Search, Events, Resources, Links, Contact, and Public. The main content area is divided into several sections:

- COMET Initiative**: A section with a heading and a paragraph explaining the initiative's purpose: "The COMET (Core Outcome Measures in Effectiveness Trials) Initiative brings together people interested in the development and application of agreed standardised sets of outcomes, known as 'core outcome sets' (COS). These sets represent the minimum that should be measured and reported in all clinical trials of a specific condition, and are also suitable for use in clinical audit or research other than randomised trials. The existence or use of a core outcome set does not imply that outcomes in a particular trial should be restricted to those in the relevant core outcome set. Rather, there is an expectation that the core outcomes will be collected and reported, making it easier for the results of trials to be compared, contrasted and combined as appropriate; while researchers continue to explore other outcomes as well. COMET aims to collate and stimulate relevant resources, both applied and methodological, to facilitate exchange of ideas and information, and to foster methodological research in this area."
- When searching the COMET database, please note that a systematic review is currently underway to identify eligible material, and we are continually updating the database as we identify eligible studies. Therefore, the records retrieved by any search might increase on a daily basis.**
- Search COMET database**: A section with a search bar and a "Search" button. Below the search bar, it states: "The COMET database currently contains 873 references of planned, ongoing and completed work." It also includes instructions on how to use the search bar and a link to "View full search options".
- Core resource pack**: A section with a heading and a paragraph: "Useful references for core outcome set developers. This includes an overview of the problems with outcomes in trials, key issues to consider in the development of a core outcome set, examples of core outcome set development, and things to think about once a COS is agreed. To read more, click [here](#)."
- Latest News**: A section with a heading and a list of news items. The first item is: "Thursday 23 February, 2017 - Do you have a consensus meeting planned or coming up? If you are planning an upcoming consensus meeting and would be happy for an early career researcher to observe the meeting in order to learn from the experience, please let us know. This would be an invaluable opportunity to gain experience in the development of core outcome sets for potential COS developers. Please email info@comet-initiative.org". The second item is: "Thursday 23 February, 2017 - Call out for funding contacts overseas".
- Follow us on Twitter**: A social media link.
- Help, I want to...**: A section with a list of links: "Search COMET", "Send general feedback/enquiry", "Tell us about a new project/study", "Report a missing study", "Find out about how to measure", and "COMET blogs".

At the bottom of the page, there are logos for the European Commission, the Seventh Framework Programme, the Medical Research Council (MRC), and the NHS National Institute for Health Research. A footer at the very bottom contains a link to the privacy policy and cookie usage statement.

Reporting guidelines



Enhancing the **QUALITY** and **Transparency Of** health Research



EQUATOR resources in Portuguese | Spanish

- Home
- Library
- Toolkits
- Courses & events
- News
- Blog
- Librarian Network
- About us
- Contact

Your one-stop-shop for writing and publishing high-impact health research

find reporting guidelines | improve your writing | join our courses | run your own training course | enhance your peer review | implement guidelines



Library for health research reporting

The Library contains a comprehensive searchable database of reporting guidelines and also links to other resources relevant to research reporting.



Search for reporting guidelines



Not sure which reporting guideline to use?



Reporting guidelines under development



Visit the library for more resources



Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions	Other
Observational studies	STROBE	Extensions	Other
Systematic reviews	PRISMA	Extensions	Other
Case reports	CARE	Extensions	Other
Qualitative research	SRQR	COREQ	Other
Diagnostic / prognostic studies	STARD	TRIPOD	Other
Quality improvement studies	SQUIRE		Other
Economic evaluations	CHEERS		Other
Animal pre-clinical studies	ARRIVE		Other
Study protocols	SPIRIT	PRISMA-P	Other
Clinical practice guidelines	AGREE	RIGHT	Other

[See all 358 reporting guidelines](#)

UK EQUATOR Centre Publication School
The secrets of success in writing and publishing research articles

Do you want to get published, and be praised for it? Do you want your medication to be recognised for its excellent publication record? Do you want to make a real difference with your research? Then, this is the course for you!

A large number of published research articles are rejected yearly. This guide, available in paperback or e-book format, explains and defines the most common reasons for rejection and offers the best ways to avoid them. It is a must-read for all researchers, clinicians, and students who want to publish their research in a peer-reviewed journal.

Join us this summer for an intensive, practical course in the heart of health research. You will learn how to write a high-quality research article for a journal.

Guides cover topics: Dr Elizabeth Higgs; Dr Lisa Wilson, and Professor David Jones

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Getting reporting guidelines such as CONSORT and STROBE to guarantee the quality of your research
Choosing the perfect journal and negotiating editorial responses
Getting and handling constructive peer review
Communicating about research with patients, the public, and practitioners
Making the most of social media
The secrets of success in writing and publishing research articles

UK EQUATOR Centre Publication School, June 2017, St Catherine's College, Oxford

Toolkits

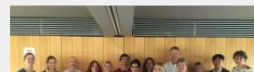
Find practical help and resources to support you in:



Writing research

EQUATOR highlights

8/07/2016 - Taking research to the next level with EQUATOR Publication School



Twenty researchers and clinicians joined us for a week-long journey to create well-reported, clear research

News

Checklist for the Reporting of Updated Guidelines (CheckUp)

18/01/2017

International Ethical Guidelines for Health-related Research Involving Humans

5/01/2017

Hubs for Trials Methodology Research

Secure | <https://www.methodologyhubs.mrc.ac.uk>

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Hubs for Trials
Methodology Research

Improving health by improving trials



Network of Hubs for
Trials Methodology Research



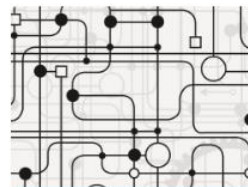
Guidance



Workshops



Webinars

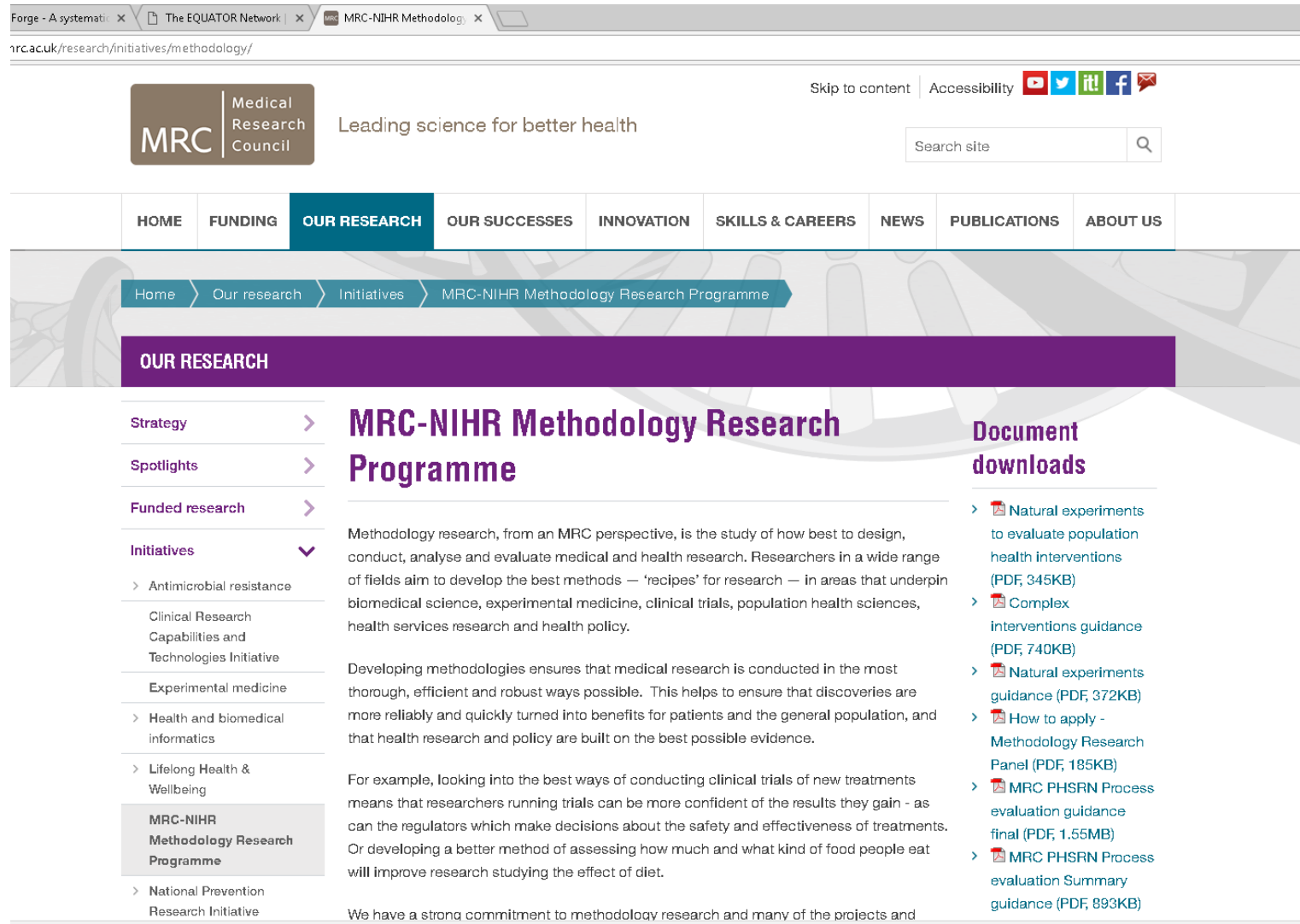


Working Groups



Publications

MRC-NIHR MRP



The screenshot shows a web browser with three tabs: 'Forge - A systemati...', 'The EQUATOR Network', and 'MRC-NIHR Methodolog...'. The address bar shows 'mrc.ac.uk/research/initiatives/methodology/'. The page header includes the MRC Medical Research Council logo, the tagline 'Leading science for better health', and a search bar. A navigation menu contains links for HOME, FUNDING, OUR RESEARCH (highlighted), OUR SUCCESSES, INNOVATION, SKILLS & CAREERS, NEWS, PUBLICATIONS, and ABOUT US. A breadcrumb trail reads: Home > Our research > Initiatives > MRC-NIHR Methodology Research Programme. The main content area features a purple header for 'OUR RESEARCH' and a central section for 'MRC-NIHR Methodology Research Programme'. On the left, a sidebar lists categories: Strategy, Spotlights, Funded research, and Initiatives (expanded to show Antimicrobial resistance, Clinical Research Capabilities and Technologies Initiative, Experimental medicine, Health and biomedical informatics, Lifelong Health & Wellbeing, MRC-NIHR Methodology Research Programme, and National Prevention Research Initiative). The central text describes methodology research as the study of how best to design, conduct, analyse and evaluate medical and health research, aiming to develop 'recipes' for research in areas like biomedical science, experimental medicine, clinical trials, population health sciences, health services research and health policy. It notes that developing methodologies ensures research is conducted in the most thorough, efficient and robust ways possible, leading to more reliable and quickly turned benefits for patients and the general population. An example is given: looking into the best ways of conducting clinical trials of new treatments means that researchers running trials can be more confident of the results they gain - as can the regulators which make decisions about the safety and effectiveness of treatments. Or developing a better method of assessing how much and what kind of food people eat will improve research studying the effect of diet. A footer note states: 'We have a strong commitment to methodology research and many of the projects and'. On the right, a 'Document downloads' section lists: Natural experiments to evaluate population health interventions (PDF, 345KB), Complex interventions guidance (PDF, 740KB), Natural experiments guidance (PDF, 372KB), How to apply - Methodology Research Panel (PDF, 185KB), MRC PHSRN Process evaluation guidance final (PDF, 1.55MB), and MRC PHSRN Process evaluation Summary guidance (PDF, 893KB).



Health services research
Research



Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies



Kerry N L Avery¹, Paula R Williamson², Carrol Gamble², Elaine O'Connell Francischetto¹, Chris Metcalfe¹, Peter Davidson³, Hywel Williams⁴, Jane M Blazeby^{1,5} members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research

[Author affiliations +](#)

Abstract

Objectives Designing studies with an internal pilot phase may optimise the use of pilot work to inform more efficient randomised controlled trials (RCTs). Careful selection of preagreed decision or 'progression' criteria at the juncture between the internal pilot and main trial phases provides a valuable opportunity to evaluate the likely success of the main trial and optimise its design or, if necessary, to make the decision not to proceed with the main trial. Guidance on the appropriate selection and application of progression criteria is, however, lacking. This paper outlines the key issues to consider in the optimal development and review of operational progression criteria for RCTs with an internal pilot phase.

Design A structured literature review and exploration of stakeholders' opinions at a Medical Research Council (MRC) Hubs for Trials Methodology Research workshop. Key stakeholders included trialists, methodologists, statisticians and funders.

Results There is considerable variation in the use of progression criteria for RCTs with an internal pilot phase, although 3 common issues predominate: trial recruitment, protocol adherence and outcome data. Detailed and systematic reporting around the decision-making process for stopping, amending or proceeding to a main trial is uncommon, which may hamper understanding in the research community about the appropriate and optimal use of RCTs with an internal pilot phase. 10 top tips for the development, use and reporting of progression criteria for internal pilot studies are presented.

Conclusions Systematic and transparent reporting of the design, results and evaluation of internal pilot trials in the literature should be encouraged in order to facilitate understanding in the research community and to inform future trials.

<http://dx.doi.org/10.1136/bmjopen-2016-013537>

BMJ Global Health

Comprehensive cohort with multiple embedded RCTs – CASPER

NHS

*National Institute for
Health Research*

– Gilbody et al

- One in 7 older people suffer depression
- Although individual treatments help, but elements (drugs and psychosocial) often fail to be integrated into primary care
- CASPER cohort of older people with depressive symptoms with regular measurement of outcomes
- CASPER trial – evaluation of collaborative care for those with sub-threshold depression
- CASPER PLUS – collaborative care for those with above threshold depression



Case crossover study

- IDEA study (Thornhill et al)

- Do invasive dental procedures (IDP) need antibiotics to prevent infective endocarditis (IE) in those at higher risk
- Standard practice for 60 years, but NICE recommended cessation in 2008
- Infective endocarditis has risen since
- IDEA-Study will link national data on courses of dental treatment and on hospital admissions for IE
- Is incidence of IDP higher in the 3 months immediately preceding an IE diagnosis than in earlier 3 month matched control periods



Cluster crossover – BRIDGE-IT

Cameron et al

- 26 pharmacies in 3 UK regions
- 2080 women presenting emergency oral contraception (EC)
- Compares standard EC to EC plus 3 months of progesterone only pill to “bridge” time taken to make appointment to see GP or family planning for regular contraception advice



IPD then cohort – QUIDS – Stock et al

- Women with suspected preterm labour
- Value of fetal fibronectin at different thresholds
- IPD of 4 European studies to develop prognostic model to rule out preterm birth within 7 days
- Validated in prospective cohort



eStudy – eCRT2 – Gulliford et al

- Aim to reduce unnecessary antibiotics in primary care
- Practices participating in CPRD
- Cluster randomised to multicomponent intervention or usual care
- INT = prescribing feedback, decision support and webinars
- Primary outcome = no. antibiotic prescriptions per resp. tract infection per 1000 patient years measured through CPRD



MAMS – anti-PD1 for melanoma

Danson et al

- **Discontinuation trial to evaluate optimal duration of anti-PD1 (pembrolizumab and nivolumab) in melanoma**
- **Ipilumamab given for 12 weeks, yet 40% on anti-PD1 are on it 1-2 years (because that's how it was done in clinical trials)**
- **Trade-off between melanoma recurrence and adverse effects including lung and bowel inflammation**
- **Non-inferiority**
- **Three intermediate stages for analysis**



MAMS – ROSSINI II Trial (Pinkney et al)

- Prevention of surgical site infections (abdominal operations)
- 8 arms (control, impregnated drape, gentamicin-impregnated collagen wound sponges, 2% chlorhex. skin prep and combinations)
- Three planned interim analyses (final at 6613 patients)



Efficient study designs: SIMPLIFIED National Institute for Health Research

registry trial: Hiemstra et al

- Dialysis patients
- Unclear whether active vitamin D compounds needed
- High dose native vitamin D (cholecalciferol)
- Versus standard care
- All outcomes captured by UK Renal Registry and the Health and Social Care Information Centre
- N= 4200 over 3 years – will conclude once 2200 events occurred



NIHR research makes a difference

- **to lives**

The STOP II trial is helping children with peanut allergy live without fear

- **to costs**

The IVAN trial's comparison of drugs for an eye condition could save the NHS £80 million a year, if implemented

- **to services**

The Birthplace England study showed giving birth in a midwife-led unit is as safe as hospital for most women

- **to the economy**

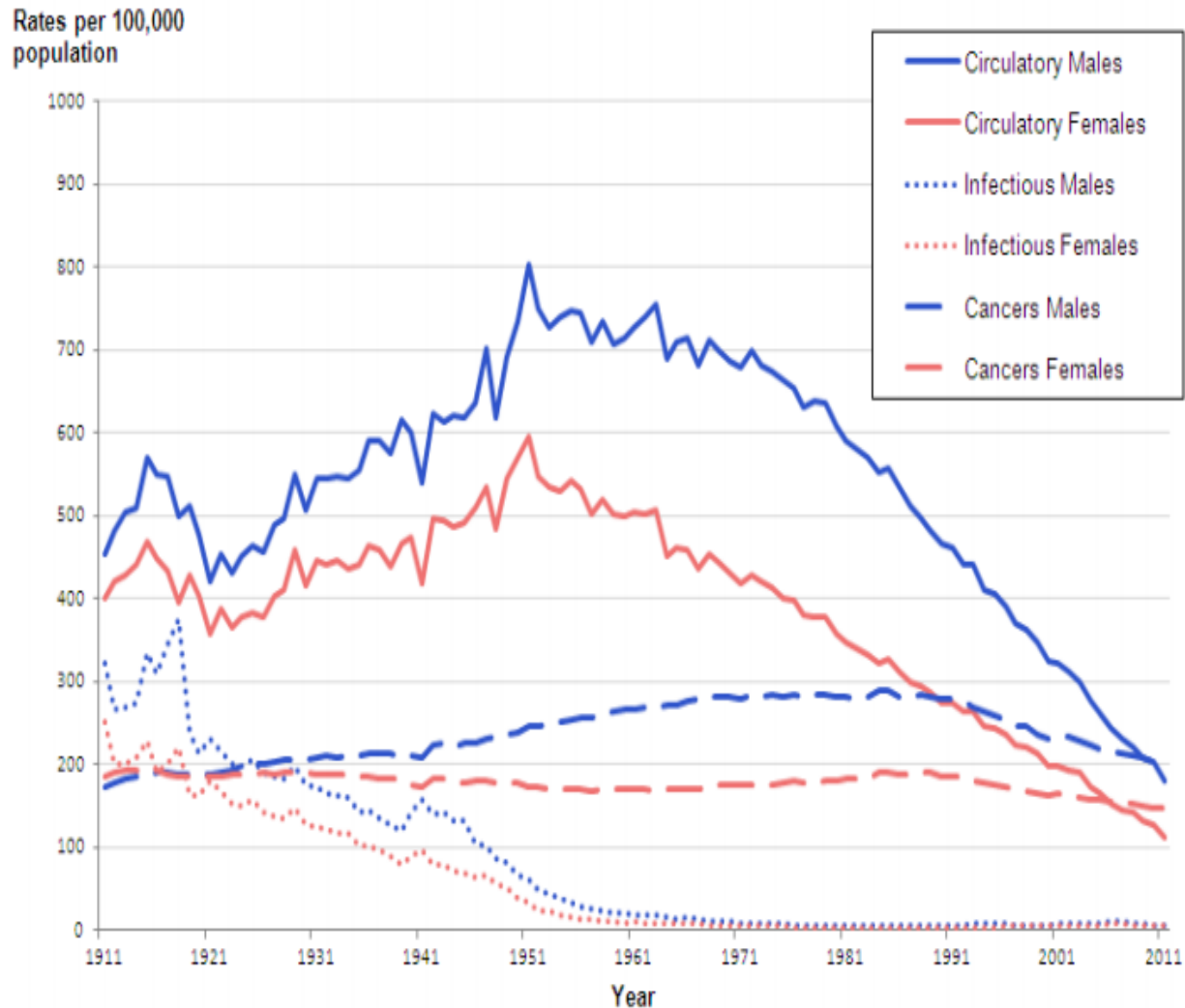
“Each £1 of public/charitable investment in UK medical research earns an extra £1.10-£2.50 GDP per year”

Pragmatic Trials @ 50

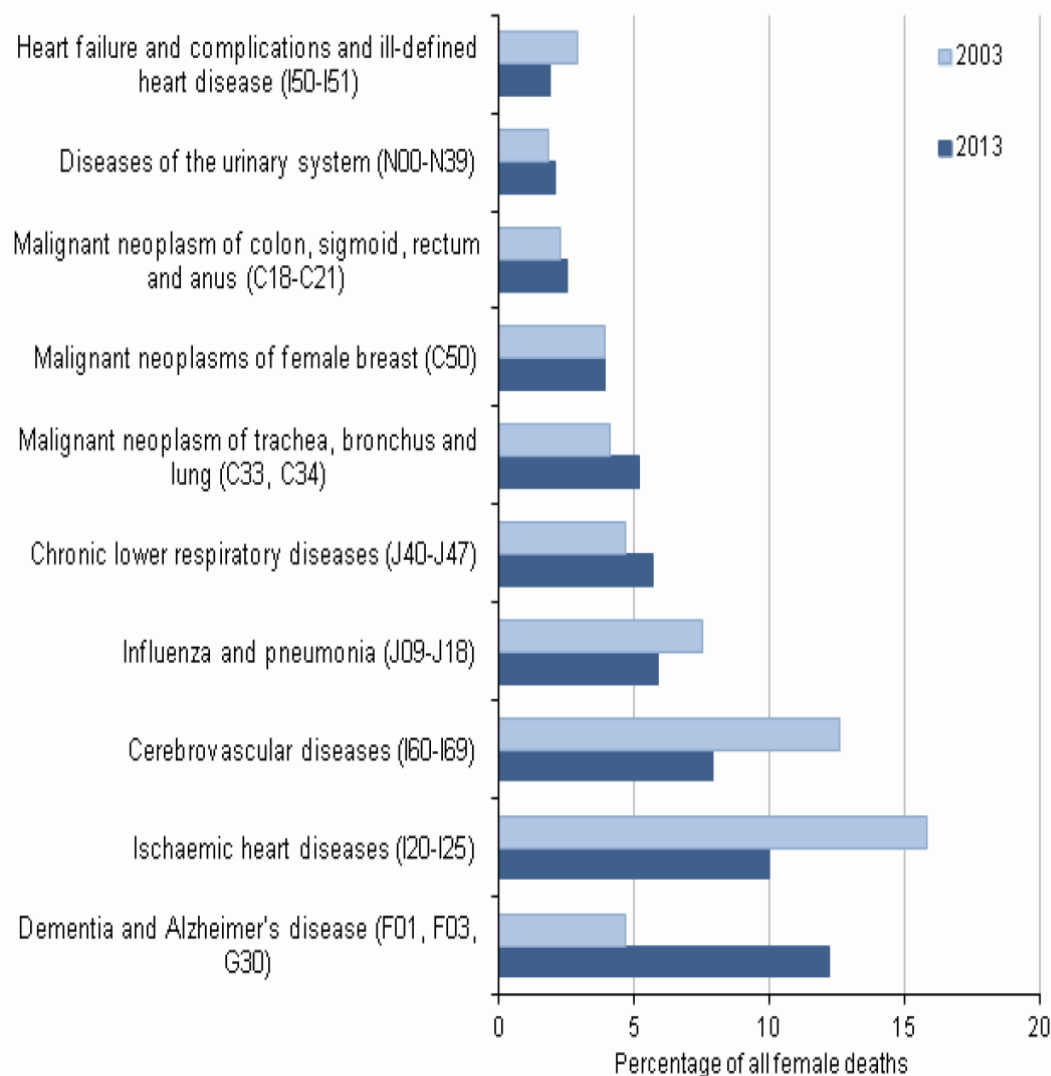
- Past
- Present
- Future



Age-standardised mortality rates England and Wales (ONS 2014)

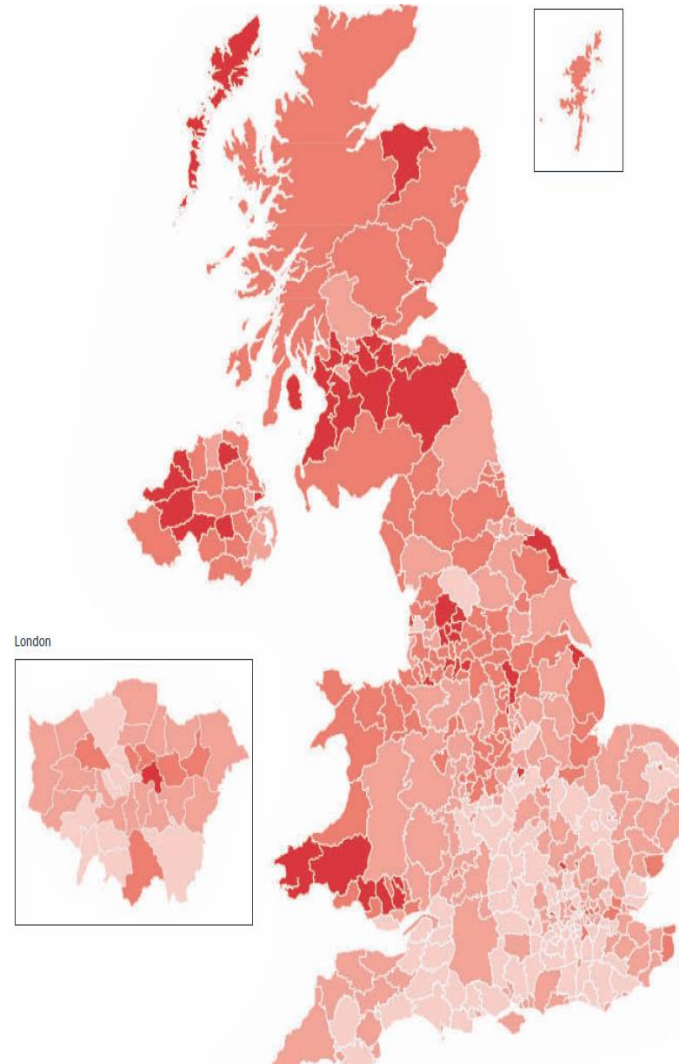
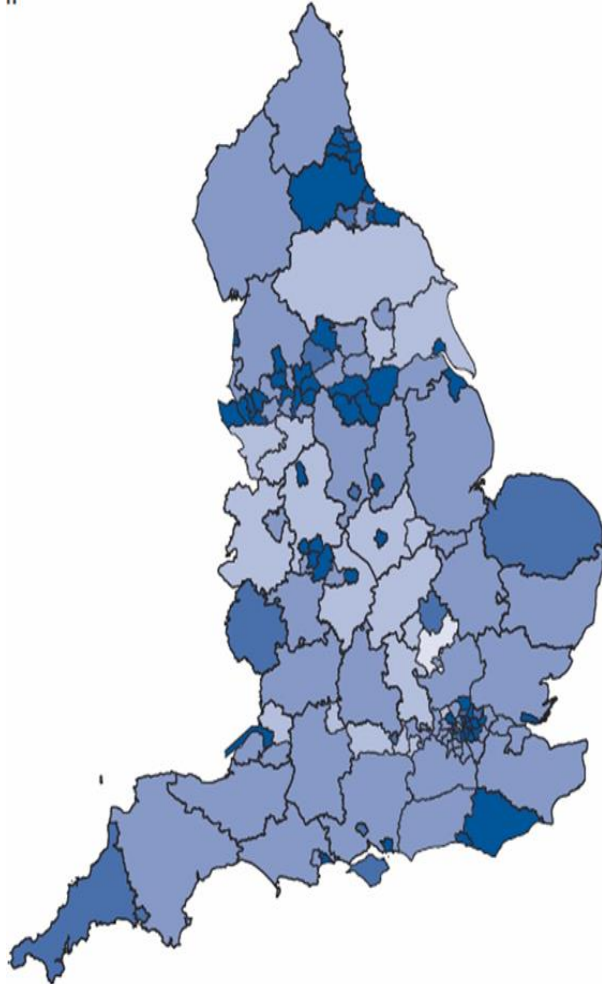


Ten leading causes of death in females, 2003-2013, England & Wales (ONS)

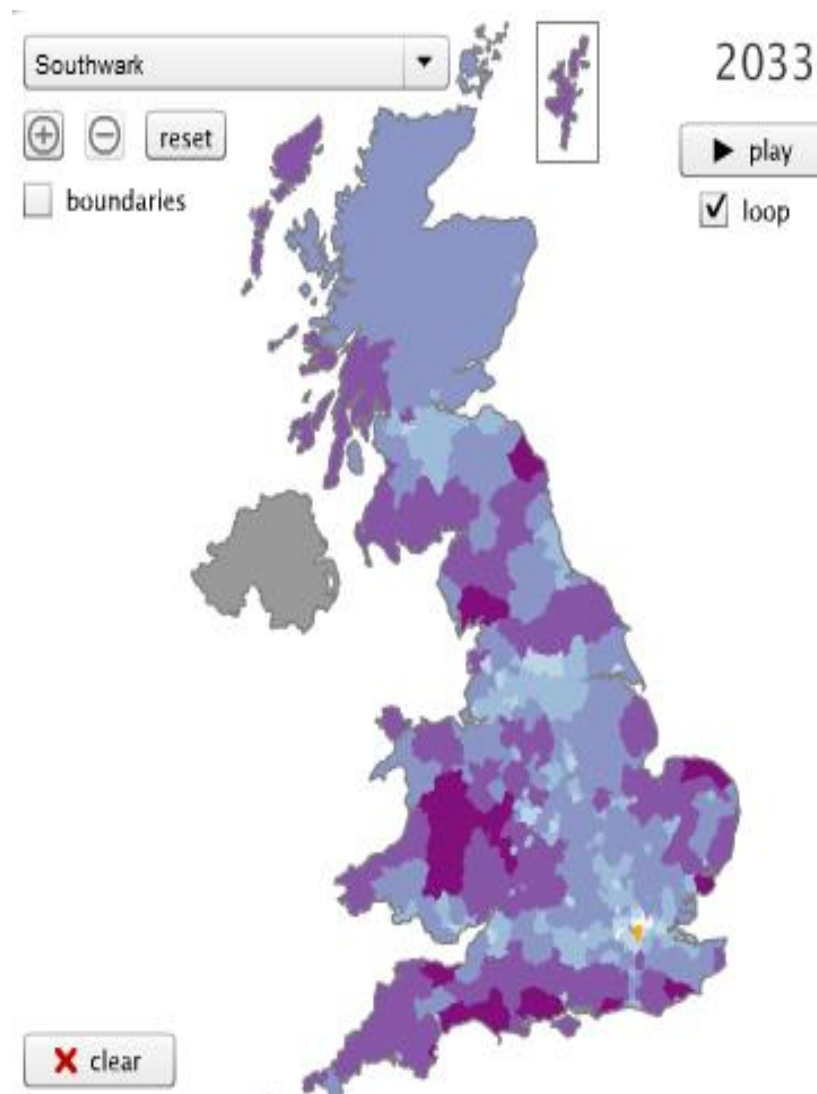
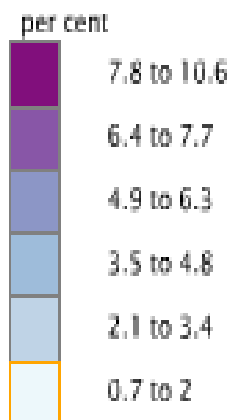
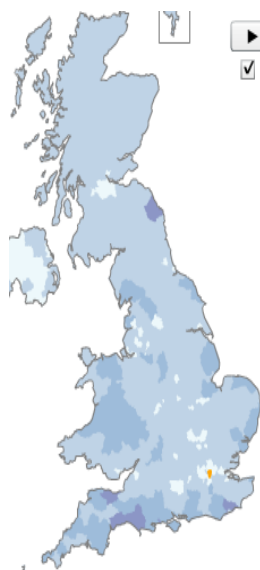


Must take account of distribution of need. Dementia in women (L), heart disease (R)

n



Population 85 and over: 1992, 2015, 2033 (ONS).



Enhanced dissemination

Dissemination Centre

National Institute for
Health Research

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We help NHS clinicians, commissioners and patients to make evidence-based decisions.
Find out more



Signals



Highlights



Themed Reviews

- Big future topics like multiple morbidities in older people
- Needed but neglected areas like end of life care
- Efficient processes – new standard application form
- Threaded publications
- More on dissemination

- Underlying design and statistical principles don't change
- External validity – linking trial to population data
- Efficient studies – e-studies
- Personalized medicine adds new complexity- experience building in cancer, but less so in other areas yet
- The future holds important new challenges for researchers in trials and trials methodology

Thanks and disclaimer

Slides 'borrowed' from

- Hywel Williams
- Chris Whitty

This presentation included independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.