

The importance of public funding for clinical trials: international perspectives

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30th November 2023 13.20-13.50



Why do clinical trials?

- RCT are necessary to create new knowledge, inform care and policy, improve the care of patients and the public, and develop new drugs and de

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P.,
and Richard Peto, F.R.S.

Conclusions of observational data and RCTs may differ in half of
the cases

Who should sponsor clinical trials?

- Commercial sponsors
 - to seek drug approval(safety & efficacy, **not** comparative benefit), label extension, expansion of market share, and an increase in shareholder value.
- **Public sponsors/funders**
 - to optimize therapy for a particular disease, create new knowledge, and improve patient and public health
 - in areas that are not commercially viable (eg rare diseases, non-commercial interventions eg surgery, screening and prevention strategies)
 - Difficult to study populations (children, pregnancy etc)
 - In areas that nevertheless are important to patients/health service, eg multimorbidity
 - Reduced bias in design – expectation of publication etc
 - and more important outcomes – not just progression free survival but overall survival, quality of life, health economics etc
 - Pragmatic, high external validity – conduct comparators, patient selection
 - Explore methodology
 - To inform change practice and policy

 **FREE ACCESS** | Research Article | 5 September 2016

Publicly funded practice-oriented clinical trials: of importance for healthcare payers

Authors: Mattias Neyt , Thierry Christiaens, Jacques Demotes, Tom Walley, and Frank Hulstaert | [AUTHOR INFO & AFFILIATIONS](#)

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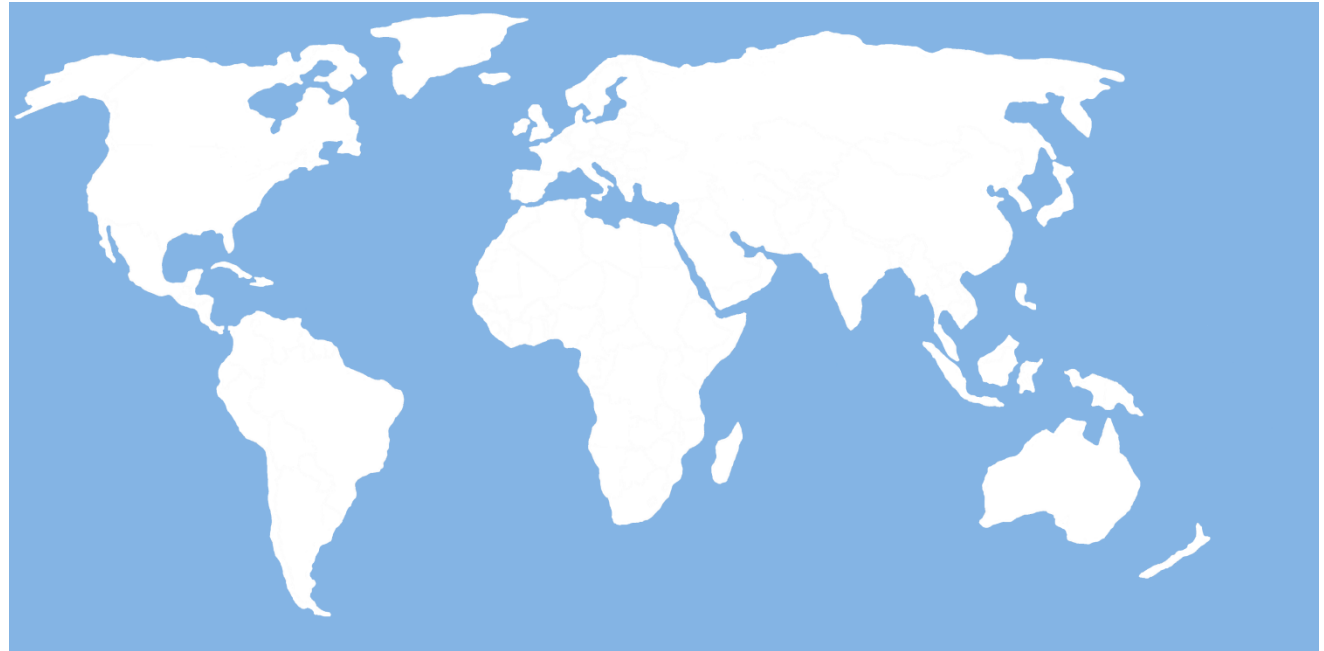
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Abstract

Aim: Many questions of relevance to patients/society are not answered by industry-sponsored clinical trials. We consider whether there are benefits to governments in funding practice-oriented clinical trials. **Methodology:** A literature search including publications on institutions' websites was performed and supplemented with information gathered from (inter)national stakeholders. **Results:** Areas were identified where public funding of clinical trials is of importance for society, such as head-to-head comparisons or medical areas where companies have no motivation to invest. The available literature suggests publicly funded research programs could provide a positive return on investment. The main hurdles (e.g., sufficient funding and absence of equipoise) and success factors (e.g., selection of research questions and research infrastructure) for the successful conduct of publicly funded trials were identified. **Conclusion:** Governments should see public funding of pragmatic practice-oriented clinical trials as a good opportunity to improve the selection and quality of treatments and stimulate efficient use of limited resources.

International HTA

- UK- NIHR
- Aus - NHMRC
- USA - PCORI
- Netherlands - ZonMw
- Belgium - KCE



Research in the UK NHS

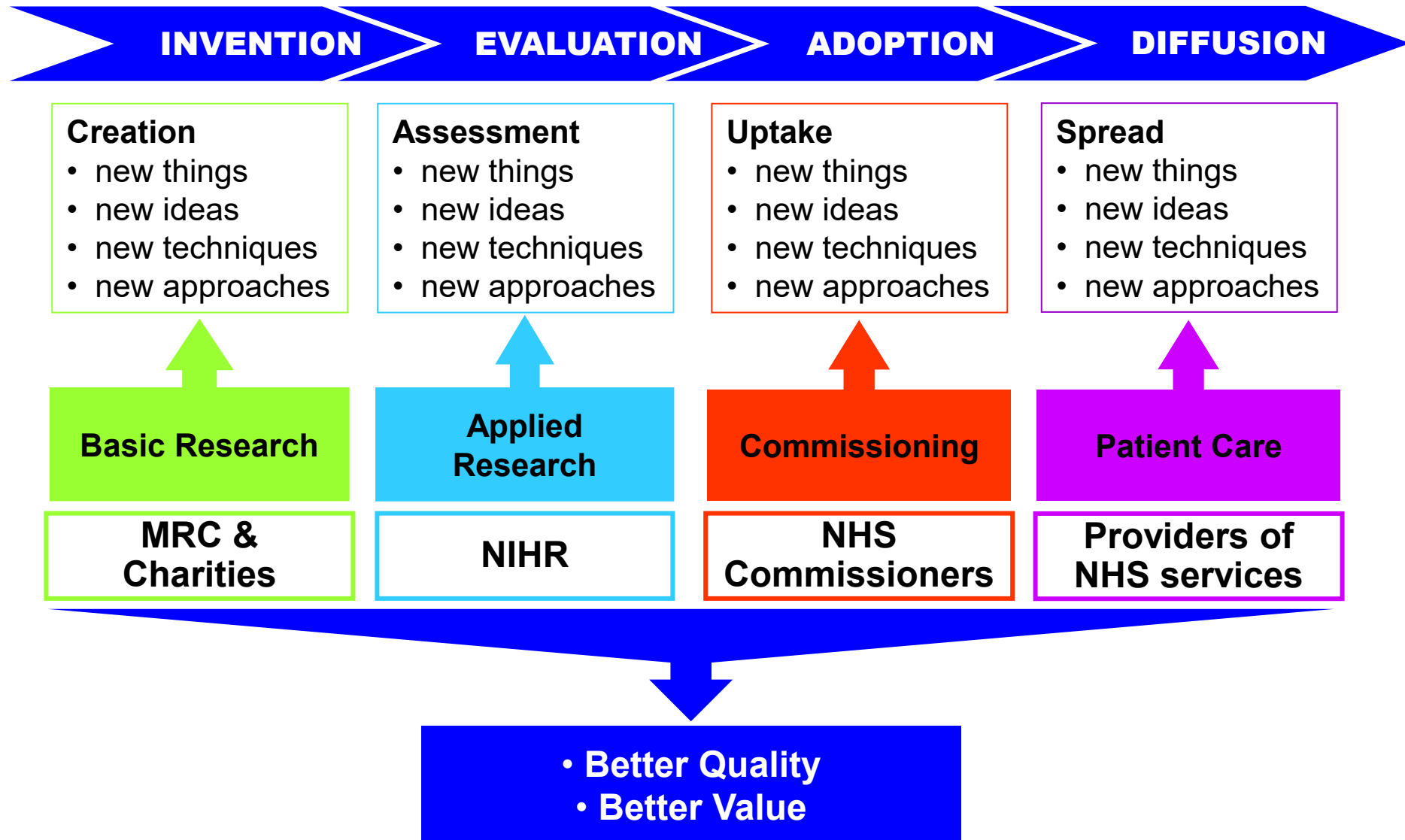
- NHS as a customer for research
- NHS as a top class environment for the conduct of research
- NHS as a driver of health and wealth
 - Decrease lost productivity
 - Research as a driver of wealth creation via life sciences industries
- Research as a core activity in the NHS, not an optional extra
 - NHS Charter 1948, NHS constitution 2009, GMC 2022
- NIHR's mission is to improve the health and wealth of the nation through research, as the research arm of the NHS
- Work in partnerships – charities, other funders (international, industry), patients and the public

NHS R&D Strategy 2006

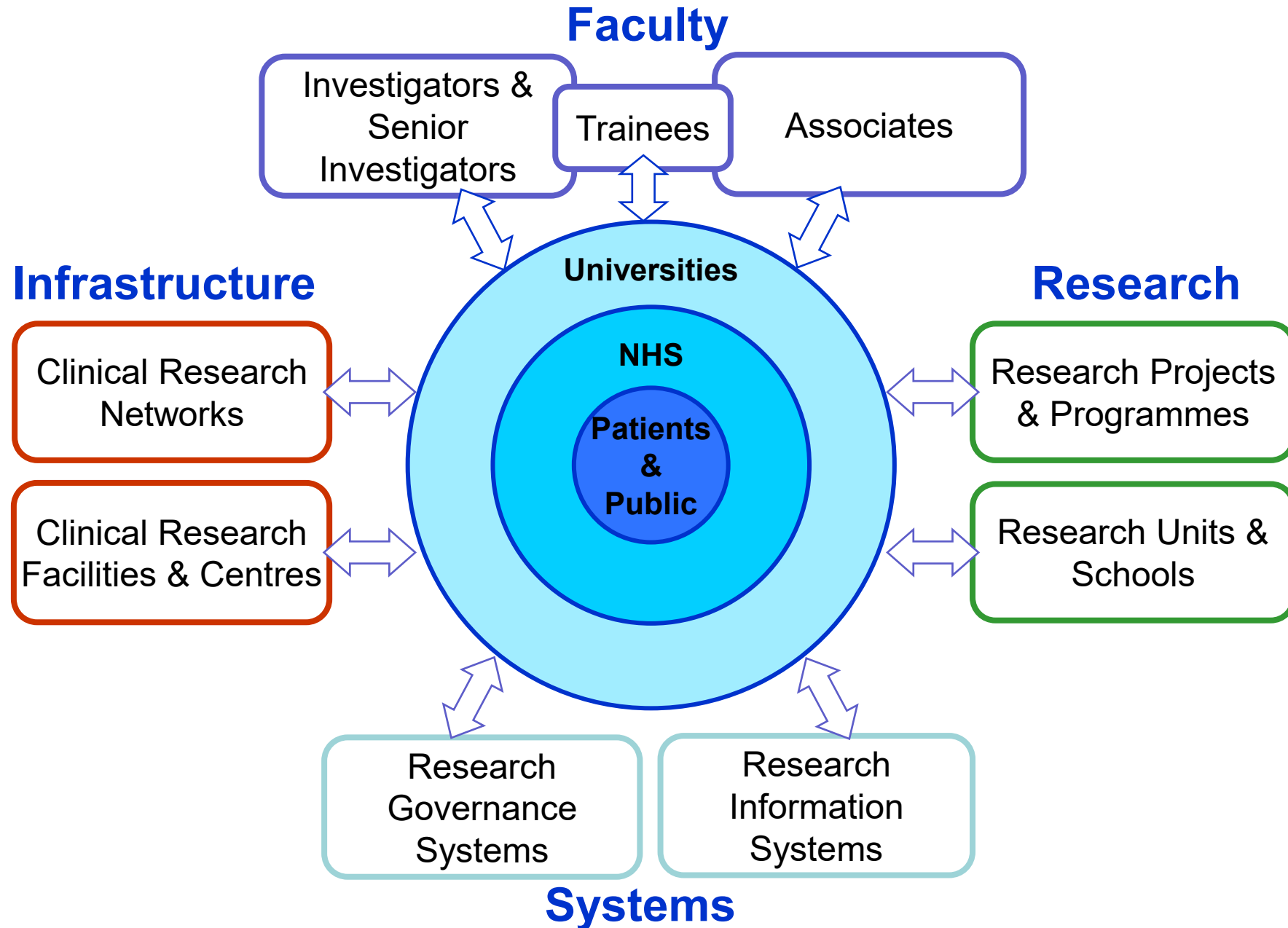
- To **transform** research in the NHS
- To create a **health research system** in which the NHS supports **outstanding individuals**, working in **world-class facilities**, conducting **leading-edge research**, **focused on the needs of patients and the public**
- Created the National Institute of Health Research (NIHR) – a government funded organisation for NHS research



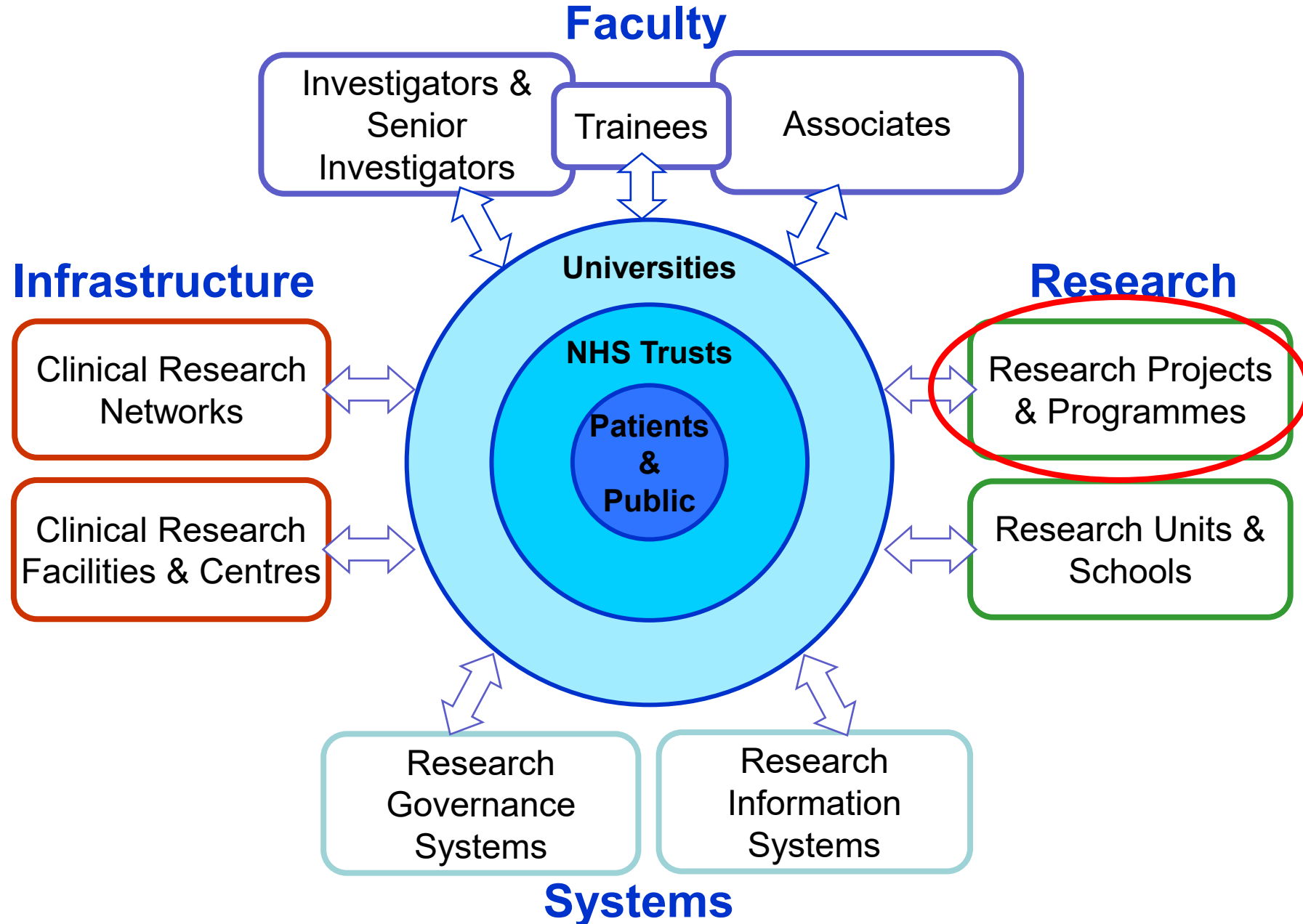
The Innovation Pathway



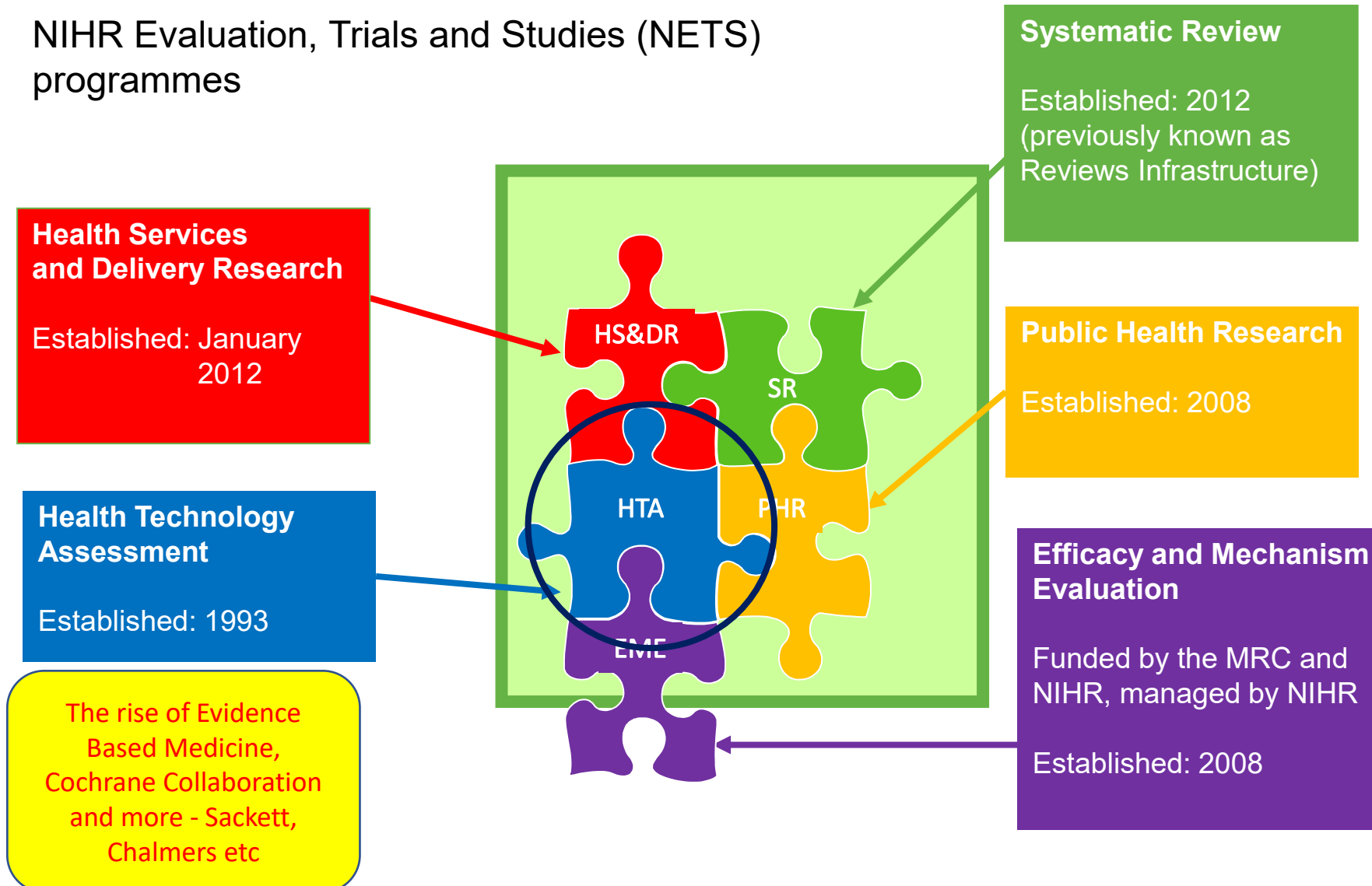
National Institute for Health Research NIHR



National Institute for Health Research



NIHR Evaluation, Trials and Studies (NETS) programmes



What do we mean by “health technology assessment”?

- A health technology is any technology that might be used in treating diagnosing or preventing ill health
 - Drugs:
 - Devices: such as pacemakers, dialysis machines, hearing aids
 - Procedures: eg surgical techniques, acupuncture, counselling
 - Screening: for cancer, sexually transmitted diseases, stroke
- HTA is the process of assessing these in the widest sense – clinical and cost effectiveness, and more
- NIHR HTA programme – to assess by whatever means is best: systematic reviews, **clinical trials – original data generation**, cohort studies, modelling studies

NICE National Institute for
Health and Care Excellence

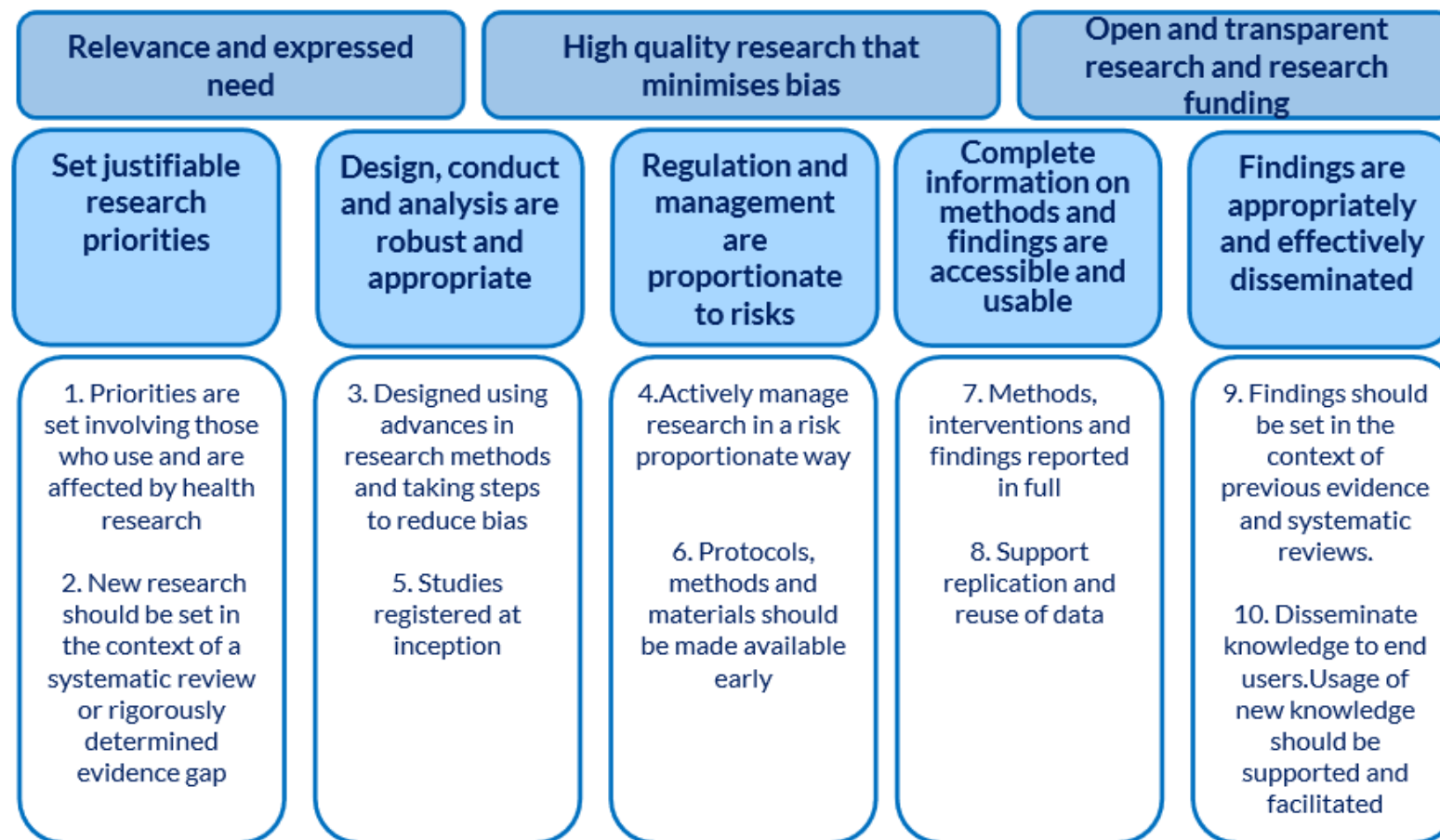
- NICE HTA (1999) typically by systematic review, and modelling and extrapolation of trial data, **to inform policy decisions quickly**

The HTA Programme

- The Health Technology Assessment Programme produces **independent** research about the **effectiveness** of different healthcare treatments and tests
- For those who use, manage and provide care in the UK National Health Service.
- Patient and public involvement (PPI) throughout
- It identifies the most important questions that the NHS needs the answers to by consulting widely
- The programme is:
 - **Needs- led** (relevance to the NHS)
 - **Science- added** (seeks to add value at every stage)

NIHR Adding Value in Research Framework

Raising the probability of benefits to society from health-related research for the tangible and intangible costs involved



Other NHS & NIHR support for trials

- NHS pays to treat the patient
 - Also pays for treatment in clinical trials
 - eg trial of anti-TNF agents in Rheumatoid arthritis
- **NIHR Local Clinical Research Networks**
infrastructure to support clinical research for NIHR, charities, industry
 - Access to a local network of 15000 skilled research support staff (eg research nurses)
 - Access to service departments such as pharmacy, radiology, laboratories
 - Access to free training opportunities
 - Dedicated research time for clinicians



Number of participants recruited to research studies in England per year

Year	Total research participants
2017/18	853,904
2018/19	870,250
2019/20	732,176
2020/21	1,390,483
2021/22	1,289,937
2022/23	952,789

This international clinical trial is identifying treatments that may be beneficial for people hospitalised with suspected or confirmed COVID-19

GLOBAL CUMULATIVE TOTALS

48603 Participants

190 Active sites

FUNDERS

This trial is supported by grants to the University of Oxford from the [National Institute for Health and Care Research \(NIHR\)](#), [UK Research and Innovation](#), [Wellcome](#), and [Flu Lab](#) and by core funding provided by the [Bill and Melinda Gates Foundation](#), the [Foreign, Commonwealth & Development Office](#), [Health Data Research UK](#), the [Medical Research Council Population Health Research Unit at the University of Oxford](#), the [NIHR Oxford Biomedical Research Centre](#), [NIHR Clinical Trials Unit Support Funding](#), and [Wellcome](#).

Reducing deaths from head trauma



The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients

I Roberts, H Shakur, T Coats, B Hunt, E Balogun, L Barnettson, L Cook, T Kawahara, P Perel, D Prieto-Merino, M Ramos, J Cairns and C Guerriero

- **CRASH-2** involved 20,211 subjects across 40 countries
- A large randomised placebo controlled trial among trauma patients with significant haemorrhage of the effects of an antifibrinolytic treatment on death and transfusion requirement
- Given within three hours of injury, tranexamic acid reduces deaths in people who are bleeding heavily. Potential to save 100,000 lives/yr worldwide

International TXA Studies

- Crash 2 – TXA in trauma,
 - 2006, NIHR, 20,000 pts, 1% in the UK (10%)
- Crash 3 – TXA in isolated head injury, 10,000 pts
 - UK - NIHR
 - International- MRC/Wellcome
- HALT-IT - TXA in GI bleeding
 - NIHR funding, 8000 pts, 40% in the UK
- TICH-2 - TXA in SAH
 - NIHR, 2000 pts, 80% in the UK

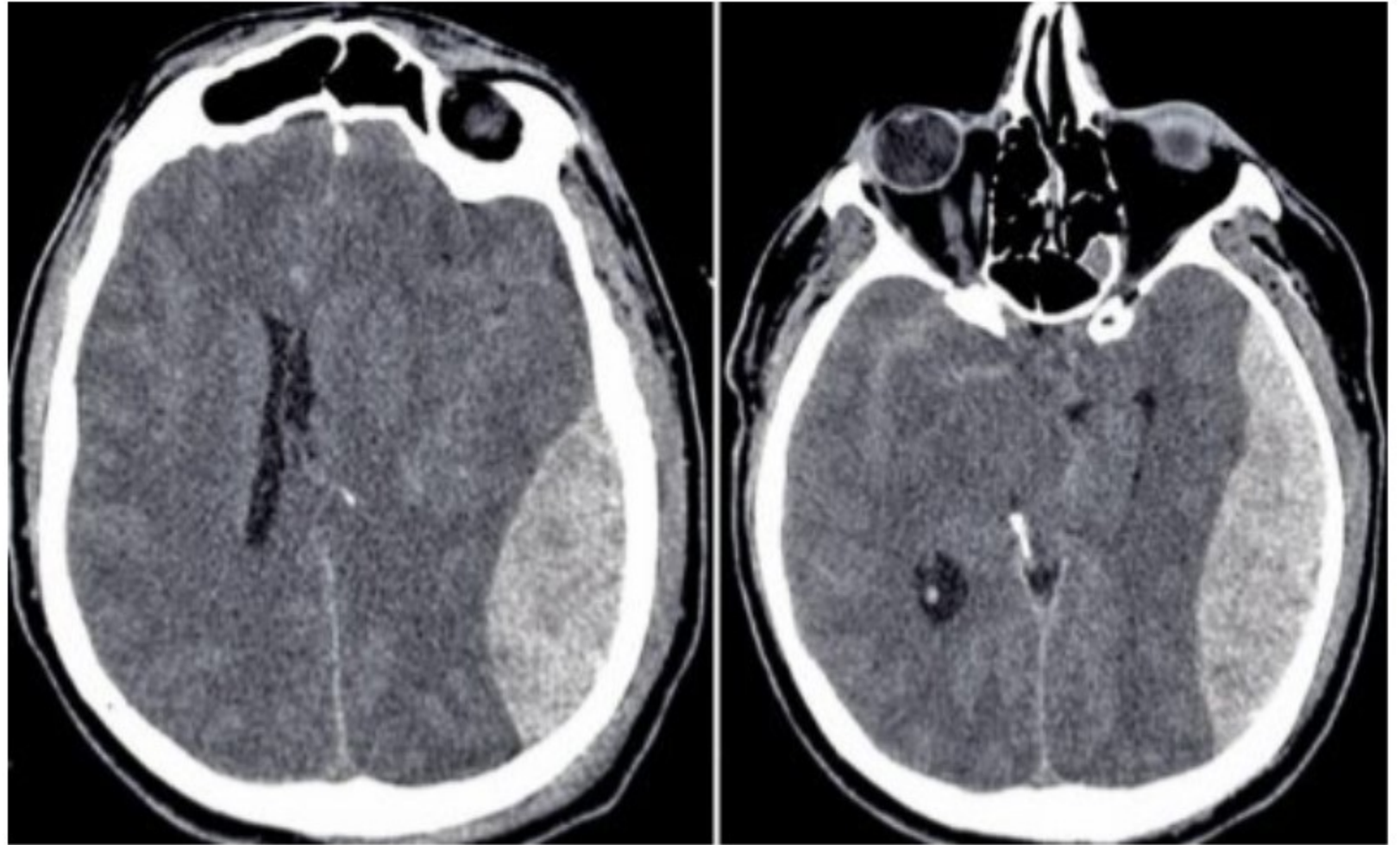
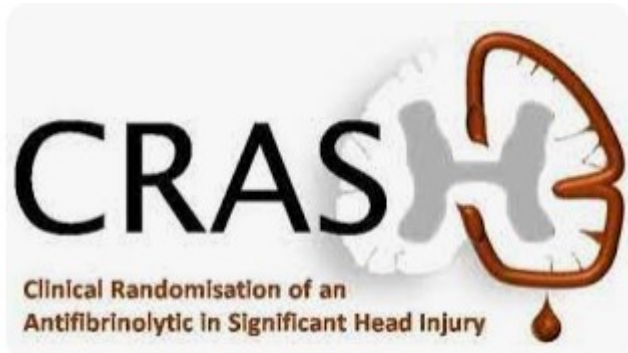
CRASH-2 follow on studies

- Follow on Project
- CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury, a nested randomised, placebo-controlled trial
- Follow on Project
- Development and validation of a risk score for trauma patients with haemorrhage The CRASH-2 score



CRASH-3

- 12, 000 patients,
175 hospitals
over 29 countries



CRASH-3: a win for patients with traumatic brain injury

Early treatment with tranexamic acid could save 'hundreds of thousands of lives worldwide'

To read the paper, visit the [The Lancet website](#) or watch "[CRASH-3 trial: The world's first drug for traumatic brain injury](#)" on YouTube.

Intramuscular tranexamic acid for the treatment of symptomatic mild traumatic brain injury in older adults: a randomised, double-blind, placebo-controlled trial



- Funded by HTA programme in 2023
- The CRASH-4 trial aims to provide reliable evidence about the effects of early intramuscular TXA on intracranial haemorrhage, disability, death and dementia in older adults with symptomatic head injury.
- Tranexamic acid (TXA) reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots.

Does it change practice?

Effects of tranexamic acid on death, vascular events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised placebo-controlled trial

Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial

Gavin D Perkins, Ranjit Lall, Tom Quinn, Charles D Deakin, Matthew W Cooke, Jessica Horton, Sarah E Lamb, Anne-Marie Slowther, Malcolm Woollard, Andy Carson, Mike Smyth, Richard Whitfield, Amanda Williams, Helen Pocock, John JM Black, John Wright, Kyee Han, Simon Gates, PARAMEDIC trial collaborators*

Summary

Background Tranexamic acid can reduce bleeding in patients undergoing early administration of a short course of tranexamic acid on death, vascular events, and blood transfusion in trauma patients.

Methods This randomised controlled trial was undertaken in 274 patients with, or at risk of, significant bleeding were randomly assigned (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or randomised to manual chest compressions according to the first trial vehicle to arrive on scene. The primary outcome was survival at 30 days following cardiac arrest and was analysed by intention to treat. Ambulance dispatch staff and those collecting the primary outcome were masked to treatment allocation. Masking of the ambulance staff who delivered the interventions and reported initial response to treatment was not possible. The study is registered with Current Controlled Trials, number ISRCTN08233942.

Findings 10 096 patients were allocated to tranexamic acid or placebo. All-cause mortality was significantly reduced in the LUCAS-2 group (104 [6%] of 1652 patients) compared with the manual CPR group (193 [7%] of 2819 patients; adjusted odds ratio [OR] 0.86, 95% CI 0.64–1.15). No serious adverse events were reported in the LUCAS-2 group (three patients with chest bruising, two with chest lacerations, and two with blood in mouth).

Interpretation Tranexamic acid safely reduced the risk of death and blood transfusion in trauma patients. These results, tranexamic acid should be considered for use in trauma patients.

Funding UK NIHR Health Technology Assessment Programme.

Methods The pre-hospital randomised assessment of a mechanical compression device in cardiac arrest (PARAMEDIC) trial was a pragmatic, cluster-randomised open-label trial including adults with non-traumatic, out-of-hospital cardiac arrest from four UK Ambulance Services (West Midlands, North East England, Wales, South Central). 91 urban and semi-urban ambulance stations were selected for participation. Clusters were ambulance service vehicles, which were randomly assigned (1:2) to LUCAS-2 or manual CPR. Patients received LUCAS-2 mechanical chest compression or manual chest compressions according to the first trial vehicle to arrive on scene. The primary outcome was survival at 30 days following cardiac arrest and was analysed by intention to treat. Ambulance dispatch staff and those collecting the primary outcome were masked to treatment allocation. Masking of the ambulance staff who delivered the interventions and reported initial response to treatment was not possible. The study is registered with Current Controlled Trials, number ISRCTN08233942.

Findings We enrolled 4471 eligible patients (1652 assigned to the LUCAS-2 group, 2819 assigned to the control group) between April 15, 2010 and June 10, 2013. 985 (60%) patients in the LUCAS-2 group received mechanical chest compression, and 11 (<1%) patients in the control group received LUCAS-2. In the intention-to-treat analysis, 30 day survival was similar in the LUCAS-2 group (104 [6%] of 1652 patients) and in the manual CPR group (193 [7%] of 2819 patients; adjusted odds ratio [OR] 0.86, 95% CI 0.64–1.15). No serious adverse events were noted. Seven clinical adverse events were reported in the LUCAS-2 group (three patients with chest bruising, two with chest lacerations, and two with blood in mouth).

Lancet 2015; 385: 947–55
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See Comment page 920
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Peri-operative Anaesthesia
Critical care collaborative
Research Group

Why undertake international collaborative studies/trials

- For:
 - We all face similar problems
 - We can only afford to do so many studies
 - Question too big to be answered in any one country?
 - Rare disease trials not possible otherwise
- Against
 - Problem is specific to one country?
 - Care (or healthcare systems) differ too much

Ranibizumab and Bevacizumab for Neovascular Macular Degeneration

The CATT Research Group*

ABSTRACT

BACKGROUND

Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS

In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

RESULTS

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm , $P=0.03$ by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab ($P>0.20$). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

CONCLUSIONS

At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00122493.)



CoverMe

Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial



Usha Chakravarthy, Simon P Harding, Chris A Rogers, Susan M Downes, Andrew J Lotery, Lucy A Culliford, Barnaby C Reeves, on behalf of the IVAN study investigators*

Summary

Background Bevacizumab has been suggested to have similar effectiveness to ranibizumab for treatment of neovascular age-related macular degeneration. The Inhibition of VEGF in Age-related Choroidal Neovascularisation (IVAN) trial was designed to compare these drugs and different regimens. Here, we report the findings at the prespecified 2-year timepoint.

Methods In a multicentre, 2x2 factorial, non-inferiority randomised trial, we enrolled adults aged at least 50 years with active, previously untreated neovascular age-related macular degeneration and a best corrected distance visual acuity (BCVA) of at least 25 letters from 23 hospitals in the UK. Participants were randomly assigned (1:1:1:1) to intravitreal injections of ranibizumab (0.5 mg) or bevacizumab (1.25 mg) in continuous (every month) or discontinuous (as needed) regimens, with monthly review. Study participants and clinical assessors were masked to drug allocation. Allocation to continuous or discontinuous treatment was masked up to 3 months, at which point investigators and participants were unmasked. The primary outcome was BCVA at 2 years, with a prespecified non-inferiority limit of 3.5 letters. The primary safety outcome was arterial thrombotic event or hospital admission for heart failure. Analyses were by modified intention to treat. This trial is registered, number ISRCTN92166560.

Findings Between March 27, 2008, and Oct 15, 2010, 628 patients underwent randomisation. 18 were withdrawn; 610 received study drugs (314 ranibizumab; 296 bevacizumab) and were included in analyses. 525 participants reached the visit at 2 years: 134 ranibizumab in continuous regimen, 137 ranibizumab in discontinuous regimen, 127 bevacizumab in continuous regimen, and 127 bevacizumab in discontinuous regimen. For BCVA, bevacizumab was neither non-inferior nor inferior to ranibizumab (mean difference -1.37 letters, 95% CI -3.75 to 1.01; $p=0.26$). Discontinuous treatment was neither non-inferior nor inferior to continuous treatment (-1.63 letters, -4.01 to 0.75; $p=0.18$). Frequency of arterial thrombotic events or hospital admission for heart failure did not differ between groups given ranibizumab (20 [6%] of 314 participants) and bevacizumab (12 [4%] of 296; odds ratio [OR] 1.69, 95% CI 0.80-3.57; $p=0.16$), or those given continuous (12 [4%] of 308) and discontinuous treatment (20 [7%] of 302; 0.56, 0.27-1.19; $p=0.13$). Mortality was lower with continuous than discontinuous treatment (OR 0.47, 95% CI 0.22-1.03; $p=0.05$), but did not differ by drug group (0.96, 0.46-2.02; $p=0.91$).

Interpretation Ranibizumab and bevacizumab have similar efficacy. Reduction in the frequency of retreatment resulted in a small loss of efficacy irrespective of drug. Safety was worse when treatment was administered discontinuously. These findings highlight that the choice of anti-VEGF treatment strategy is less straightforward than previously thought.

Funding UK National Institute for Health Research Health Technology Assessment programme.

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See Comment page 1230
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IVAN (NIHR, UK) CATT (NIH, USA), collaborations with funders on these parallel trials to ensure complementary outcomes and shared outputs for future meta-analysis.

Treatment of Barth Syndrome by CARDIOLipin MANipulation (CARDIOMAN): A randomised placebo-controlled pilot trial conducted by the nationally commissioned Barth Syndrome Service

Plain English Summary:

Barth Syndrome is a life threatening genetic disease which affects young males. It is caused by abnormal fats (lipids) in the powerhouses of cells (mitochondria). Those affected may be stillborn or develop heart failure, bacterial infections, poor growth or feeding problems during childhood. 26 males are alive with the disease

[Read more](#) ▼

Abstract:

HYPOTHESIS & AIMS Barth Syndrome patients show their inner mitochondrial membranes. In vitro studies produce major improvement in the abnormal MLCL/L

[Read more](#) ▼

Chief Investigator(s):

[Dr Guido Piele](#) 

Co-investigators:

[Dr Beverly Tsai-goodman](#), [Dr Chiara Bucciarelli-Ducci Sutton](#) , [Dr Matthew Toth](#), [Dr Paul Verkade](#), [Dr Rose Greenwood](#) , [Dr Vanessa Garratt](#), [Mrs Michaela Dam](#)

Searle et al. *Orphanet J Rare Dis* (2021) 16:404
<https://doi.org/10.1186/s13023-021-02027-5>

Orphanet Journal of
Rare Diseases

RESEARCH

Open Access

Self-regulation in Barth syndrome: a qualitative perspective of adolescents, adults and parents in the U.K



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can

Aidan Searle^{1*} , Georgia Herbert¹, Lucy Dabner², Colin G. Steward³, Michaela Damin⁴ and Guido Piele^{5,6}

Abstract

Background: Barth syndrome (BS) is a life-threatening genetic disease caused by abnormal lipids in the mitochondria of cells and mostly affects young males. Those living with BS have severe exercise intolerance, lethargy and fatigue due to muscle disease which affect their daily life. Previous research suggests a need for qualitative exploration of self-regulation in BS and the inter-personal processes at play in family life. Therefore this study aimed to explore self-regulation and coping strategies and inter-personal responses in individuals and families affected by Barth syndrome. A multi-perspective qualitative study based on face to face, semi-structured, in-depth interviews with 11 participants (9–27 years, mean 15 years) with BS and/or their parents participating in a randomised double-blind clinical drug trial (CARDIOMAN). Interviews were transcribed verbatim and managed in NVivo prior to conducting a thematic analysis (AS and GH).

Results: Four key themes were identified: diagnosis and treatment, social support, identity and social integration, symptoms and self-regulation. The present findings suggest that self-regulation and coping in boys with BS was inter-personal and contingent on parental awareness such that parents were aware that their child had a limited energy reserve and that had to be managed due to the implications of fatigue for daily living.

Conclusion: The findings support previous quantitative work demonstrating that children and parents tend to share a coherent view of BS. However, there is a need for greater awareness from others within the wider context of social and employment networks to minimise adverse implications for future life choices.

Keywords: Barth syndrome, Male, Self-regulation, Qualitative

[it](#)

CARDIOMAN

- Barth Syndrome is a rare disease with 18 patients in UK
- Collaboration on parallel study with USA
- Similar protocols developed to allow pooled analysis

- Sepsis Rivers
- protocol therapy department mortality has been results for potential for implementation

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Therapy for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek E. Timothy J. Coats, M.D., Mervyn Singer, M.D., and Kathryn M. Rowan, Ph.D., for the Pro

ABSTRACT

BACKGROUND

Early, goal-directed therapy (EGDT) is recommended for the resuscitation of patients presenting with early septic shock, but the evidence for its effectiveness remains limited, and uncertainty about its effectiveness remains.

RESULTS
In 31 emergency departments in the United States, we randomly assigned 1600 enrolled patients, 796 were assigned to the EGDT group and 804 to the usual care group. Primary outcome was all-cause mortality at 28 days. The primary outcome was all-cause mortality at 28 days.

METHODS

In 31 emergency departments in the United States, we randomly assigned 1600 enrolled patients, 796 were assigned to the EGDT group and 804 to the usual care group. Primary outcome was all-cause mortality at 28 days. The primary outcome was all-cause mortality at 28 days.

“the addition of continuous central venous oxygen saturation (ScvO₂) monitoring and strict protocolisation did not improve outcomes in the EGDT group. Our results complete the planned trio of studies of EGDT, all of which showed that EGDT was not superior to usual care.”

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ABLE

Age of Transfused Blood in Critically Ill Adults

Jacques Lacroix, M.D., Paul C. Hébert, M.D., Dean A. Fergusson, Ph.D., Alan Tinmouth, M.D., Deborah J. Cook, M.D., John C. Marshall, M.D., Lucy Clayton, M.Sc., Laura Lyn McIntyre, M.D., Jeannie Callum, M.D., Alexis F. Turgeon, M.D., Morris A. Blajchman, M.D., Timothy S. Walsh, M.D., Simon J. Stanworth, F.R.C.P., Helen Campbell, D.Phil., Gilles Capellier, M.D., Pierre Tiberghien, M.D., Laurent Bardiaux, M.D., Leo van de Watering, M.D., Nardo J. van der Meer, M.D., Elham Sabri, M.Sc., and Dong Vo, B.Eng., for the ABLE Investigators and the Canadian Critical Care Trials Group*

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Drs. Lacroix, Hébert, Fergusson, and Tinmouth contributed equally to this article.

*A complete list of investigators in the Age of Blood Evaluation (ABLE) study is provided in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND

Fresh red cells may improve outcomes in critically ill patients by enhancing oxygen delivery while minimizing the risks of toxic effects from cellular changes and the accumulation of bioactive materials in blood components during prolonged storage.

METHODS

In this multicenter, randomized, blinded trial, we assigned critically ill adults to receive either red cells that had been stored for less than 8 days or standard-issue red cells (the oldest compatible units available in the blood bank). The primary outcome measure was 90-day mortality.

RESULTS

Between March 2009 and May 2014, at 64 centers in Canada and Europe, 1211 patients were assigned to receive fresh red cells (fresh-blood group) and 1219 patients were assigned to receive standard-issue red cells (standard-blood group). Red cells were stored a mean ($\pm$ SD) of 6.1 ± 4.9 days in the fresh-blood group as compared with 22.0 ± 8.4 days in the standard-blood group ($P < 0.001$). At 90 days, 448 patients (37.0%) in the fresh-blood group and 430 patients (35.3%) in the standard-blood group had died (absolute risk difference, 1.7 percentage points; 95% confidence interval [CI], -2.1 to 5.5). In the survival analysis, the hazard ratio for death in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9 to 1.2 ; $P = 0.38$). There were no significant between-group differences in any of the secondary outcomes (major illnesses; duration of respiratory, hemodynamic, or renal support; length of stay in the hospital; and transfusion reactions) or in the subgroup analyses.

CONCLUSIONS

Transfusion of fresh red cells, as compared with standard-issue red cells, did not decrease the 90-day mortality among critically ill adults. (Funded by the Canadian Institutes of Health Research and others; Current Controlled Trials number, ISRCTN44878718.)

Age of Blood (ABLE)

- An international, multicenter, randomized, blinded trial comparing red cells stored for < 8 days with standard-issue red cells.
- Canadian led (CIHR): 64 centres (26 Canada; 20 UK; 10 France; 7 The Netherlands; 1 Belgium)
- Use of fresh cells did not decrease the 90-day mortality among critically ill adults compared to standard-issue red cells.

Details of first Australian-UK study NHMRC-NIHR

- ‘Early warning signs of relapse in schizophrenia’
- (from a JLA PSP)



- 13/154/04 EMPOWER: Early Signs Monitoring to Prevent Relapse and PrOmote Wellbeing, Engagement and Recovery.
- *Professor Andrew Gumley, University of Glasgow, £905,706*
- *Professor John Gleeson, Australian Catholic Hospital, Melbourne AU\$407,716*

The EMPOWER blended digital intervention for relapse prevention in schizophrenia: a feasibility cluster randomised controlled trial in Scotland and Australia

Andrew I Gumley, Simon Bradstreet, John Ainsworth, Stephanie Allan, Mario Alvarez-Jimenez, Lorna Aucott, Maximillian Birchwood, Andrew Briggs, Sandra Bucci, Sue M Cotton, Lidia Engel, Paul French, Reeve Lederman, Shôn Lewis, Matthew Machin, Graeme MacLennan, Hamish McLeod, Nicola McMeekin, Cathy Mihalopoulos, Emma Morton, John Norrie, Matthias Schwannauer, Swaran P Singh, Suresh Sundram, Andrew Thompson, Chris Williams, Alison R Yung, John Farhall, John Gleeson

Summary

Background Early warning signs monitoring by service users with schizophrenia has shown promise in preventing relapse but the quality of evidence is low. We aimed to establish the feasibility of undertaking a definitive randomised controlled trial to determine the effectiveness of a blended digital intervention for relapse prevention in schizophrenia.

Methods This multicentre, feasibility, cluster randomised controlled trial aimed to compare Early signs Monitoring to





Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial



The AVERT Trial Collaboration group*

Summary

Background Early mobilisation after stroke is thought to contribute to the effects of stroke-unit care; however, the intervention is poorly defined and not underpinned by strong evidence. We aimed to compare the effectiveness of frequent, higher dose, very early mobilisation with usual care after stroke.

Methods We did this parallel-group, single-blind, randomised controlled trial at 56 acute stroke units in five countries. Patients (aged ≥ 18 years) with ischaemic or haemorrhagic stroke, first or recurrent, who met physiological criteria were randomly assigned (1:1), via a web-based computer generated block randomisation procedure (block size of six), to receive usual stroke-unit care alone or very early mobilisation in addition to usual care. Treatment with recombinant tissue plasminogen activator was allowed. Randomisation was stratified by study site and stroke severity. Patients, outcome assessors, and investigators involved in trial and data management were masked to treatment allocation. The primary outcome was a favourable outcome 3 months after stroke, defined as a modified Rankin Scale score of 0–2. We did analysis on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12606000185561.

Findings Between July 18, 2006, and Oct 16, 2014, we randomly assigned 2104 patients to receive either very early mobilisation ($n=1054$) or usual care ($n=1050$); 2083 (99%) patients were included in the 3 month follow-up assessment. 965 (92%) patients were mobilised within 24 h in the very early mobilisation group compared with 623 (59%) patients in the usual care group. Fewer patients in the very early mobilisation group had a favourable outcome than those in the usual care group ($n=480$ [46%] vs $n=525$ [50%]; adjusted odds ratio [OR] 0.73, 95% CI 0.59–0.90; $p=0.004$). 88 (8%) patients died in the very early mobilisation group compared with 72 (7%) patients in the usual care group (OR 1.34, 95% CI 0.93–1.93, $p=0.113$). 201 (19%) patients in the very early mobilisation group and 208 (20%) of those in the usual care group had a non-fatal serious adverse event, with no reduction in immobility-related complications with very early mobilisation.

Interpretation First mobilisation took place within 24 h for most patients in this trial. The higher dose, very early mobilisation protocol was associated with a reduction in the odds of a favourable outcome at 3 months. Early mobilisation after stroke is recommended in many clinical practice guidelines worldwide, and our findings should affect clinical practice by refining present guidelines; however, clinical recommendations should be informed by future analyses of dose–response associations.

Funding National Health and Medical Research Council, Singapore Health, Chest Heart and Stroke Scotland, Northern Ireland Chest Heart and Stroke, UK Stroke Association, National Institute of Health Research.

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50140-6736(15)60690-0

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Members listed in the appendix

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See Online for appendix

AVERT

- International parallel group single blind, randomised trial (2104 patients)
- Australian (NHMRC) led trial in 56 Stroke units across 5 countries (Australia, New Zealand, Singapore, Malaysia and the UK)
- NIHR funded UK arm
- Trial assessing frequent, very early mobilisation after stroke with usual care



ORIGINAL ARTICLE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

J.J. McNeil, R. Wolfe, R.L. Woods, A.M. Tonkin, G.A. Donnan, M.R. Nelson, C.M. Reid, J.E. Lockery, B. Kirpach, E. Storey, R.C. Shah, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, C.I. Johnston, J. Ryan, B. Radziszewska, M. Jelinek, M. Malik, C.B. Eaton, D. Brauer, G. Cloud, E.M. Wood, S.E. Mahady, S. Satterfield,* R. Grimm, and A.M. Murray, for the ASPREE Investigator Group†

ABSTRACT

BACKGROUND

Aspirin is a well-established therapy for the secondary prevention of cardiovascular events. However, its role in the primary prevention of cardiovascular disease is unclear, especially in older persons, who have an increased risk.

METHODS

We fund comparative clinical effectiveness research (CER), which compares two or more medical treatments, services, or health practices to help patients and other stakeholders make better informed decisions

About PCORI

PCORI is the leading funder of patient-centered comparative clinical effectiveness research in the United States.

Research Done Differently®

Our strategic plan reflects PCORI's holistic approach to generating and promoting the use of patient-centered evidence, which is at the heart of what we do. There are four essential elements to this approach:

- **Funding of patient-centered CER**—to address questions important to patients and other stakeholders and to generate meaningful evidence that will allow them to make better informed health and healthcare decisions.
- **Engagement**—involving patients and all key health decision makers across the continuum of PCORI's work, from research topic selection to dissemination and implementation of results, to produce research findings that are useful, relevant, and trustworthy to those we serve.
- **Dissemination and Implementation**—to ensure that the results of PCORI-funded studies are easily accessible and can be used by those who need them to make better informed decisions on health and healthcare.
- **Research Infrastructure**—including enhancing the ability of PCORnet® to improve capacity to conduct clinical research more efficiently, improving the science and methods of CER, and supporting the continuing development of the health research workforce.

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Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease

W.S. Jones, H. Mulder, L.M. Wruck, M.J. Pencina, S. Kripalani, D. Muñoz, D.L. Crenshaw, M.B. Effron, R.N. Re, K. Gupta, R.D. Anderson, C.J. Pepine, E.M. Handberg, B.R. Manning, S.K. Jain, S. Girotra, D. Riley, D.A. DeWalt, J. Whittle, Y.H. Goldberg, V.L. Roger, R. Hess, C.P. Benziger, P. Farrehi, L. Zhou, D.E. Ford, K. Haynes, J.J. VanWormer, K.U. Knowlton, J.L. Kraschnewski, T.S. Polonsky, D.J. Fintel, F.S. Ahmad, J.C. McClay, J.R. Campbell, D.S. Bell, G.C. Fonarow, S.M. Bradley, A. Paranjape, M.T. Roe, H.R. Robertson, L.H. Curtis, A.G. Sharlow, L.G. Berdan, B.G. Hammill, D.F. Harris, L.G. Qualls, G. Marquis-Gravel, M.F. Modrow, G.M. Marcus, T.W. Carton, E. Nauman, L.R. Waitman, A.N. Kho, E.A. Shenkman, K.M. McTigue, R. Kaushal,

CONCLUSIONS

In this pragmatic trial involving patients with established cardiovascular disease, there was substantial dose switching to 81 mg of daily aspirin and no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily. (Funded by the Patient-Centered Outcomes Research Institute; ADAPTABLE ClinicalTrials.gov number, NCT02697916.)

ORIGINAL ARTICLE

A Randomized Trial of a Multifactorial Strategy to Prevent Serious Fall Injuries

S. Bhasin, T.M. Gill, D.B. Reuben, N.K. Latham, D.A. Ganz, E.J. Greene, J. Dziura, S. Basaria, J.H. Gurwitz, P.C. Dykes, S. McMahon, T.W. Storer, P. Gazarian, M.E. Miller, T.G. Trivison, D. Esserman, M.B. Carnie, L. Goehring, M. Fagan, S.L. Greenspan, N. Alexander, J. Wiggins, F. Ko, A.L. Siu, E. Volpi, A.W. Wu, I. Rich, S.C. Waring, R.B. Wallace, C. Casteel, N.M. Resnick, I. Magaziner

CONCLUSIONS

A multifactorial intervention, administered by nurses, did not result in a significantly lower rate of a first adjudicated serious fall injury than enhanced usual care. (Funded by the Patient-Centered Outcomes Research Institute and others; STRIDE ClinicalTrials.gov number, NCT02475850.)

[Home](#) > [Find funding](#) > [Programmes](#) > [Programmes](#)

Programmes

ZonMw stimulates knowledge development by funding projects in the field of health care, care and wellbeing. This takes the form of a range of grant programmes. These programmes are characterised by specific objectives, target groups and priorities in terms of content, for instance. You can find an overview of all our programmes on the Dutch website.

31 results

Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life

The SILENCE Randomized Clinical Trial

Harriette J. van Esch, MD; Lia van Zuylen, MD, PhD; Eric C. T. Geijteman, MD, PhD; Esther Oomen-de Hoop, PhD; Bregje A. A. Hulsman, MD; Helke S. Noordzij-Nooteboom, MD; Renske Boogaard, RN; Agnes van der Heide, MD, PhD; Carin C. D. van der Rijt, MD, PhD

CONCLUSIONS AND RELEVANCE Among patients near the end of life, prophylactic subcutaneous scopolamine butylbromide, compared with placebo, significantly reduced the occurrence of the death rattle.

Colchicine in Patients with Chronic Coronary Disease

S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal,
S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag,
A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper,
M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins,
W.A. Bax, M. Dirksen, M. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen,
J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*

ABSTRACT

Supported by the National Health Medical Research Council of Australia, a grant from the Sir Charles Gairdner Research Advisory Committee, the Withering Foundation the Netherlands, the Netherlands Heart Foundation, the Netherlands Organization for Health Research and Development, and a consortium of Teva, Disphar, and Tiofarma in the Netherlands.

Specificities

- ✓ Pragmatic & practice oriented
- ✓ Comparative effectiveness
(drugs, devices, surgery, physiotherapy, psychotherapy...)
- ✓ Drug repurposing
- ✓ Non-commercial
- ✓ Potential for return on investment
- ✓ Transparency and data sharing

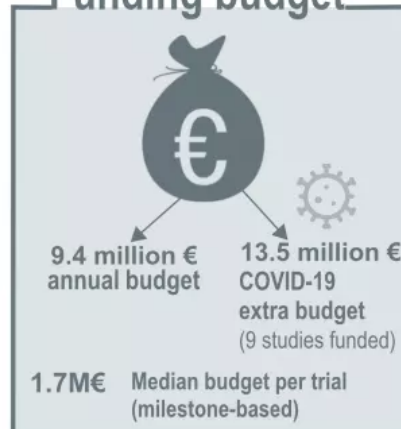
Quality support

- Sponsor capacity assessed for all trials 
- Training for Clinical Trials Centres 
- Coaching of funded teams 
- External audits of ongoing trials 

Calls for research proposals



Funding budget



Funded trials



Impact



2022 - BeNeFIT III: Third BeNeFIT call for comparative effectiveness studies with ZonMw

In September 2022 the Belgian Health Care Knowledge Centre (KCE) and The Netherlands Organisation for Health Research and Development (ZonMw) agreed to invest 9 million euros in the third call of the Belgium-Netherlands Funding of International Trials (BeNeFIT) program.

In clinical practice, many treatments have not been thoroughly evaluated, making it unclear whether a patient benefits from a particular treatment, or which treatment is actually preferable. Evaluation of clinical practice is relevant to health care stakeholders in Belgium and the Netherlands and by working together, clinical evaluation trials can be carried out more quickly and efficiently.

Health care efficiency research compares the effectiveness and cost-effectiveness of treatments that are part of health care in daily practice. Studies are focused on health benefits for the patient, but also evaluate costs. In Belgium the government finances these studies through KCE Trials and in the Netherlands funding is provided by the ZonMw programs 'Efficiency Studies' and 'Rational Pharmacotherapy', commissioned by the Ministry of Health, Wellbeing and Sports.

In 2017 KCE Trials and ZonMw launched the joint program BeNeFIT. In this initiative, a new funding selection process was developed that integrates approaches from both organisations. The main focus of the program is to provide funding for non-commercial practice-oriented research that is immediately relevant to patients, caregivers and policymakers in Belgium and the Netherlands and is conducted in collaboration by research institutions from both

CONTACT

KCE Trials

✉ trials@kce.fgov.be

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RECEIVE NEWS

FOLLOW KCE TRIALS



Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial



Jozefien Declercq*, Karel F A Van Damme*, Elisabeth De Leeuw*, Bastiaan Maes*, Cedric Bosteels*, Simon J Tavernier, Stefanie De Buyser, Roos Colman, Maya Hites, Gil Verschelden, Tom Fizez, Filip Moerman, Ingel K Demedts, Nicolas Dauby, Nicolas De Schryver, Elke Govaerts, Stefaan J Vandecasteele, Johan Van Laethem, Sebastien Anguille, Jeroen van der Hilst, Benoit Misset, Hans Slabbynck, Xavier Wittebole, Fabienne Liénart, Catherine Legrand, Marc Buyse, Dieter Stevens, Fre Bauters, Leen J M Seys, Helena Aegerter, Ursula Smole, Victor Bosteels, Levi Hoste, Leslie Naesens, Filomeen Haerynck, Linos Vandekerckhove, Pieter Depuydt, Eva van Braeckel, Sylvie Rottey, Isabelle Peene, Catherine Van Der Straeten, Frank Hulstaert, Bart N Lambrecht

Summary

Background Infections with SARS-CoV-2 continue to cause significant morbidity and mortality. Interleukin (IL)-1 and IL-6 blockade have been proposed as therapeutic strategies in COVID-19, but study outcomes have been conflicting. We sought to study whether blockade of the IL-6 or IL-1 pathway shortened the time to clinical improvement in patients with COVID-19, hypoxic respiratory failure, and signs of systemic cytokine release syndrome.

Methods We did a prospective, multicentre, open-label, randomised, controlled trial, in hospitalised patients with COVID-19, hypoxia, and signs of a cytokine release syndrome across 16 hospitals in Belgium. Eligible patients had a proven diagnosis of COVID-19 with symptoms between 6 and 16 days, a ratio of the partial pressure of oxygen to the fraction of inspired oxygen ($\text{PaO}_2:\text{FiO}_2$) of less than 350 mm Hg on room air or less than 280 mm Hg on supplemental oxygen, and signs of a cytokine release syndrome in their serum (either a single ferritin measurement of more than

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See [Comment](#) page 1353

*Contributed equally

Laboratory of Mucosal
Immunology, VIB-UGhent
Center for Inflammation

Interpretation Drugs targeting IL-1 or IL-6 did not shorten the time to clinical improvement in this sample of patients with COVID-19, hypoxic respiratory failure, low SOFA score, and low baseline mortality risk.

Funding Belgian Health Care Knowledge Center and VIB Grand Challenges program.

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

Florence Ader, Maude Bouscambert-Duchamp, Maya Hites, Nathan Peiffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Greil, Jérémie Guedj, Jose-Artur Paiva, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet, France Mentré*, and the DisCoVeRy Study Group*

Summary

Background The antiviral efficacy of remdesivir against SARS-CoV-2 is still controversial. We aimed to evaluate the clinical efficacy of remdesivir plus standard of care compared with standard of care alone in patients admitted to hospital with COVID-19, with indication of oxygen or ventilator support.

Methods DisCoVeRy was a phase 3, open-label, adaptive, multicentre, randomised, controlled trial conducted in 48 sites in Europe (France, Belgium, Austria, Portugal, Luxembourg). Adult patients (aged ≥ 18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and illness of any duration were eligible if they had clinical evidence of hypoxaemic pneumonia, or required oxygen supplementation. Exclusion criteria included elevated liver

Interpretation No clinical benefit was observed from the use of remdesivir in patients who were admitted to hospital for COVID-19, were symptomatic for more than 7 days, and required oxygen support.

Funding European Union Commission, French Ministry of Health, Domaine d'intérêt majeur One Health Île-de-France, REACTing, Fonds Erasme-COVID-Université Libre de Bruxelles, Belgian Health Care Knowledge Centre, Austrian Group Medical Tumor, European Regional Development Fund, Portugal Ministry of Health, Portugal Agency for Clinical Research and Biomedical Innovation.

ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*

ABSTRACT

CONCLUSIONS

The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion. (Funded by the Belgian Health Care Knowledge Center; ADVOR ClinicalTrials.gov number, NCT03505788.)

Pragmatic trials → RWE

Pragmatic	Explanatory
Representative participants	Highly selected participants
Interventions slotted into usual care	Intervention requires additional resources
Flexibility in delivery and adherence	Very standardised delivery, highly controlled adherence
Follow-up = usual care	More extensive follow-up
Primary outcome relevant to participants	Primary outcome not relevant to participants

BMJ Open Does the engagement of clinicians and organisations in research improve healthcare performance: a three-stage review

Annette Boaz,¹ Stephen Hanney,² Teresa Jones,² Bryony Soper²

To cite: Boaz A, Hanney S, Jones T, *et al*. Does the engagement of clinicians and organisations in research improve healthcare performance: a three-stage review. *BMJ Open* 2015;5:e009415. doi:10.1136/bmjopen-2015-009415

ABSTRACT

Objective: There is a widely held assumption that engagement by clinicians and healthcare organisations in research improves healthcare performance at various levels, but little direct empirical evidence has previously been collated. The objective of this study was to address the question: Does research engagement (by clinicians and organisations) improve healthcare performance?

Strengths and limitations of this study

- This review brings together for the first time a diverse body of literature addressing whether engaging clinicians and healthcare organisations

Conclusions: Current evidence suggests that there is an association between the engagement of individuals and healthcare organisations in research and improvements in healthcare performance. The mechanisms through which research engagement might improve healthcare performance overlap and rarely act in isolation, and their effectiveness often depends on the context in which they operate.

Pathways to implementation

- Embed expectation and conduct of research within the health systems
- If we have asked the right question and involved NHS in the trial, implementation should be easy!?
- ProtecT, PERSEPHONE, IVAN, CLOTS, ARTISTIC, CRASH,
- Need a clear pathway to implementation: roles for collaboration with eg NICE guidelines
- ...but it doesn't always work, eg EVAR

Are publicly funded trials worthwhile?

- “The main purpose of publicly funded health research is to improve the health of the general population in the form of better quality of life and increased longevity. However, **the direct and indirect cost of running a research program and the time to implementation of results should not be underestimated**. A government should try to invest its limited resources wisely. The opportunity cost of investing in clinical research might have as an outcome not to reimburse another intervention. Therefore, it is **important to evaluate the efficiency of such a government funded program**”.

Returns on research funded under the NIHR Health Technology Assessment (HTA) Programme

Economic analysis and case studies

Based on this analysis, if 12 per cent of the potential net benefit of implementing the findings of this sample of 10 studies for one year was realised, it would cover the cost of the HTA Programme from 1993 to 2012...

Need a clear pathway to implementation: roles for collaboration with eg NICE guidelines

How can trials help us deal with future challenges?

- The expected unexpected eg Pandemic response
 - Recovery, vaccines and more
 - (are we better placed for the next time?)
- The Expected
 - Multimorbidity
 - Ageing
 - Climate change
- The unexpected
 - ?

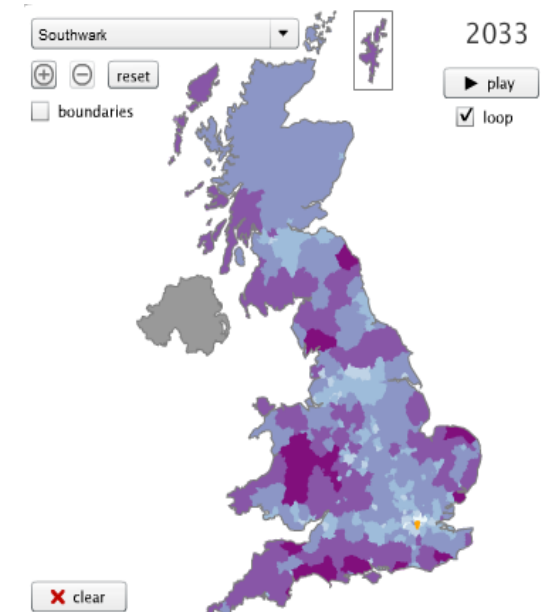
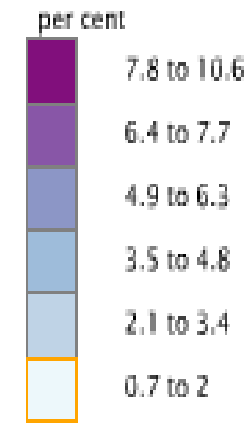
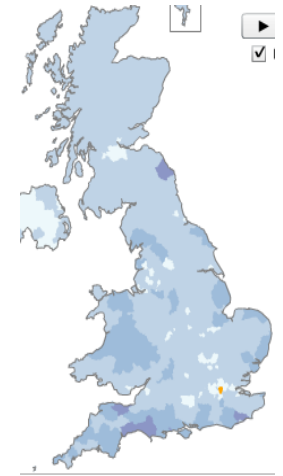
How can trials help us deal with future challenges?

- The expected unexpected eg Pandemic response
 - Recovery, vaccines and more
 - (are we better placed for the next time?)
- The Expected
 - Multimorbidity
 - Ageing
 - Climate change
- The unexpected
 - ?



How can trials help us deal with future challenges?

- The expected unexpected eg Pandemic response
 - Recovery, vaccines and more
 - (are we better placed for the next time?)
- The Expected
 - Multimorbidity
 - Ageing (eg over 85s, 2015, 2033)
 - Climate change
- The unexpected
 - ?



To sum up...

- Publicly funded trials
 - Address areas of no/limited commercial interest but of major interest to patients, health care professionals and policy makers
 - inform practical care and policy
 - are essential to improve our effectiveness in our care for patients and our efficiency
- Need a clear process of prioritisation
- Need partnership with health care providers, patients and more
- Should ideally be pragmatic and vested in its health service
- Should be of the highest quality
- Need methodological development needed, eg more efficiency in RCTs e.g. registry-based or adaptive platform RCTs that recruit a broad patient population, reflect routine care and test patient relevant outcomes

Congratulations to KCE on its 20th birthday!

for the excellence of the science it has promoted

for its contribution to public well being and to policy

for its role in developing our understanding of the importance of public funding for clinical trials – in Belgium and beyond

