Happy 21st Birthday to York Trials Unit
from the
NIHR Health Technology Assessment Programme

Hywel Williams
Director of the NIHR Health Technology Assessment Programme
What I plan to talk about…

• Some background on the “NIHR journey”
• How the NIHR HTA pushes and pulls research
• The important role of Clinical Trial Units
• More about York Trials Unit
• Some thoughts about HTA going forward
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

- Faculty:
  - Investigators and Senior Investigators
  - Trainees
  - Associates

- Universities

- Infrastructure:
  - Clinical Research Network
  - Clinical Research Facilities, Centres and Units

- Systems:
  - Research Information Systems
  - Faster easier clinical research

- Research:
  - Research projects and programmes
  - Research Schools

NHS Trusts

Patients and Public
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

National Institute for Health Research
NIHR RESEARCH CAREER PATHWAYS

Methodologists
- Research Methods Programme
  - Masters Studentship in Health Economics or Medical Statistics
  - Systematic Reviews Fellowship and Research Methods Fellowship and Internship
- Knowledge Mobilisation Research Fellowship
  - Clinical Trials Fellowship
    - Doctoral Research Fellowship
    - Post-Doctoral Fellowship
    - Career Development Fellowship
- Translational Research Fellowship
  - Research Professorship
  - Senior Research Fellowship

Fellowships for all
- HEE/NIHR Integrated Clinical Academic Programme
  - HEE/NIHR Clinical Lectureship
  - HEE/NIHR Clinical Doctoral Research Fellowship
  - HEE/NIHR Masters in Clinical Research Studentship

Healthcare Professionals (non-doctors/dentists)
- HEE/NIHR Clinical Lectureship

Doctors and Dentists
- Clinical Lectureship
- Clinician Scientist Award
- In-Practice Fellowship
- Academic Clinical Fellowship

Chair
- Senior/Pre-Chair
- Post-Doctoral (early to senior)
- Doctoral
- Pre-Doctoral
- Undergraduate
NIHR Networks - 15 Local Clinical Research Networks (LCRN)

Infrastructure to support clinical research for NIHR, charities, industry

A local and national support network to ensure the successful set up and delivery of research projects

• 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
State-of-play:

- Research is becoming more embedded
- 99% of NHS Trusts now research-active
- Progress with “hard-to-reach areas”

Sources: 2011/12 NIHR CRN annual report; Guardian Clinical Research Zone
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.
Some NIHR programmes

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

- Health Technology Assessment
  Established: 1993
- Health Services and Delivery Research
  Established: January 2012
- Systematic Review
  Established: 2012 (previously known as Reviews Infrastructure)
- Public Health Research
  Established: 2008
- Efficacy and Mechanism Evaluation
  Established: 2008
  Funded by the MRC and NIHR, managed by NIHR
Getting innovations into practice

Effectiveness and cost-effectiveness

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

EmE

Safety and efficacy

HTA

Effectiveness and cost-effectiveness

What if it is done in the NHS?

Should it be done in the NHS - appraisal

General clinical use

Appraisal (NICE)

Specialist commissioning

Horizon-scanning

Basic biomedical research

MRC, Various funders

Translational research

MRC
di4i

HS&DR

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MRC
di4i
The HTA Programme (1993)

- 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.
- It identifies the most important questions that the NHS needs the answers to by consulting widely.
- Patient and public involvement (PPI) throughout.
Clinical trials funded by NIHR HTA

NIHR established

£13M

£76M
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
HTA sits in a complex adaptive system

- International HTA
- Government priorities
- Pipeline: from RfPB and PgFAR and BRCs
- Trainees
- CTUs
- HTA themed
- HTA response
- Commercial sector
- Changing demographics
- Regulatory
- Delivery CRN

Changing demographics

International HTA

Pipeline: from RfPB and PgFAR and BRCs

HTA themed

Trainees

CTUs

HTA response

Commercial sector

Changing demographics

Delivery CRN

Regulatory

Network of Hubs for Methodology Research (HTA)
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Commissioned research: us pulling the community to do “less attractive but needed” research
Commissioned workstream

Advisory Panel Meeting

Methods Group

Prioritisation Group

6 Panels
- Primary Care, Community and Preventive Interventions
- Maternal, Neonatal and Child Health
- Interventional Procedures
- Mental, Psychological and Occupational Health
- Elective and Emergency Specialist Care
- Prioritisation Research Methods Advisory Group

Vignettes developed

Dissemination
- HTA monograph
- Peer reviewed publications
- Conference presentations

Commissioning Board
- Outline applications

Full applications

Expert review

Commissioning Board Teleconference

RESEARCH

Expert review

PG Post Funding Board

Advertised Commissioning Briefs

Panel Topics developed

Topic suggestions

Final Vignettes

Commissioned workstream

Outline applications

Expert review
Stages of Assessment

Prioritisation Panels
- Clinicians and Patients
- NHS focused
- Needs Led

Prioritisation Group
- Initial look at feasibility and value
- Portfolio balancing

Commissioning Board
- Academics
- Focused on the deliverability of proposals and value for money
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

• PROFHER (Rangan et al JAMA) – challenged role of surgery for displaced fractures of proximal humerus
Responsive mode – the research community pulling us
Examples of responsive mode

IVAN (Chakravarthy et al, Lancet) – compared generic bevacizumab vs ranibizumab to inhibit VEGF in Age-related choroidal Neovascularisation

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

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

EVerT (Cockayne et al BMJ) – challenged ritual of freezing plantar warts when compared with salicylic acid
HTA - the importance of testing “market failures” – examples from the world of skin and wounds

• The Bullous Pemphigoid Steroids and Tetracyclines Study (BLISTER - Lancet)

• Venous ulcers (VenUS IV - Lancet)

• Emollients for primary prevention of eczema (BEEP)
Themed calls – across all NIHR

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Themed Call</th>
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<tbody>
<tr>
<td>2015</td>
<td>Prevention and treatment of obesity</td>
</tr>
<tr>
<td>2015</td>
<td>Multimorbidities in older people</td>
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<tr>
<td>2014</td>
<td>Mesothelioma</td>
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<tr>
<td>2014</td>
<td>Long-term conditions in children and young people</td>
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<tr>
<td>2013</td>
<td>Antimicrobial resistance  <em>Ongoing highlight notice</em> in this area</td>
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<tr>
<td>2013</td>
<td>Primary care interventions</td>
</tr>
<tr>
<td>2012</td>
<td>Applied health research in surgery</td>
</tr>
<tr>
<td>2012</td>
<td>Applied clinical research on very rare diseases</td>
</tr>
<tr>
<td>2011</td>
<td>Applied health research on dementia</td>
</tr>
<tr>
<td>2011</td>
<td>Pandemic flu (HTA Programme)</td>
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<tr>
<td>2009</td>
<td>Obesity (HTA and PHR Programmes)</td>
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<tr>
<td>2009</td>
<td>Diagnostic tests and test technologies (HTA Programme)</td>
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<tr>
<td>2008</td>
<td>Healthcare associated infection (HTA Programme)</td>
</tr>
<tr>
<td>2007</td>
<td>Emergency medicine, pre-hospital care and trauma (HTA Programme)</td>
</tr>
<tr>
<td>2005</td>
<td>Medicines for children (HTA Programme)</td>
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</tbody>
</table>
Where NIHR gets published
(all original research May to Oct 2016)

Thanks to Rachel Mumford from DH
HTA specifically

- Of 29 HTA trials completed in 2014, 65.5% published in AIM journals
- 80% RCTs recruit 80% of planned sample size (Walters et al, BMJ Open 2017)
- All HTA trials funded in 2013 included a systematic review (Burke et al BMC Methodology Research 2015)
- Raft of other research on research studies….
Methodology strength in boards

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

• Must refer to relevant systematic reviews

• Point to COMET for core outcomes

• Must register trials

• protocols and publish them

• Reporting guidance such as CONSORT

• Must publish as HTA monograph
Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies

Kerry N L Avery¹, Paula R Williamson², Carol Gamble³, Elaine O’Connell Francischetti¹, Chris Metcalfe¹, Peter Davidson³, Hywel Williams⁴, Jane M Blazeby¹, ²

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.

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
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CTUs (and RDS)
Clinical Trial Units and the HTA

• Highly valued – supported expansion with funding and schemes

• For trial design, conduct, delivery and dissemination

• Diversity of CTUs – primary care, complex interventions, evidence synthesis, surgical trials, health economics modelling, value of information, prognostic modelling

• Appropriate methodological diversity

• Training and capacity building
Good CTU engagement at outline stage

• …. is usually obvious

• Absence of cut and paste patchwork quilt

• Outline costs reasonable and justified

• Different designs OK if appropriate to the question

• Convincing PPi threaded throughout
Good CTU engagement at .... at full application

- Can replicate sample size
- Sample size relates to primary outcome and is consistent
- Patient pathways well described
- Justification of non-inferiority design ie what trade-off for potentially lower effectiveness might be
- Various work-packages are well linked in time
- HE and qualitative work well specified and not underestimated
Good CTU engagement at monitoring and contract variations

- Good, open communication – “love thy monitoring research manager”
- More than one CTU involved? – more costs and bickering
- Involve TSC and DMEC in requests
- Choose the right time – steady state
- Build up some underspend during activity lull
- Be guided by monitoring team
- Keep costs down and only for essential work
Future CTU challenges

• Capacity

• Multi morbidities in older people

• Bridging social care

• Fragmented NHS and private providers

• Staying lean and efficient – NHS essentials

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YTU excels in...

- Pre-empted NIHR back in 1996
- Strong in methodology: health economics, evidence syntheses, complex interventions, complex trials, social sciences
- Strong in topic areas: musculoskeletal, surgery, chronic wounds, falls prevention, addiction, mental health, infectious diseases
- Long track record in successful delivery of important HTA trials
- Critical mass of staff
- Courses, teaching and capacity building
Comprehensive cohort with multiple embedded RCTs – CASPER – 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
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HTA themes going forward

• Efficient studies – e-studies
• Better connection with trial methodology hubs
• 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
A systematic approach to making trials more efficient

The evidence base for how to make the trials process efficient is remarkably thin. Trial Forge aims to change this.

**Trials**
Randomised controlled trials are the gold standard for evaluating healthcare treatments; 1000s are done every year.

**Essential**
Randomised trials are the cornerstone of evidence-based healthcare because they offer the fairest tests of treatments, therapies and initiatives.

**Inefficient**
The evidence base for how to make the trials process efficient is remarkably thin. Trial Forge aims to change this.
More than the final report...?
Stages of waste in the production and reporting of research evidence relevant to clinicians and patients

Adding value/avoiding waste
5 STAGES: FROM QUESTION TO REPORT

Questions relevant to users of research?
- Low priority questions addressed
- Important outcomes not assessed
- Clinicians and patients not involved in setting research agendas

Appropriate research design, conduct and analysis?
- Over 50% studies designed without reference to systematic reviews of existing evidence
- Over 50% of studies fail to take adequate steps to reduce biases, e.g. unconcealed treatment allocation

Efficient research regulation and delivery?
- Hyper-regulation of research
- Inefficient delivery of research
- Poor re-use of data

Accessible, full research reports?
- Over 50% of studies never published in full
- Biased under-reporting of studies with disappointing results

Unbiased and usable reports?
- Over 30% of trial interventions not described enough
- Over 50% planned study outcomes not reported
- Most new research not interpreted in context of systematic assessment of relevant evidence

Opportunities to add value
Proportion of clinical trials registered by 1999 and published by 2007

1. Chalmers I, Glasziou P, Godlee F. All trials must be registered and the results published. BMJ 2013; 346:f105

How do we do it?
- Expectation
- Contract
- Own journal
- Pay for publication in other journals (threats…)

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NIHR track record on reducing research waste – external evidence

• Nasser et al searched 11 international funder websites
  • Including UK: NIHR, MRC, Australia: NHMRC, Canada: CIHR, US: NIH, Germany: DFG, France: FOH, ANR, Dutch ZonMw, Denmark: DR, Norway: RH
  • On registration, access to protocols, access to completed data, promotion reporting guidelines, support systematic reviews, require SRs of existing evidence, research on research
  • Only NIHR achieved 5 green ratings (plus two yellow)
  • ZonMw: 2 green, 3 yellow and 2 reds
  • NIH 1 green, 3 amber, 3 reds

Enhanced dissemination

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

- NHMRC
- PCORI
- ZonMw
- Belgium
- Others
Conclusions: The National Institute for Health Research:

improving the health and wealth of the nation through research

Established by the Department of Health, NIHR:

• funds high quality research to improve health

• trains and supports health researchers

• provides world-class research facilities

• works with the life sciences industry and charities to benefit all

• involves patients and the public at every step
Getting the balance right between pushing and pulling research
Happy Birthday
Thanks and disclaimer

• Steve Goodacre, Deborah Ashby, Andrew Farmer
• Tom Walley
• Chris Whitty
• Rachel Mumford
• Dotty Gobles
• Fay Chinnery
• Steph Garfield-Birkbeck

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