# The Challenges and Opportunities for Statisticians working with NIHR funded research

Professor Deborah Ashby School of Public Health Imperial College London



- Past: A brief history of clinical trials
- Present: NIHR@10
- Future: Emerging challenges and opportunities



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"Prove thy servants, I beseech thee, ten days; and let them give us pulse to eat and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the king's meat: and as thou seest, deal with thy servants." So he consented to them in this manner and proved them ten days. And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat. Thus Melzar took away the portion of their meat, and the wine that they should drink; and gave them pulse."

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"On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the forehold; and had one diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like. Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day ... Two others took two spoonfuls of vinegar three times a day ... Two of the worst patients were put on a course of sea-water ... Two others had each two oranges and one lemon given them every day ... The two remaining patients, took ... an electary recommended by a hospital surgeon ... The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty ... The other was the best recovered of any in his condition; and ... was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects ..."

- first double blind comparative trial with concurrent controls in the general population in recent times.
- nationwide study enrolled over a thousand British office and factory workers suffering from colds- quite a challenging endeavor in wartime
- the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin.

### Imperial College London

- first randomized control trial of streptomycin in pulmonary tuberculosis was carried out in 1946 by MRC of the UK; trial began in 1947.
- amount of streptomycin available from US was limited, so ethically acceptable for the control subjects to be untreated by the drug—a statistician's dream.
- patients not told before admission that they were to get special treatment. C patients did not know that they were control patients in a special study -treated as they would have been in the past, the sole difference being that they had been admitted to the centre more rapidly than was normal. Usually they not in the same wards as S patients, but the same regime maintained
- the trial quickly became a model of design and implementation and continues to be referred to as ground breaking

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# The NIHR health research system





# **NIHR-Supported Facilities**



### **Clinical Trials Units**



### Imperial College London

### **Imperial Clinical Trials Unit**





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The Lancet Respiratory Medicine Volume 3, Issue 9, September 2015, Pages 684-691



#### Articles

CM

Repeated nebulisation of non-viral CFTR gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial

Prof Eric W F W Alton, FMedSci<sup>b, †,</sup> . W David K Armstrong, MB ChB<sup>9</sup>, Prof Deborah Ashby, CStat<sup>b</sup>, Katie J Bayfield, BSc<sup>b</sup>, Prof Diana Bilton, FRCP<sup>a</sup>, Emily V Bloomfield, BSc<sup>b</sup>, A Christopher Boyd, PhD<sup>f,†</sup>, June Brand, BSc<sup>f</sup>, Ruaridh Buchan, MPharm<sup>c</sup>, Roberto Calcedo, PhD<sup>i</sup>, Paula Carvelli, BN<sup>b</sup>, Mario Chan, MSc<sup>b</sup>, Seng H Cheng, PhD<sup>i</sup>, D David S Collie, MRCVS<sup>e</sup>, Steve Cunningham, MB ChB<sup>9,†</sup>, Heather E Davidson<sup>f</sup>, Gwyneth Davies, MBChB<sup>b</sup>, Prof Jane C Davies, FRCPCH<sup>b, †</sup>, Lee A Davies, DPhil<sup>h</sup>, Maria H Dewar, BSc<sup>c</sup>,



### Central commissioning facility:

The CCF manages the following research funding programmes: <u>Invention for Innovation (i4i)</u> <u>Programme Grants for Applied Research (PGfAR)</u> <u>Programme Development Grants (PDG)</u> <u>Research for Patient Benefit (RfPB)</u>

The CCF also manages the Research for Innovation, Creativity and Risk (RISC) programme, the <u>Research Design Service</u> (RDS) to support applicants and the following research schools, centre and units: <u>Blood and Transplant Research Units (BTRUs)</u> <u>Health Protection Research Units (HPRUs)</u> <u>School for Primary Care Research (SPCR)</u> <u>School for Public Health Research (SPHR)</u> <u>School for Social Care Research (SSCR)</u> <u>Surgical Reconstruction and Microbiology Research Centre (SRMRC).</u>

# NIHR Networks - 15 Local Clinical **Research Networks (LCRNs)**

North East and North Cumbria AHSN Area

Breater

West Midlands AHSN Area

West of England

AHSN Area

Yorkshire and nberside AHSN Area

> East Midlands AUSN Ares

> > UCL Partners

South London

AHSN Area

AHSN Area

ent, Surrey and

perial Partners AHSN Area

Oxford AHSN Area

Infrastructure to support clinical research for NIHR, charities,

# industry

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

 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 South West Peninsul

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



### State-of-play:

- Research is becoming more embedded
- 99% of NHS Trusts now research-active
- Progress with "hardto-reach areas"



NHS Trusts by number of studies recruiting patients in 2011/12

- Past: A brief history of clinical trials
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What I am going to do:

- What is the NIHR Health Technology Assessment programme for?
- How we push and pull research needed by the NHS
- Our strong respect for appropriate methodology
- Where we are going in the future



### Methodology strength in boards



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

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### **Clinical Trials Toolkit**

NHS National Institute for Health Research



The Clinical Trials Toolkit provides practical advice to researchers in designing and conducting publicly funded clinical trials in the UK. Through the use of an interactive routemap, this site provides information on best practice and outlines the current legal and practical requirements for conducting clinical trials.

The Toolkit is primarily focused on Clinical Trials of Investigational Medicinal Products (CTIMPs) and the regulatory environment and requirements associated with these. However researchers and R&D staff working on trials in other areas will also find useful information and guidance of relevance to the wider trials environment.

Please note the Toolkit describes the requirements for Clinical Trials of Investigational Medicinal Products (CTIMPs) brought about by the introduction of the European Commission Directive 2001/20/EC. A proposal to repeal Directive 2001/20/EC and replace it with a European Regulation has been published. As this new Regulation has not been finalised, its content is not widely discussed within this Toolkit at this stage. However, the site will consider the implications of any confirmed change in due course and provide updated information and guidance as agreed.

uggestions on h oolkit. Please he ip-to-date by rep	ne your feedback and ow we can improve the lp to keep the toolkit orting any out-of-date
ontent or broken	

#### **Mailing list**

Sign up to our newsletter and stay up to date on the latest news from the Clinical Trials Toolkit

Newsletter sign up

**NIHR Funding Opportunities** 

The NIHR funds and manages a number of health research programmes, with ongoing funding opportunities. If you would like information on current NIHR calls for proposals. please visit

#### Get started with the Routemap

#### Latest Clinical Trials Toolkit news

### Core outcome sets



### **Reporting guidelines**



Twenty researchers and clinicians

joined us for a week-long journey to

create well-reported, clear research

International Ethical Guidelines for Healthrelated Research involving Humans 5/01/2017

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Writing research

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### Hubs for Trials Methodology Research



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enquiries@methodologyhubs.mrc.ac.uk

### Five MRC Hubs

ologyhubs.mrc.ac.uk/about/hubs/

Home Research	Workshops	Funding	Advice	Resources	About	Search	MRC Hubs for Trials Methodology Research
About	Home /	Home / About / Hubs					Guidance
Network	Hul	bs	workshops				
Hubs		are MRC-fund					
Jobs	titles b	aspects of trial methodology. For more information on individual Hubs use the links in the titles below. The Network and Hubs are supported by research funding from the UK Medical Research Council. Our Hub members are key participants in our Working Groups, and membership is also open to interested individuals who are active in trials methodology research. Hub Directors and external Hub sites					al Webinars
Annual meeting							en (1)
Network projects	to inte						Working Group
PhD Studentships	Hub						Publications
	• P • P	Professor Paul Professor Rory	la Williams y Collins, I	ar, London Hub son, North Wes MRC Clinical Tri Biostatistics U	st Hub al Service U	nit Hub (CTSU general website)	

• Professor Jane Blazeby, (Network Chair) ConDuCT II Hub

🛿 2015 Medical Research Council - Hubs for Trials Methodology Research .

### **MRC-NIHR MRP**

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		will improve research studying the effect of diet. We have a strong commitment to methodology research and many of the projects and					evaluation Summary guidance (PDF, 893KB)				

### Joint workshops

### **BMJ** Open

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Abstract

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Alerts

**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.

Informing efficient randomised controlled trials: exploration of

challenges in developing progression criteria for internal pilot studies

Williams<sup>4</sup>, Jane M Blazeby<sup>1, 5</sup> members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research

Kerry N L Avery<sup>1</sup>, Paula R Williamson<sup>2</sup>, Carrol Gamble<sup>2</sup>, Elaine O'Connell Francischetto<sup>1</sup>, Chris Metcalfe<sup>1</sup>, Peter Davidson<sup>3</sup>, Hvwel

**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 triallists, 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

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### **CTUs and RDS**



### **Trial Forge**



What I am going to do:

- What is the NIHR Health Technology Assessment programme for?
- How we push and pull research needed by the NHS
- Our strong respect for appropriate methodology
- Where we are going in the future



Crunch question - how methodologically diverse are we?



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



### Series of N-of-1 randomised double blind placebo controlled trials Statin-WISE trial – Smeeth et al

- To determine whether muscle adverse events attributed to statin use by patients are caused by statins
- Patients in primary care recently stopped using statins or considering due to perceived adverse effects
- Statin medication (atorvastatin 20mg) compared to a placebo in six two-month treatment blocks of either statin or placebo, with the order of treatments randomly allocated.



### 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



### Flexible group sequential RCT design – Denison et al

- Got-it trial of glycerin trinitrate vs placebo for retained placenta
- With aim of reducing need for manual removal painful and increased hospital stay
- Trial can stop early for either overwhelming evidence of benefit (e.g. large treatment effect and/or low variability in the outcome measure)
- Or due to pre-defined futility
- Uses a Lan-DeMets alpha spending function with O'Brien Fleming boundaries and 5 planned interim evaluations, pre-specifying a two sided test, with asymmetry for efficacy and futility boundaries)



### 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

# Morning after pill

Emergency contraception available in store today

No prescription required Speak to your pharmacist


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)



Bayesian group sequential: UKREBOA study – Jansen et al

- Life threatening torso trauma
- INT. = Resuscitative Endovascular Balloon Occlusion of the Aorta
- Standard major trauma centre care
- Randomisation in seconds using smartphone website
- 90 day mortality; data linkage ++ TARN, ONS



# Efficient study designs: SIMPLIFIED 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



# Why do applications fail?

- Unconvincing scientific quality
- Unconvincing deliverability
- Insufficient team experience
- Lack of clarity
- Lack of depth
- Lousy patient/public involvement
- Poor value for money

But NOT not innovative study design

Was that a select sample?





- Underlying design and statistical principles don't change
- Using routine data sources presents many challenges
- 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

Imperial Clinical Trials Unit

- Statistics and statisticians are pivotal to MRC and NIHR and very much valued by them as organisations.
- There are many opportunities for grant funding and fellowships open to statisticians.
- If you want 'time out' to work on something that is important, where you think you can make a contribution and which will prepare you for the best stage in your research career, a Fellowship could be your next step!

#### NIHR RESEARCH CAREER PATHWAYS





•Methodology pivotal to NIHR research, so methodological applications welcome at all levels

•MRC has Strategic Skills fellowships, so need to think through which is more appropriate, based on motivation, level of fellowship and scope of work



•Statistics, modelling, health economics, trial design, monitoring of trials, methods for evaluation of diagnostic/ prognostic markers, trial conduct, qualitative methods.....

•How can the research tools be sharpened to allow NIHR and MRC to do its research more effectively and efficiently? Imperial College How to succeed with a methodological fellowship

•Showing relevance to NIHR

•Demonstrating benefit to patients within 3-5 years

•Explaining the ideas to non-methodologists

•Planning methodology research can be harder than primary research

•What's our equivalent of 'bench to bedside'?

•Bringing recent developments out from the basic scientists in the (non-medical) parts of universities into the tool-boxes of NIHR researchers.....

•.....to the ultimate benefit of patients.



- "Have nothing in your house that you do not know to be useful, or believe to be beautiful."
  — William Morris
- "Have nothing in your research portfolio that you do not know to be useful, or believe to be beautiful."

— with thanks to William Morris

