The trials of the future

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Crisis in cardiovascular therapeutics

- **Rising cost & complexity of late-phase trials**
  - 2 recent trials of PCSK9 inhibitors cost >$1Bn each
  - 85% commercial trials fail to recruit on time and to target
  - temptation to abandon randomization for lure of observational methods
- **Distorted treatment development priorities**
  - early decisions to continue treatment development based on limited data
  - move away from preventive and long-term treatments for common diseases
  - focus on very expensive drugs for rare conditions

The future for clinical trials

How can we take advantage of technological advances
in healthcare, engineering & communications
to facilitate randomized assessments of
treatment efficacy & safety?

Requires

- quality-by-design (focused on what matters)
- efficient data services & software engineering
- relevant Good Clinical Practice guidelines

Planning & feasibility: A national example

Target: 12,000 patients with cardiovascular disease

i) Diagnosis of **HEART ATTACK**

Or

ii) Diagnosis of **STROKE**

Or

iii) Surgery for **PERIPHERAL VASCULAR DISEASE**

Patients/ hospital	Hospitals	Patients
>10,000	96	~1.5M
>15,000	54	~0.8M
>20,000	26	~0.5M

i) Diagnosis of **HEART ATTACK**

- i.e. ICD9 code: 410*, 412* and/or
- ICD10 codes: I21*, I22*, I23*, I252 and/or
- READ codes: G30*

Or

ii) Diagnosis of **STROKE**

- i.e. ICD9 codes: 433*, 434* and/or
- ICD10 codes: I63*, I64* and/or
- READ codes: G63*, G64*, G66* and/or

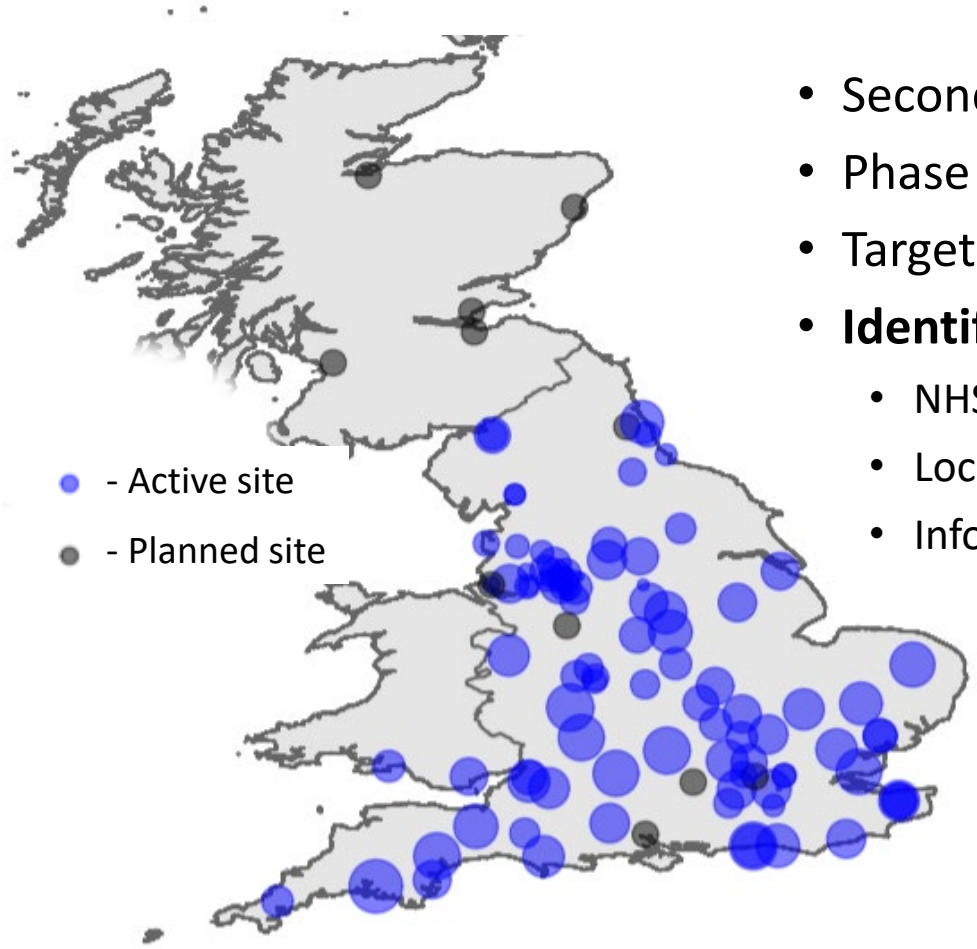
Or

iii) Surgery for **PERIPHERAL VASCULAR DISEASE**

- i.e. OPCS-4 procedure codes: L16*-28* inclusive, L48*-65* inclusive, L71*

HPS-4
TIMI 65
ORION-4

Nationwide recruitment into ORION-4 trial



- Secondary prevention of cardiovascular disease
- Phase 3 RCT of inclisiran vs. placebo
- Target: 12,000 participants at 100 UK sites
- **Identified from central NHS records**:
  - NHS Digital (England)
  - Local Health Boards in Wales
  - Information Services Division NHS Scotland

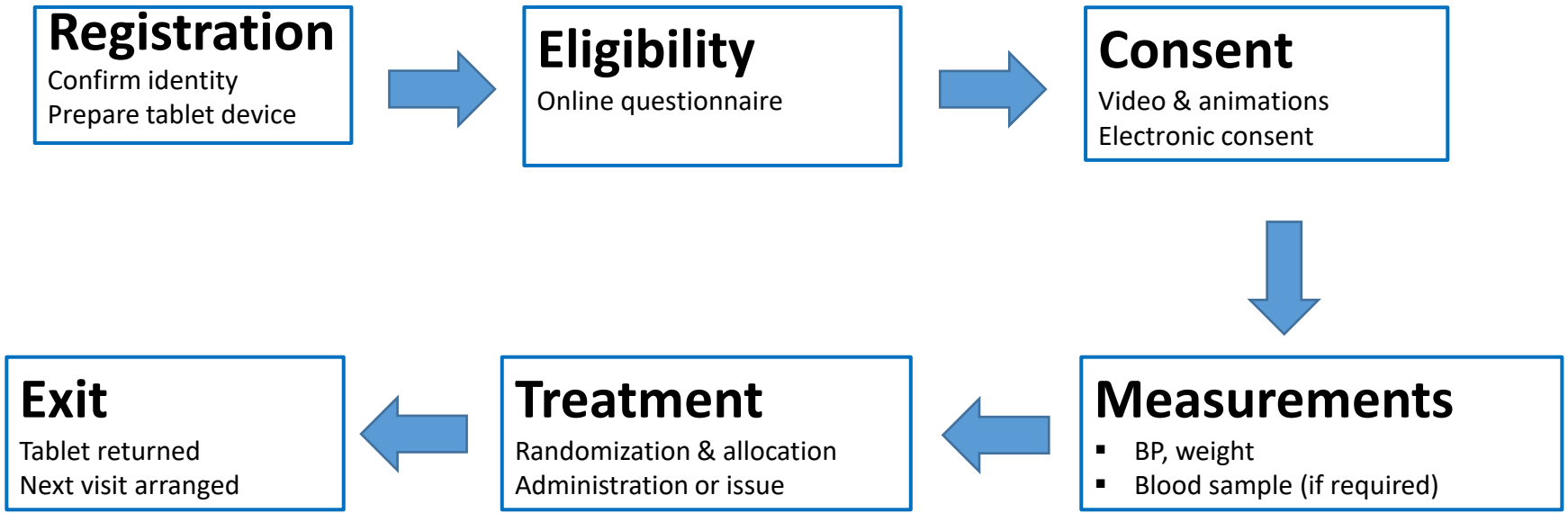
HPS-4
TIMI 65
ORION-4

Driving quality & efficiency at large hospital sites

- **Advantages:**
  - economies of scale (cost/pt reduces the more pts are recruited)
  - improved quality (research nurse is focussed on doing 1 trial well)
- **Challenges:**
  - delays in agreeing local hospital research contracts
  - poor availability of suitable clinic space
  - limited hospital parking & accessibility
  - delays at busy hospital pharmacies

The future: Conveniently located mega-clinics

10 visits per clinic per hour; 1000 participants / clinic



Using routine data to ascertain outcomes in randomized controlled trials

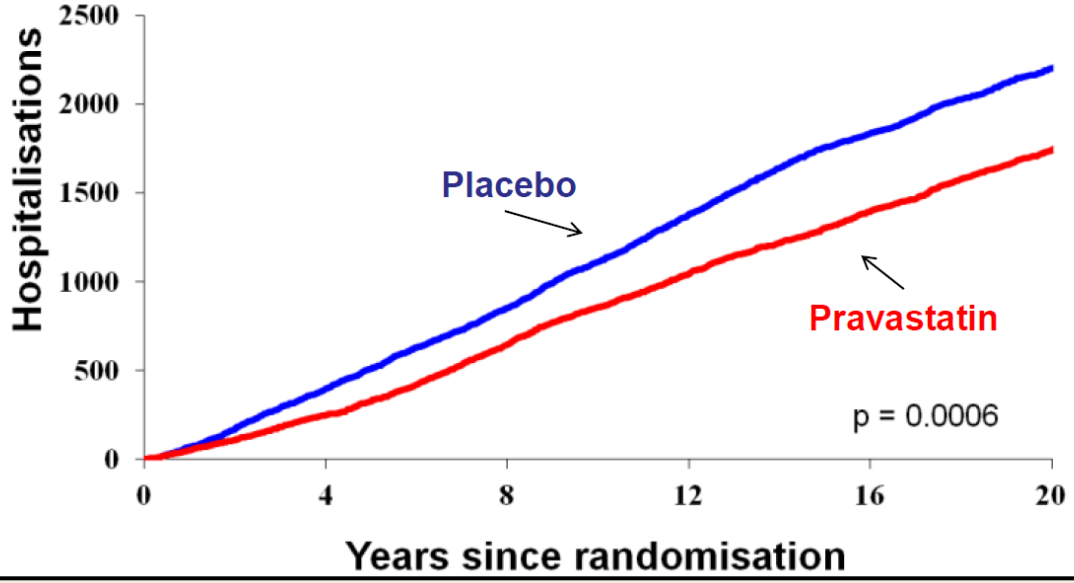
Strengths:

- *Efficient*: enable larger, more “real-world” trials
- *Comprehensive*: minimize loss-to-follow-up
- *Durable*: enable prolonged study of safety & efficacy

Current weaknesses:

- *Accessibility*: not all records are easy to access
- *Accuracy*: not all events are well coded
- *Confidence*: not all audiences or regulators are convinced

Routine data provide robust information on clinical efficacy during and for many years after clinical trial



Long-term reduction in cumulative hospital admissions for coronary heart disease following 7 years of treatment with pravastatin vs. placebo

(validation studies show trivial differences between routine collected hospital admission data versus expensively collected and adjudicated trial data)

UK Life Sciences Industry Strategy

NHS Digital and Health Data Research UK... will lead work on the creation of data services to support a 21st Century clinical trials platform.

Home | Infrastructure | The Hubs

NHS DigiTrial - The Health Data Research Hub for Clinical Trials

The Hub will focus on the development of a foundation service to improve the assessment of clinical trial feasibility - supporting improved planning and delivery of clinical trials in the UK

https://www.hdruk.ac.uk/infrastructure/the-hubs/nhs-digitrial/

NHS DigiTrials: Efficient data services for clinical trials

Addressing major challenges to quality & efficiency

Good design

Efficient recruitment

Effective engagement

Robust results

Feasibility

- Assess number & location of potential participants
- Iteration of protocol & recruitment approach
- Focus efforts & resources

Identification

- Efficient & consistent data searches
- Scalable invitation approach tailored to approved trial needs
- Latest information on opt-out, vital status, registered GP & contact details

Communication

- Enables prompt communication before, during & after trial
- Enhanced understanding of protocol, progress & emerging results
- Uses latest contact details & GP information

Outcomes

- Comprehensive data on safety & efficacy
- Minimal loss-to-follow-up at low cost
- Enables long-term assessment of effects

https://digital.nhs.uk/services/clinical-trials-service

Major issues with “GCP” regulatory guidelines for trials

- Developed by regulators with selected industry partners in 1995
- Not based on scientific principles of randomized controlled trials
- Not working well for industry trials (fewer new drugs developed) or for non-commercial trials (routine care less well assessed)
- Not appropriate for the 21st Century (e.g. the “connected world”, novel technology, new forms of treatment)
- No input from patients, academic trialists or the non-commercial sector (funders or health services)

Good Clinical Trials Collaborative

- developing & promoting adoption of rational guidelines -

Aim: Rational and proportionate GCP guidelines that enable timely, affordable and high quality assessments of the benefits & harms of health interventions

- Based on key scientific & ethical principles
- Clear, concise, consistent & proportionate guidelines
- Co-developed through an *Open Regulatory Science* approach
- Forward looking: foster innovation in health interventions & trial methods
- Broadly applicable, widely adopted and durable

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SOUNDING BOARD

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

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Re-inventing randomized trials for the 21st Century

Improved feasibility driven by data & technology

PLUS

Adherence to principles of randomized trials

SUPPORTED BY

Proportionate approaches to trials regulations & guidance

FOR THE BENEFIT OF

Patient care and public health