



The power of large pragmatic randomised clinical trials

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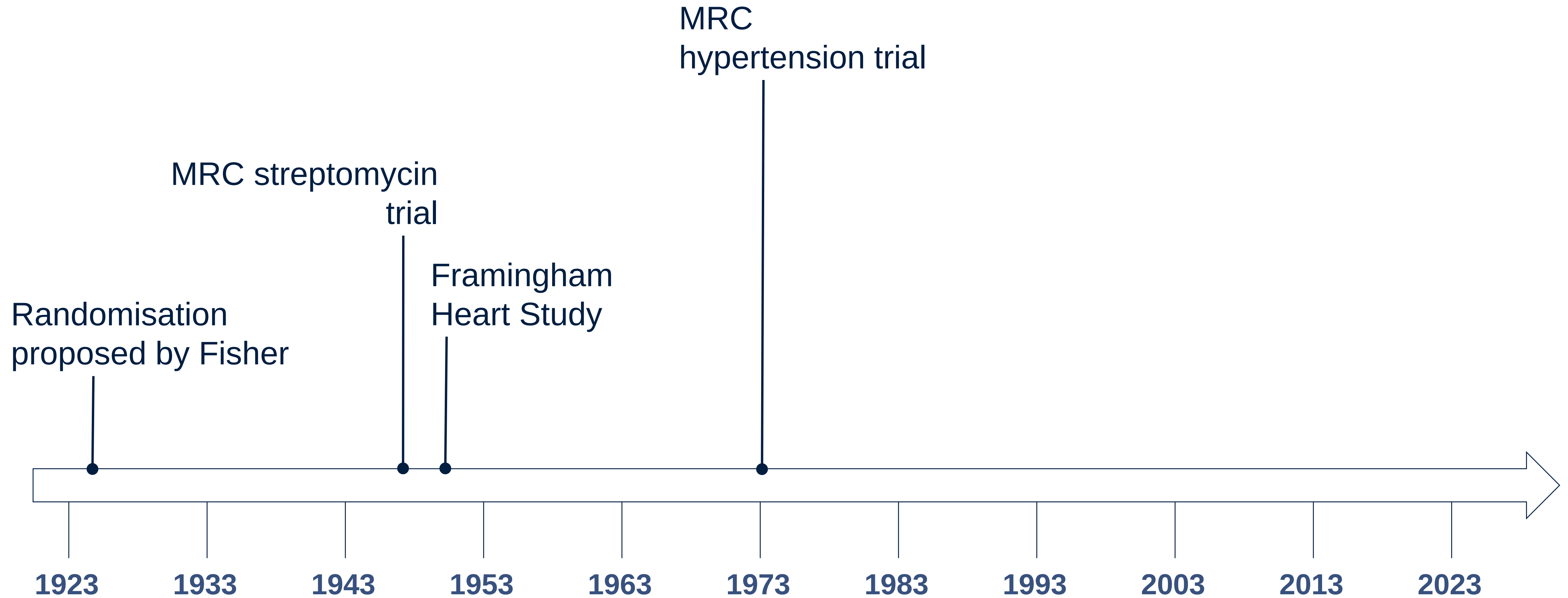
KCE Trials Symposium

Declaration of interest

- I am employed by the Nuffield Department of Population Health, University of Oxford and funded by the Oxford BHF CRE
- I have an Honorary contract with Oxford University Hospitals NHS Foundation Trust
- I receive no honoraria or personal payments from industry in compliance with the NDPH policy for maintaining scientific independence*
- I am a co-applicant on research grants from The Medicines Company/Novartis and Novo Nordisk to the University of Oxford, and work on projects funded by research grants from, or supported in kind (supply of study medication) by, Abbott, AbbVie, Bayer, Boehringer Ingelheim, Merck, Mylan, Roche, Regeneron and Solvay.

* <https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf/@@download>

Looking back 100 years

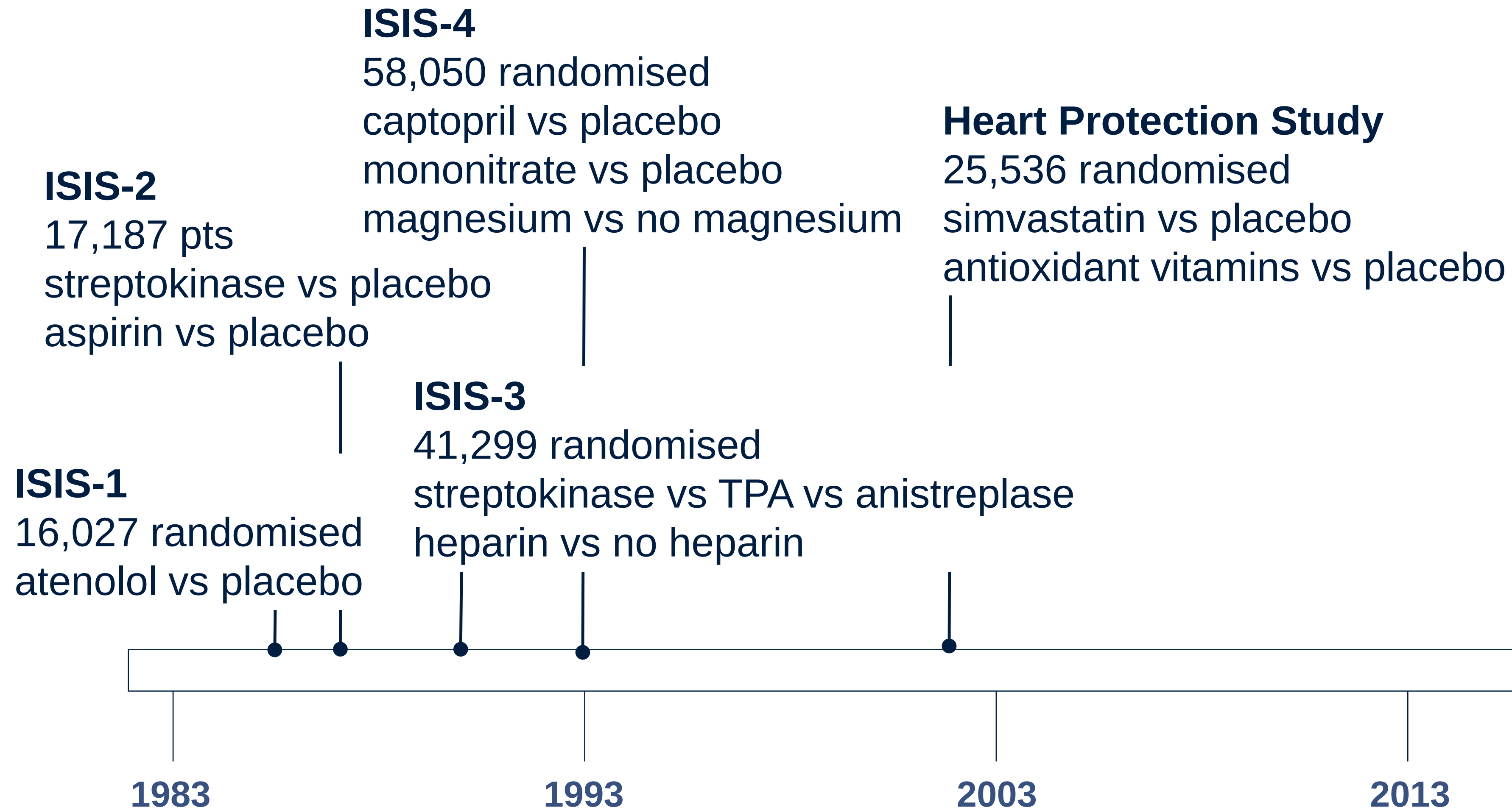


Reliable assessment of the effects of
treatment on important outcomes
requires

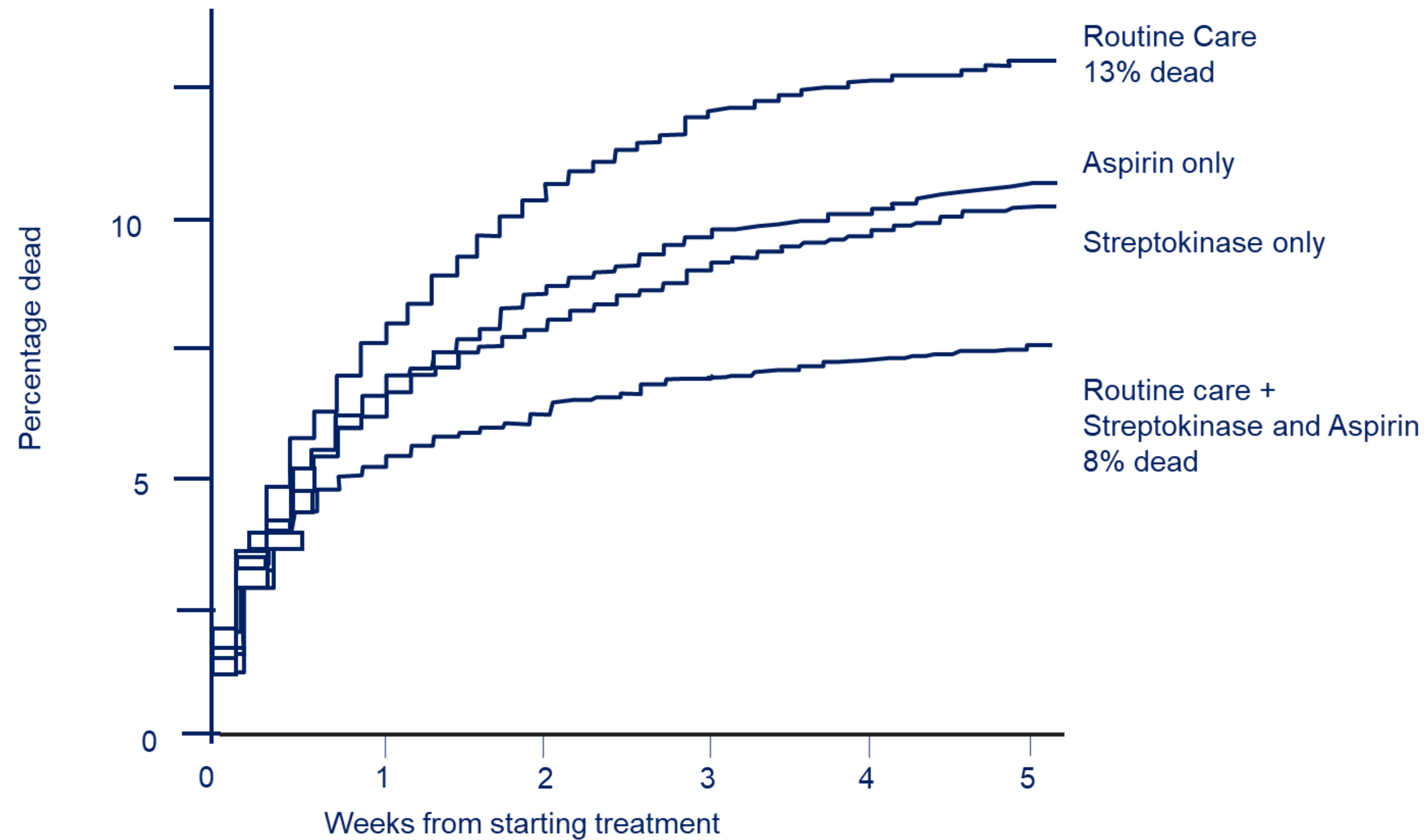
Randomisation to avoid systematic error

Large numbers to avoid random error

Looking back 40 years



Large trials change practice: Results of the ISIS-2 trial



Large streamlined trials change practice: the ISIS-2 trial

PATIENT IDENTIFIERS (Please PRINT): (for central monitoring of certified causes of death)

Hospital: _____

Surname/Family name: _____

All given name(s): _____

Date of birth: day: _____ / month: _____ / year: _____

Address: _____

Maiden name: _____

(if available)

Family doctor: _____

(if available)

TICK ☒ **PRE-TREATMENT CHARACTERISTICS**

☐ Female

☐ Previous myocardial infarction

☐ Previous diabetes

TICK ☒ **ANY DEVIATIONS FROM TRIAL TREATMENT**

☐ **STREPTOKINASE/PLACEBO** infusion interrupted, or not given

☐ **ASPIRIN/PLACEBO** calendar pack interrupted, or not given

TICK ☒ **APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO**

☐ Significant hypotension during, or just after, infusion

☐ Anaphylactic shock

☐ Rigor

☐ Rash

☐ Other (specify, eg. respiratory distress) _____

TICK ☒ **MAIN EVENTS (FATAL OR NOT) AFTER RANDOMISATION,**

_____ day / month / year

☐ "Major" bleed (transfused) _____ / _____ / _____ and s

☐ "Minor" bleed (not transfused) _____ / _____ / _____

☐ Cardiac rupture _____ / _____ / _____

☐ Reinfarction _____ / _____ / _____

☐ Ventricular fibrillation _____ / _____ / _____

☐ Other cardiac arrest _____ / _____ / _____

☐ Stroke, probable cerebral haemorrhage _____ / _____ / _____

☐ Stroke, infarct or unknown type _____ / _____ / _____ } Likely

☐ Discharge alive from hospital _____ / _____ / _____

☐ Death in hospital _____ / _____ / _____ and u

TICK ☒ **TREATMENT IN HOSPITAL**

☐ Steroids prior to streptokinase/placebo infusion

☐ Subcutaneous heparin

☐ Intravenous heparin

☐ Oral anticoagulant

☐ Intravenous beta-blocker

☐ Non-trial aspirin

☐ Other anti-platelet agent(s) _____

TICK ☒ **DRUGS ON DISCHARGE**

☐ Oral anticoagulant

☐ Non-trial aspirin

☐ Other anti-platelet agent(s) _____

☐ Beta-blocker

NAME OF PERSON COMPLETING FORM (please PRINT): _____

PLEASE SEND: — TOP COPY OF THIS FORM (retain bottom green copy)

— AND PRE-RANDOMISATION ECG (original or good photocopy)

TO: ISIS-2, FREEPOST, OXFORD OX2 6BR, UK (no stamp required with)



Consider for

ISIS-2

A multicentre randomised study of the effects of intravenous streptokinase
and of oral aspirin on mortality after acute myocardial infarction

Eligibility

(If not eligible
note reason
in ISIS - 2 log
or ward log)

- Signs or symptoms suggestive of definite or suspected acute myocardial infarction
- <24 hours since onset of episode of pain that led to admission
- No clear contra-indication to, (NOTE A) or indication for, immediate streptokinase or aspirin, in the view of the responsible physician
and, in particular, no history of stroke or gastrointestinal haemorrhage or ulcer
- No major threatening disease other than myocardial infarction
- Seek any consent that is required and check that follow up is reasonably likely (NOTE B)
- If physicians wish to use prophylactic steroids, then these should be given
- Prepare for telephone questions (ISIS - 2 randomisation note book may be useful)

Telephone randomisation

(No forms what-ever at entry)

- Telephone 24 hour direct line 008033106 or reverse charge call to Oxford (865) 53238
- Specify - Country (ie Australia)
- Hospital (NB this is hospital no)
- History of stroke, GI bleed or ulcer? (must be "NO")
- Patient's full name and date of birth
- Hours since onset of episode of pain
- Systolic blood pressure
- Any aspirin in past week
- Does 'planned' treatment include:
aspirin? Yes/No (NOTE C)
subcutaneous or mini-dose iv heparin Yes/No
full-dose iv heparin Yes/No
oral anticoagulants? Yes/No
intravenous beta-blocker? Yes/No
- When those details are complete, a TREATMENT PACK NUMBER will be allocated (Patients cannot now be withdrawn even if treatment cannot be given)

Treatment

(tablet, blood sample, infusion)

- Obtain allocated trial treatment pack, and administer as directed on pack - chew first tablet, take 5ml then 10 ml of blood into vacuainers provided, and start infusion. Instruct nurses to discontinue if side-effects occur (NOTE D)
- Give any aspirin, anticoagulants or beta-blockers that were 'planned' at the telephone randomisation (unless clear contra-indications to their devlop)
- Aspirin/platelets tablets continue once daily AFTER DISCHARGE, if NECESSARY until cardiac pain is exhausted, unless some clear contra-indication to enteric-coated aspirin emerges
- Other adjunctive therapy as indicated (NOTE E)
- A day or so after entry, if the patient is well enough for it to be reasonable to ask them to spend about half an hour on a self-administered questionnaire, then nursing staff may give them an ISIS - 2 EPIDEMIOLOGY ENVELOPE
- Strokes (NOTE F)
- Finally, after discharge or death, send:
- DISCHARGE FORM (take about 3 minutes) and
- PRE-RANDOMISATION ECG (original or photocopy) in reply paid envelope,
to: ISIS - 2
DEPT. OF CARDIOLOGY
ROYAL MELBOURNE HOSPITAL
MELBOURNE
VICTORIA 3050

After discharge

(or prior death)

A good ECG should be available

NOTE A. CLEAR INDICATIONS OR CONTRA-INDICATIONS

The fundamental criterion for entry is that the responsible physician considers there to be no clear contra-indications to, or indications for, either streptokinase or aspirin. Contra-indications might include: recent, or planned, internal operations (eg in previous 10-14 hours); recent trauma (eg surgery, head injury, reoperation in last two weeks); severe persistent hypertension (eg systolic blood pressure >200 mmHg); previous allergy to streptokinase or aspirin; negligible low risk of cardiac death (eg completely normal ECG with an unconvincing clinical history)

NOTE B. CONSENT AND FOLLOW UP

The degree and timing of consent to entering a matter for individual doctors to decide for individual patients in the light of local circumstances and advice from any relevant ethics committees. Follow up after discharge will involve enquiring routinely about vital statistics (dead/live) on January 1st 1987.

NOTE C. TREATMENT 'PLANNED' PRIOR TO RANDOMISATION

Exact planning may be expedient, especially since indications to, or contra-indications to, aspirin, anticoagulants or beta-blockers may change only later. What is essential is merely some idea of what treatment is likely to be used later in hospital.

NOTE D. TREATMENT OF RARE COMPLICATIONS OF STREPTOKINASE

(eg profound hypotension, allergy or haemorrhage). Stop streptokinase/platelet infusion and treat as necessary.

Hypotension - Tie head down. If hypotension persists, consider use of plasma expanders, atropine and vasodilators.

Allergy - Consider use of hydrocortisone and antihistamine.

Haemorrhage - Consider use of fresh frozen plasma or plasma expanders. If fibrinolytic activity may remain high, in first 6 hours or so, consider prior anti-fibrinolytic therapy, e.g. with 1g tranexamic acid, aminocaproic acid, or aspirin.

Need for removal of packing wires, long lines etc

Consider insertion of antiseptic, either than subcutaneous or internal jugular, route while coagulation may be impaired (e.g. in first 12 or 24 hours).

If it is necessary to know actual trial treatment ('Unblinding'), Telephone 008033106 or reverse charge call to OXFORD (865) 53238

NOTE E. OTHER ADJUNCTIVE THERAPY

All trial patients may be given as they wish, as indicated.

The trial treatment, however, should be interpreted only when clearly indicated needed, many physicians may choose to continue the aspirin/platelets that follows throughout treatment with intravenous heparin, oral anticoagulants, or open aspirin)

NOTE F. STROKES BEFORE DISCHARGE

These will be extremely rare in all treatment groups, for although treatment may increase the risk of haemorrhagic stroke, it may reduce the risk of occlusive stroke. If a non-fatal stroke is suspected, then information will be required on: (a) aetiology - a CT scan within 2 weeks is highly desirable, and (b) severity - an approximate prediction of the degree of eventual residual disability: non-significant (Rankin 0-1), moderate (Rankin 2-3) or severe (Rankin 4-5, ie, unable to walk without assistance).

Both should be supported by a neurological opinion, if possible.

NO OTHER FORMS REQUIRED



Second International Study of Infarct Survival

For Randomisation (and 'Unblinding')
Telephone 24 hour direct line: 008033106
(or, reverse charge call to Oxford (865)53238)

“By far the most important determinant of the success of ISIS is the extent to which, in those busy hospitals where the majority of acute MI patients are actually admitted, the responsible physicians and nurses choose to enter their patients. Hence, the extra work must be – and is – absolutely minimal.”

Large streamlined trials



streamlined

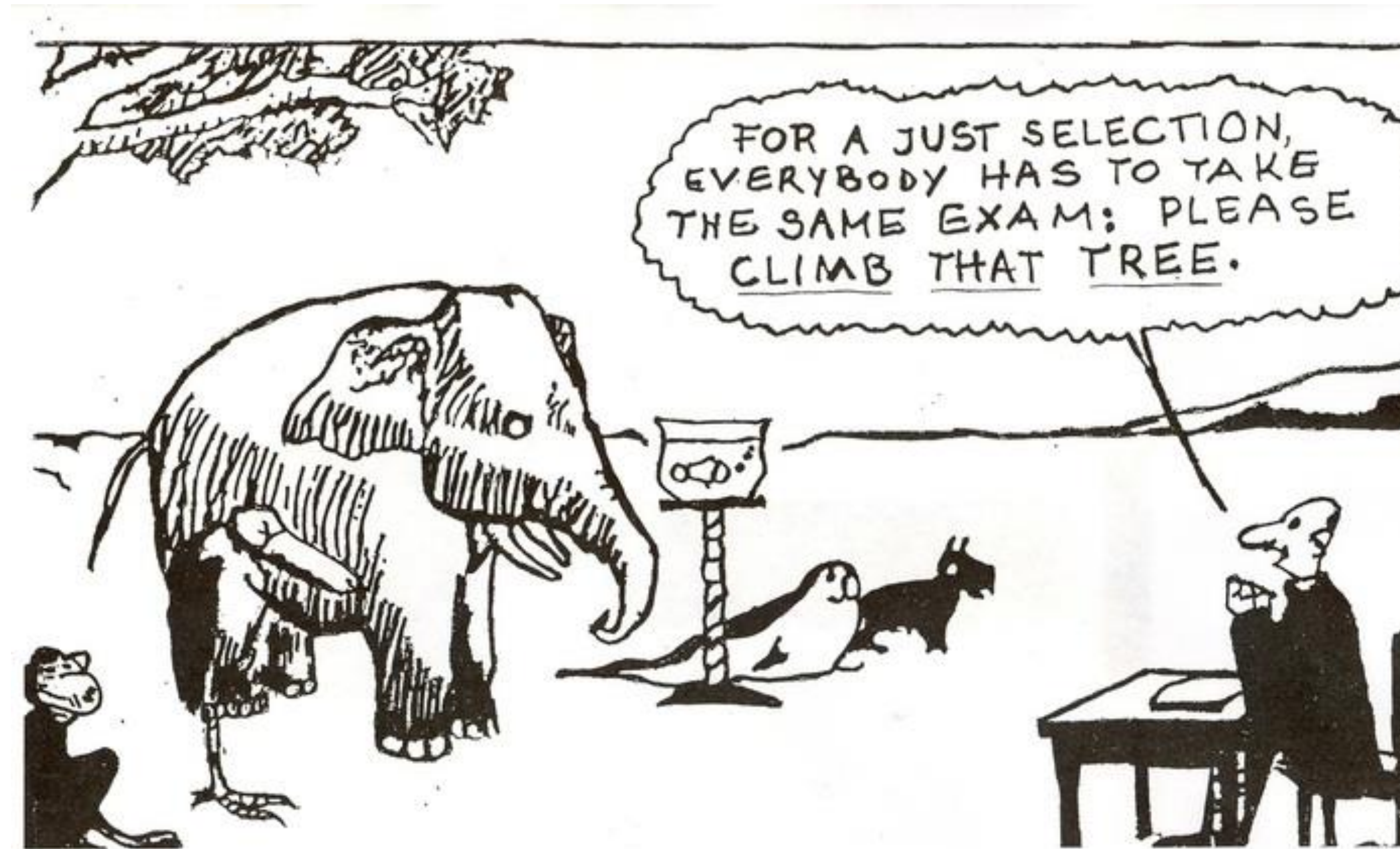
adjective

1. having a form that presents very little resistance to a flow of air or water.
"streamlined passenger trains"
2. having been made simpler and more efficient or effective.
"this streamlined approach will significantly reduce the learning curve for new users"

Streamlined trials only do
what is necessary to

To keep the individual participants safe
Produce a reliable answer

Streamlined trials must be tailored to the research question: one size does not fit all



Three examples of streamlined trials



Lipid modification
Cardiovascular disease
International clinic-based study



Aspirin, and separately, omega-3
Diabetes
UK mail-based study

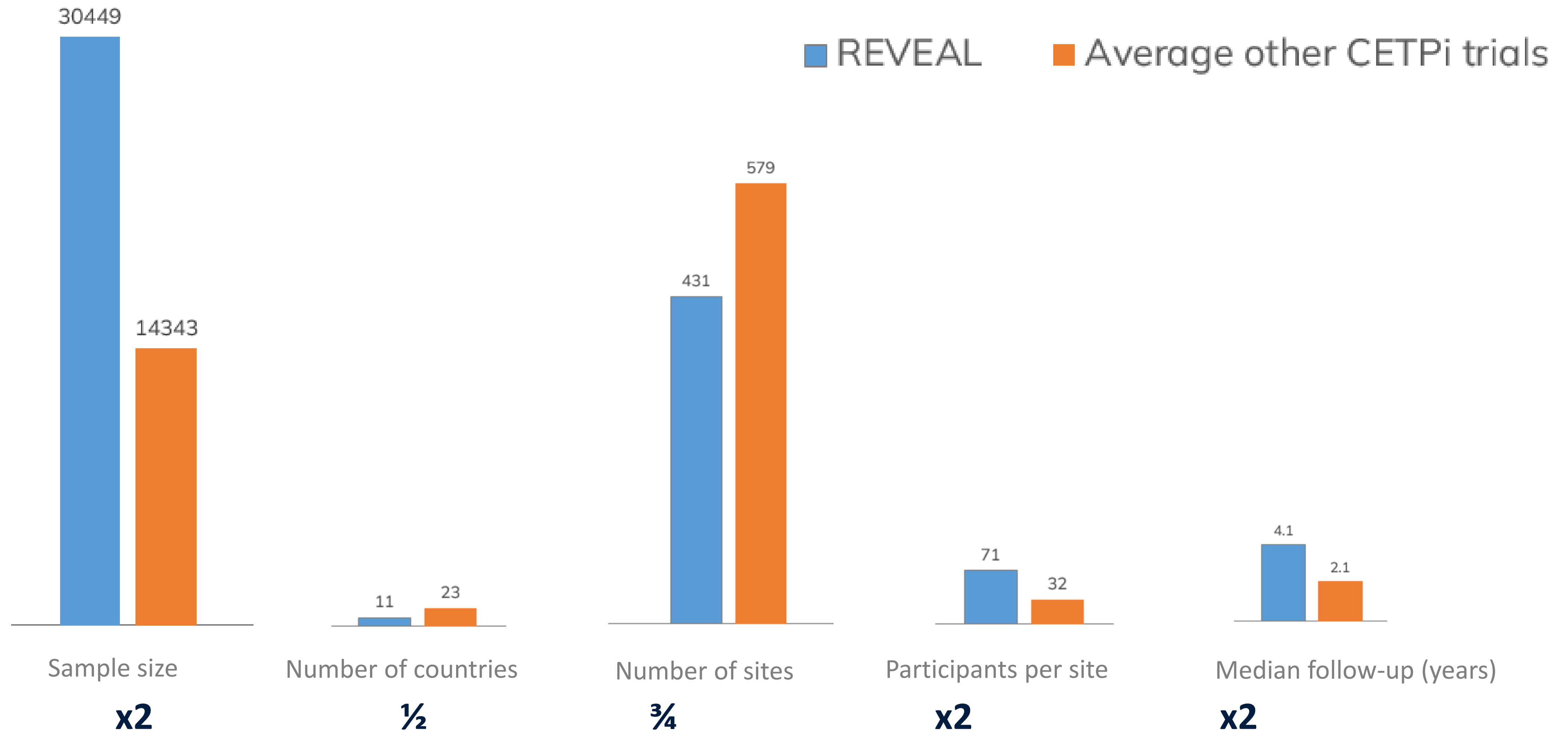


Platform trial
COVID-19
Emergency setting

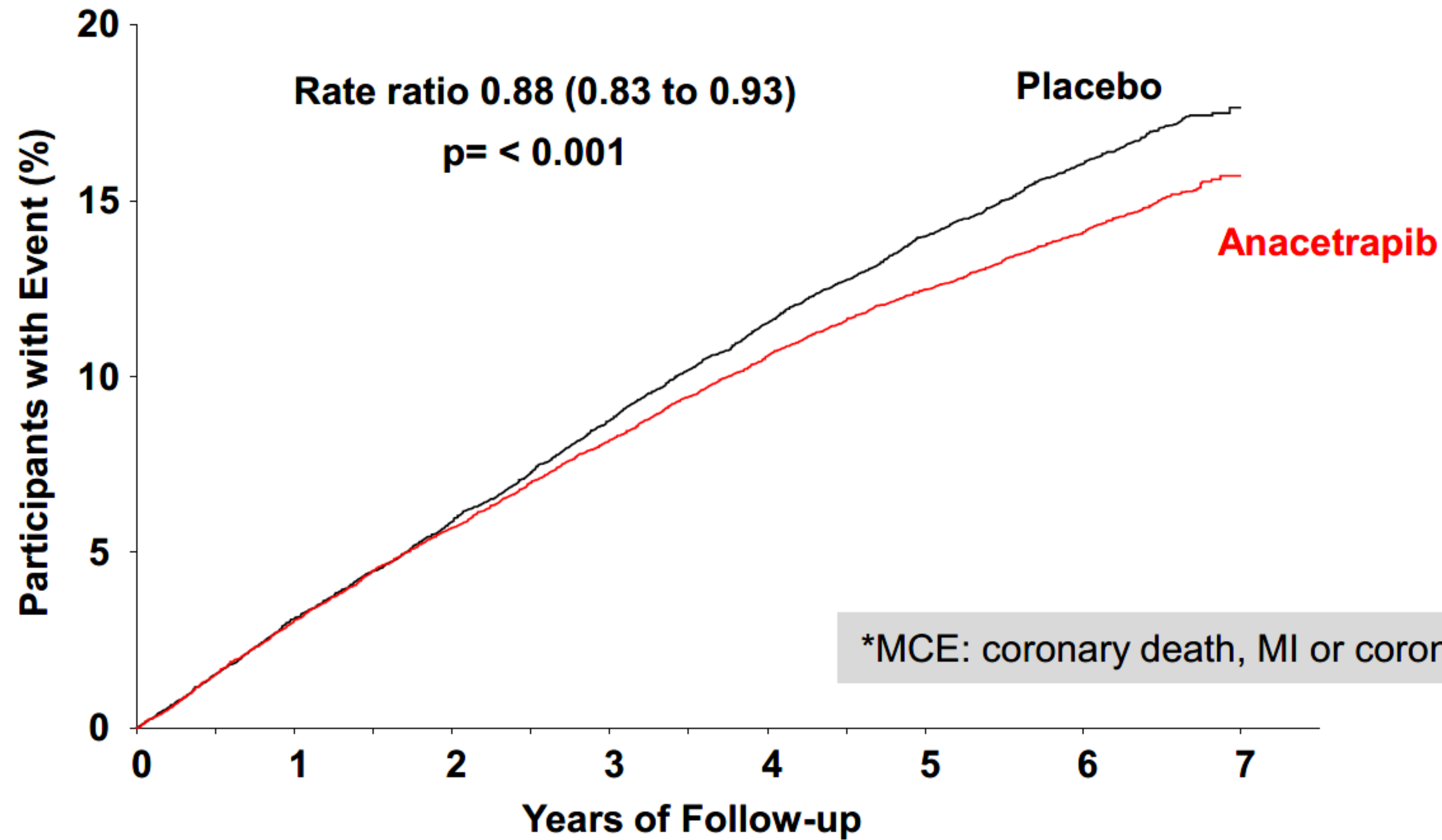
REVEAL

- 30449 participants with cardiovascular disease
 - 3443 primary outcomes (coronary death, myocardial infarction, or coronary revascularization)
 - Median 4.1 years FU during scheduled treatment period
 - 99.9% completeness of follow-up
-
- Simple eligibility criteria
 - Minimal follow-up procedures
 - Unified bespoke IT system
 - Real time data capture of participant responses
 - Single clinician adjudication blind to study treatment

REVEAL and other CETPi trials compared



REVEAL Primary Endpoint: Major Coronary Event*



Example: ASCEND trial

Eligibility: Age ≥ 40 years; any DIABETES

No prior cardiovascular disease

Participants: 15,480 UK patients

Randomisation: Aspirin 100 mg daily vs placebo

(and Omega-3 fatty acids 1 g capsule/day vs placebo)

Primary outcome: Serious vascular event (cardiovascular death*, non-fatal MI, non-fatal stroke*, TIA)

Follow-up: Mean 7.4 years

>99% complete for morbidity & mortality

* (excluding intracranial haemorrhage)

No study clinics required





Participant questionnaire

ASCEND: Follow-up Questionnaire

INSTRUCTIONS FOR COMPLETION:
Please complete the questionnaire in BLOCK CAPITALS using blue or black ink.
Please place a cross in the appropriate box, e.g. Yes ☒ No ☐
(If you make a mistake, fill the entire box and mark the correct box, e.g. Yes ☐ No ☒)
OR write clearly in the appropriate boxes, e.g. 26/01/2013

1. Contact and GP Details

Please check that these contact details are still correct. If not, then please call Freefone 0800 585323 and provide the correct information. Please quote the reference number from the covering letter on the front of this questionnaire.

Your details:
Mr Vincent Ash
5 Poplar Close
OAKWOOD
Borsetshire
BY7 9PP
Tel: 01234 654321 (day); 01234 444888 (home)

GP details:
Dr Gerald P Welby
Happy Family Health Centre
1 The Avenue
OAKWOOD
Borsetshire
BY7 1AZ

2.1. Please indicate how regularly you take your white (aspirin/placebo) tablets:
Every day ☐
Most days ☐
Only occasionally ☐
Never ☐
2.2 Are you willing to continue taking the white (aspirin/placebo) ASCEND tablets?
Yes ☐ No ☐
If No, please tell us why:
2.3 Are you willing to continue taking the brown (one or other natural oil) ASCEND capsules?
Yes ☐ No ☐
If No, please tell us why:
3. Other Current Medication
3.1 Do you currently take any of the following regularly (i.e. more than one day per week)?
Warfarin (Marevan), Acenocoumarol (Nicoumalone, Sinthrome), Phenindione, Dabigatran (Pradaxa) or Rivaroxaban (Xarelto) Yes ☐ No ☐
a) Aspirin, prescribed or over-the-counter (e.g. Anadin, Caprin, Disprin, Imazin, PostMI). Do not include your ASCEND study tablets. Yes ☐ No ☐
c) Clopidogrel (Plavix) Yes ☐ No ☐
d) Dipyridamole (Persantin, Persantin Retard or Asasantin Retard) Yes ☐ No ☐
ASCEND Follow-up Questionnaire (V2.6_310513) 2

Need help completing this form? Please call Freefone 0800 585323

4.1 Since completing your last questionnaire (If Yes, please give the date and extra space overleaf to list second occurrences of any of the medical events listed in Section 4.)
a) Heart attack
Name and town of hospital attended:
b) Admission to hospital with angina or any chest pains
Name and town of hospital attended:
c) Stroke
Name and town of hospital attended:
f) Coronary angioplasty ("balloon", "stent" insertion or PTCA)
Name and town of hospital attended:
g) Other arterial surgery or angioplasty (e.g. leg bypass)
Name and town of hospital attended:
h) Cancer (e.g. skin, breast, lung, bowel etc)
Type of cancer:
Name and town of hospital attended:
i) Bleeding for which you saw a doctor (e.g. serious nose bleed, bleeding in the eye) Do not include bleeding as a result of an accident.
Site in body of bleeding:
Were you admitted to hospital? Yes ☐ No ☐
Name and town of hospital attended:
3

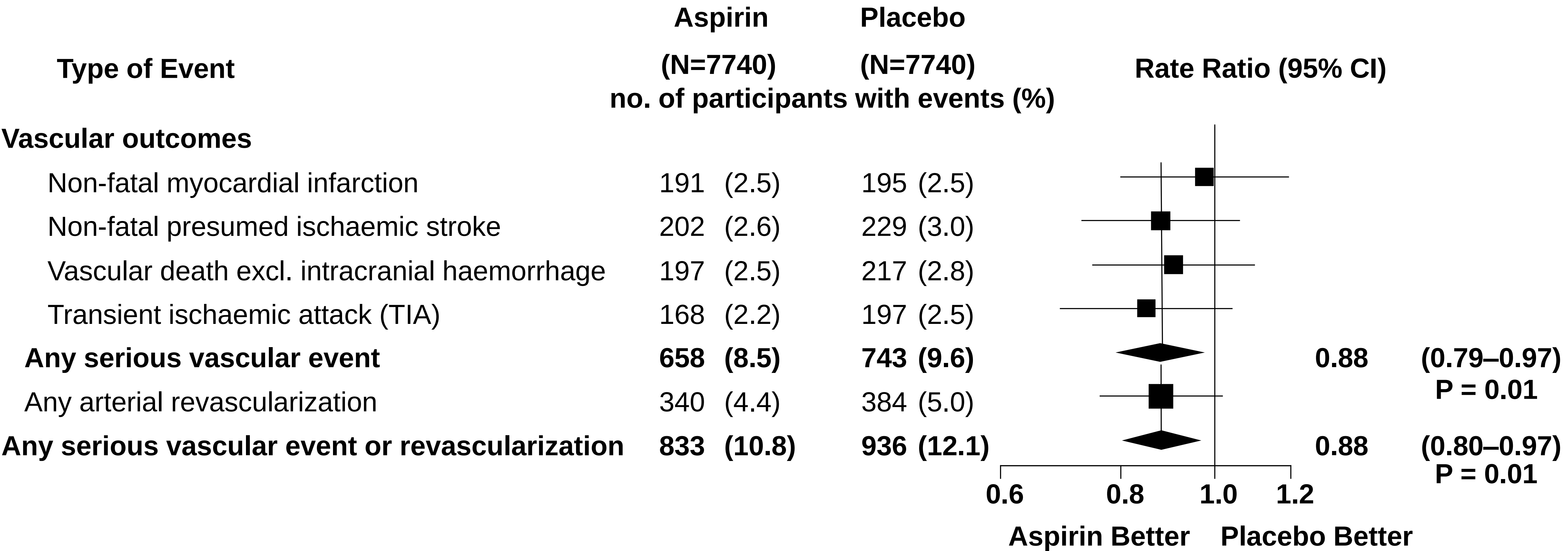
Need help completing this form? Please call Freefone 0800 585323

5. Other Serious Illnesses or Hospital Admissions
5.1 Since completing your last questionnaire on 10/03/2007 have you had ANY other serious illness or admission to hospital (e.g. pneumonia, day surgery, laser treatment to the eye)? Please give details of the illness or surgery, the date, and the name and town of the hospital you attended. (Please note you can also record second occurrences of any of the medical events listed in Section 4.)
Details of illness or admission: GALL BLADDER REMOVED
Name and town of hospital attended: VERY SUCCESSFUL NO PROBLEMS
Date: 04/06/2007
175016
Mrs. J. Smith

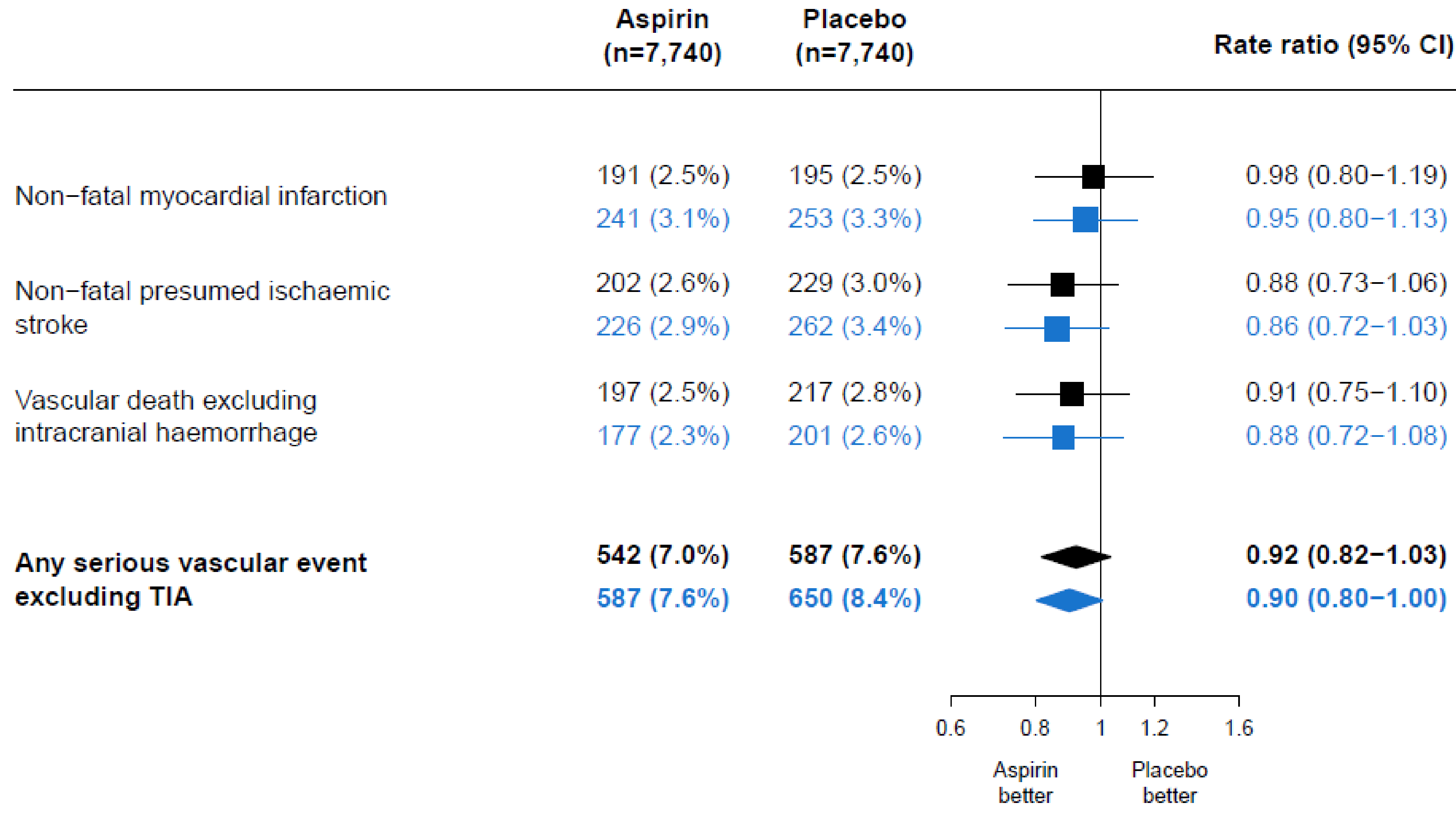
6. Personal Details
6.1 Please reconfirm your date of birth:
Thank you for completing the questionnaire.
Please SIGN and DATE the form below using blue or black ink.
Signature:
& PRINTED name:
Today's date:
Please check that you have answered every question, and signed and dated the form.
Return the completed questionnaire in the Freepost envelope provided (no stamps needed) to:
Freepost RLUJ-TKES-SURB, ASCEND, Richard Doll Building, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF
If you have any questions about the study, please contact the coordinating centre in Oxford on
FREEPHONE: 0800 585323 (preferably during office hours 9 am - 5 pm, Monday to Friday)
Thank you for your continued participation in ASCEND
4

Code	FUP?	Cat	Long Description
7810	N	6	cholecystectomy/gall bladder surgery/gall stone removal

ASCEND: Effect of aspirin on Serious Vascular Events plus revascularization



ASCEND: Effect of allocation to aspirin vs placebo on any serious vascular event using pre-adjudicated follow-up



Example: RECOVERY trial

Eligibility: Admitted to hospital with presumed or proven COVID-19 **Participants:**
>40,000 UK patients (plus international sites)

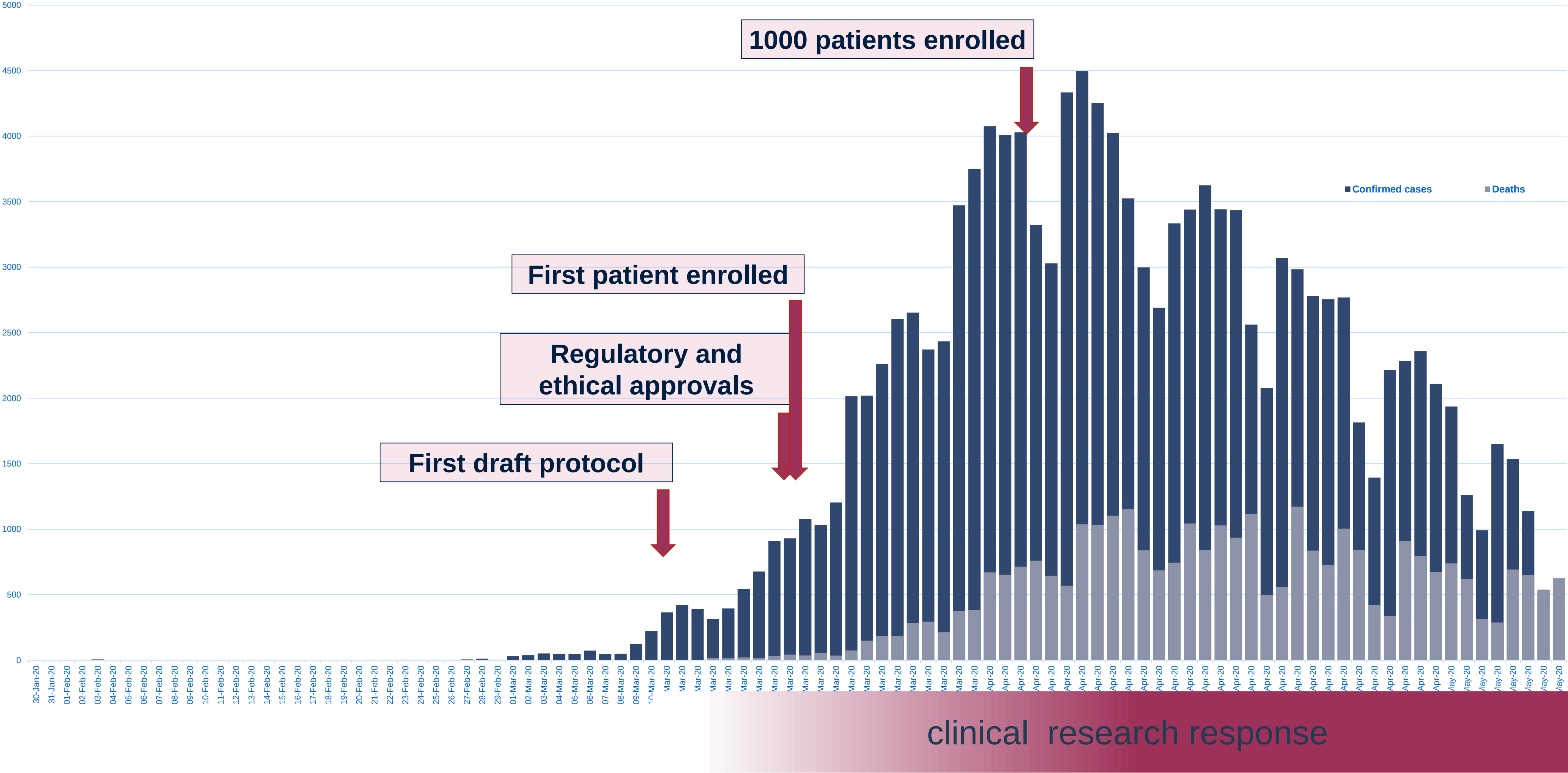
Randomisation: Platform multi-arm factorial trial

Primary outcome: Death at 28 days

Completed comparisons

Treatment	N	Conclusion
Hydroxychloroquine	4716	No effect
Dexamethasone	6425	Benefit in hypoxic patients
Lopinavir-ritonavir	5040	No effect
Azithromycin	7763	No effect
Convalescent plasma	11,558	No effect
Tocilizumab	4116	Benefit in hypoxic and inflamed patients
Colchicine	11,340	No effect
Aspirin	14,892	No effect
Casirivimab+imdevimab	9785	Benefit in seronegative patients
Baricitinib	8156	Benefit
High-dose steroid	1272	Harm
Empagliflozin	4271	No effect

Rapid set up



RECOVERY trial – Simple trial design

Simple eligibility: Hospitalised patients with proven or suspected COVID-19

Important outcome: mortality (use of ventilation, duration of hospitalisation)

Randomization: assigns patient between suitable and available treatments

Follow-up: 1 page case report form + extensive linkage to NHS datasets

Randomised evaluation of

RECOVERY

COVID-19 Therapy

OXFORD

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

OXFORD

Hospital:

Patient Name:

1. Information about the study has been provided to me: I confirm that I have read and understood the Participant Information Leaflet (V1.0 13-Mar-2020) I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. Voluntary participation: I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. Access to study data about me: I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorised individuals from this hospital, the University of Oxford, and regulatory authorities to check that the study is being carried out correctly.

4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided to the study coordinating centre both during and for up to 10 years after the scheduled follow-up period. I understand that information that identifies me will be passed securely to such bodies to make this possible and that I can opt out of this at any time by writing to the coordinating centre team.

5. Data stored on computer: I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

6. Agreement to take part: I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

PRINTED name of participant

Signature

Today's date

PRINTED name of person taking consent

Signature

Today's date

*1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes

Logged in as: Bart's Health NHS Trust

Section A: Baseline and Eligibility

Date and time of randomisation: 8 Apr 2020 17:51

Treating clinician

A1. Name of treating clinician

Patient details

A2. Patient surname

Patient forename

A3. NHS number

A4. What is the patient's sex?

Female

A4.1. Is the patient known to be pregnant?

A5. What is the patient's date of birth?

1/1/19

Inclusion criteria

A6. Has consent been taken in line with the protocol?

If answer is No patient cannot be enrolled in the study

A7. Does the patient have proven or suspected SARS-CoV-2 infection?

If answer is No patient cannot be enrolled in the study

A8. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial?

A9. COVID-19 symptom onset date

A10. Date of hospitalisation

A11. Does the patient require oxygen?

A12. Does the patient CURRENTLY require ventilation or ECMO?

Indicate mechanical ventilation or extra corporeal membrane oxygenation

Does the patient have any CURRENT comorbidities or other medical problems?

A13.1 Diabetes

A13.2 Heart disease

A13.3 Chronic lung disease

A13.4 Tuberculosis

A13.5 HIV

A13.6 Severe liver disease

A13.7 Severe kidney impairment (eGFR <30 or an dialysis)

A13.8 Known long QT syndrome

A13.9 Current treatment with macrolide antibiotics which are to continue

Macrolide antibiotics include clarithromycin, azithromycin and erythromycin

Are the following treatments UNSUITABLE for the patient?

A14.1 Lopinavir-Ritonavir

A14.2 Dexamethasone

A14.3 Hydroxychloroquine

A14.4 Azithromycin

Are the following treatments available?

A15.1 Lopinavir-Ritonavir

A15.2 Dexamethasone

A15.3 Hydroxychloroquine

A15.4 Azithromycin

Please sign off this form once complete

Surname

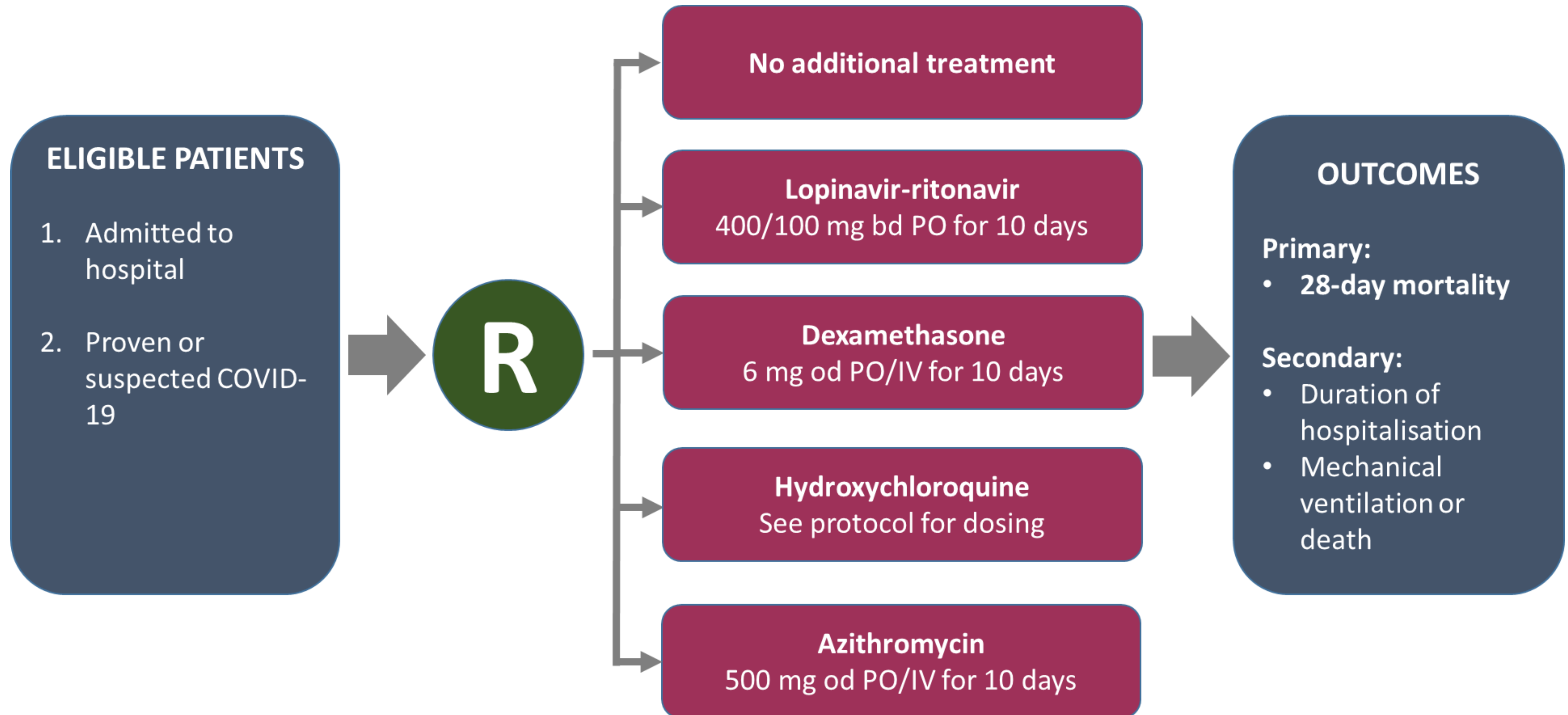
Forename

Professional email

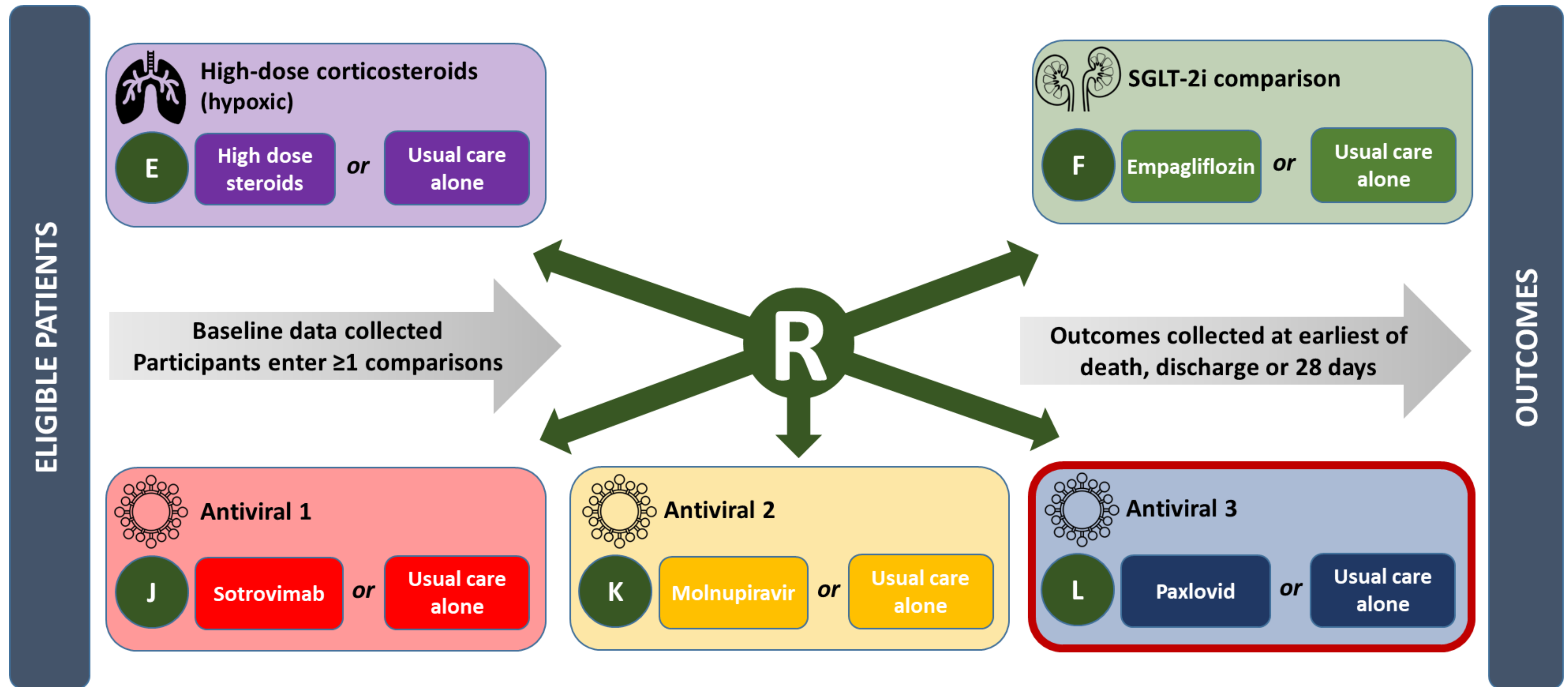
Continue

Cancel

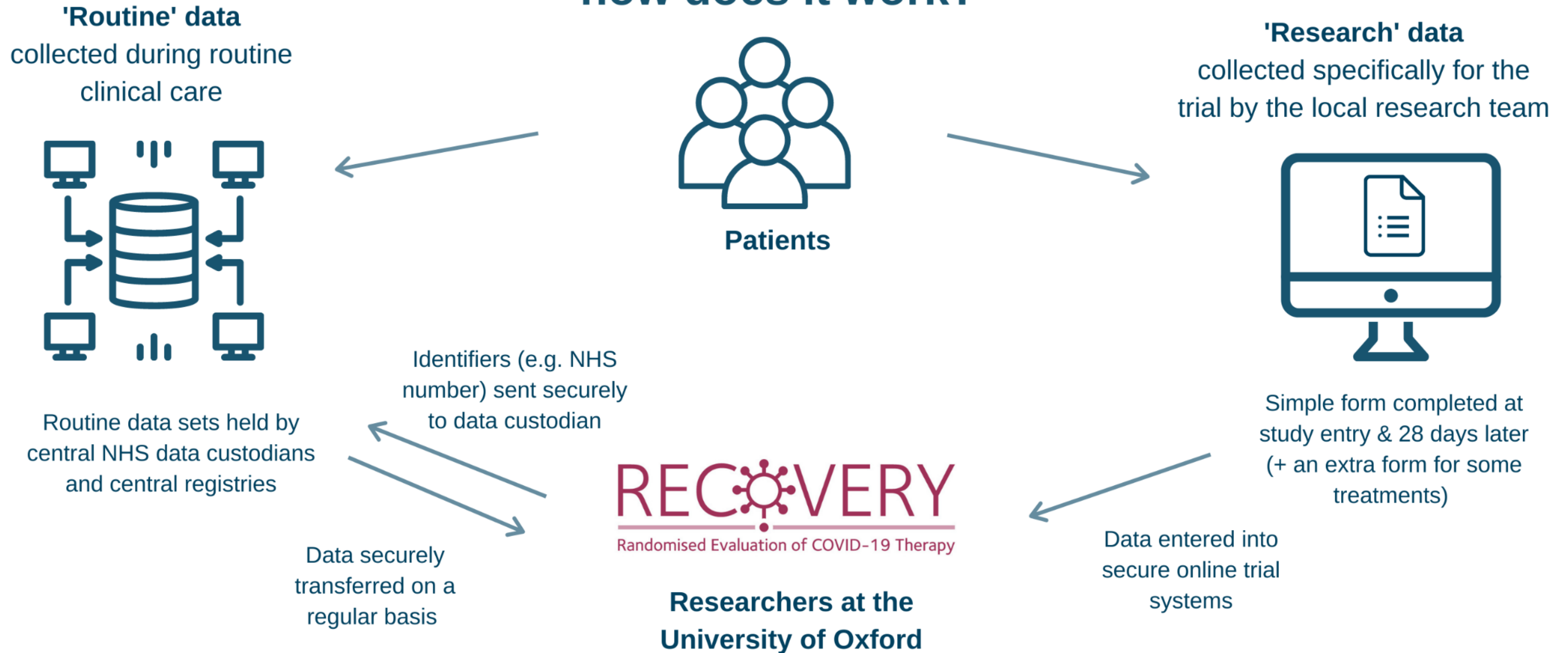
RECOVERY trial design April 2020



RECOVERY trial design April 2022



Patient data & the RECOVERY trial: how does it work?



Summary

Reliable assessment of the effects of treatments on outcomes that matter requires **large randomised trials**

To achieve sufficient scale trials must be **streamlined** focusing on only on what is essential to keep the participants safe and answer the question

There is **no one-size-fits all** methodology

Careful streamlined design can produce large-scale randomised evidence which **changes practice**