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PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Berry Consultants
Statistical Innovation

The PRINCIPLE Adaptive Platform Trial for Community Treatment of COVID-19: Innovation in Trial Design and Delivery

Ben Saville, Ph.D.
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Chris Butler, M.D.
Professor of Primary Care, University of Oxford

And PRINCIPLE Trial Team

Adaptive Platform Trials

- Master Protocol
- Focus is on the Disease
  - What is the best treatment for a unique patient with this disease?
- Typical Innovations
  - Multiple Interventions, staggered entry
  - Adaptations to accruing data
  - Frequent interim analyses (don't wait for the end of trial!)
  - Response Adaptive Randomization (RAR)
  - Graduation/Removal, "Perpetual" trials
- Applications: Oncology, infectious disease, neurological diseases, COVID-19,…

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD. Address reprint requests to Dr. LaVange at the Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Blvd., Silver Spring, MD 20993, or at lisa.lavange@fda.hhs.gov.

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype. Included under this broad definition of a master protocol are three distinct entities: umbrella, basket, and platform trials (Table 1 and Figs. 1 and 2). All constitute a

Potential Features of a Platform Trial

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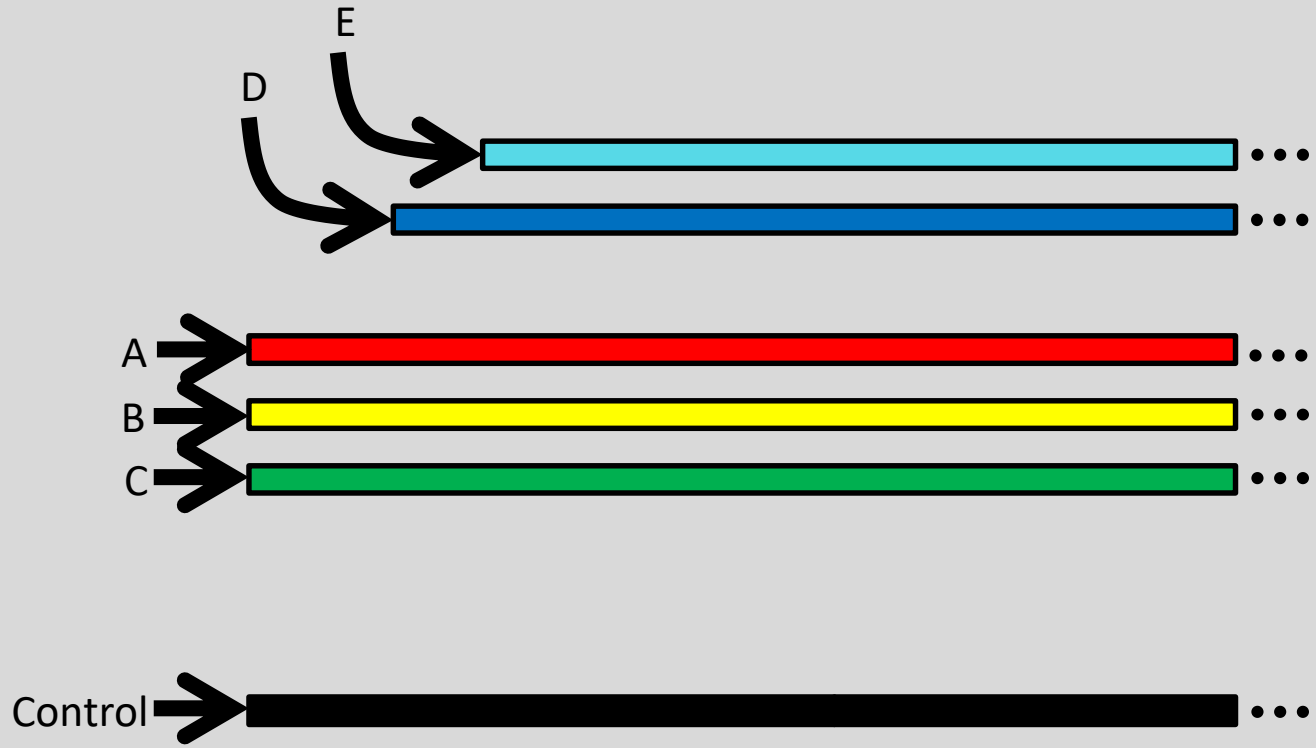
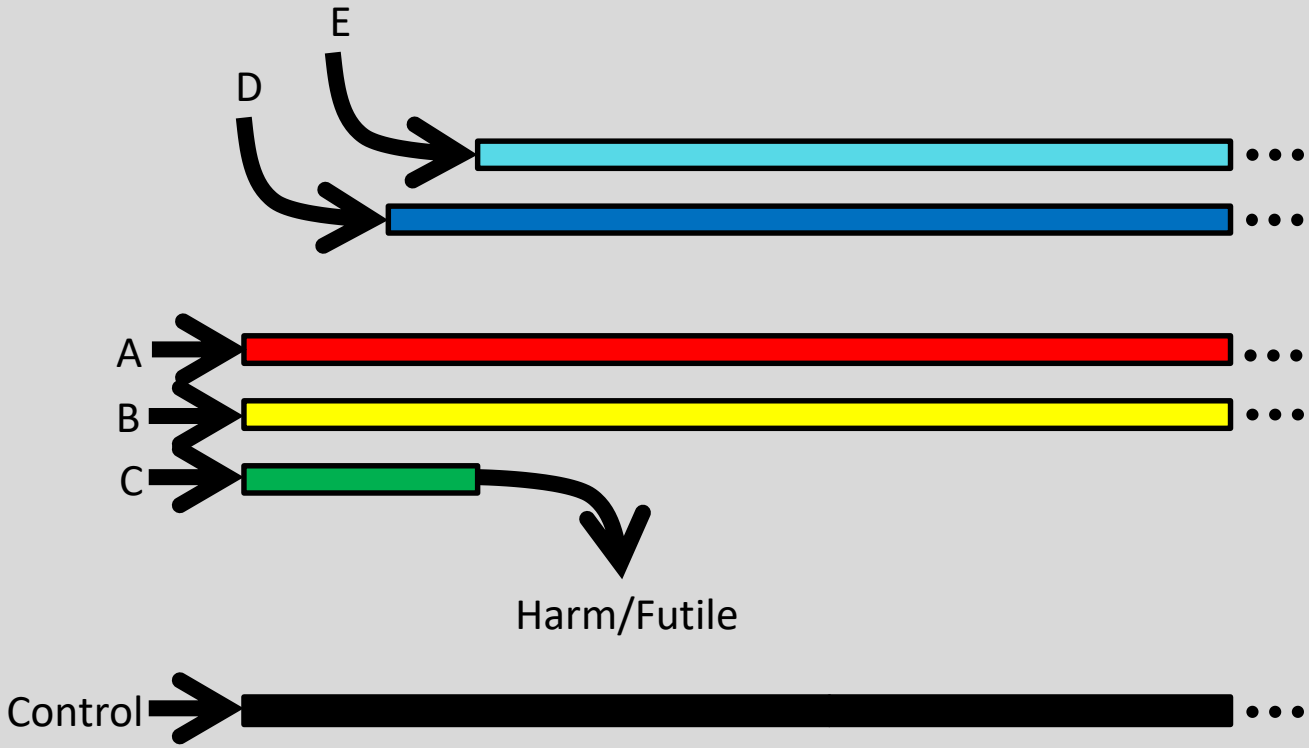
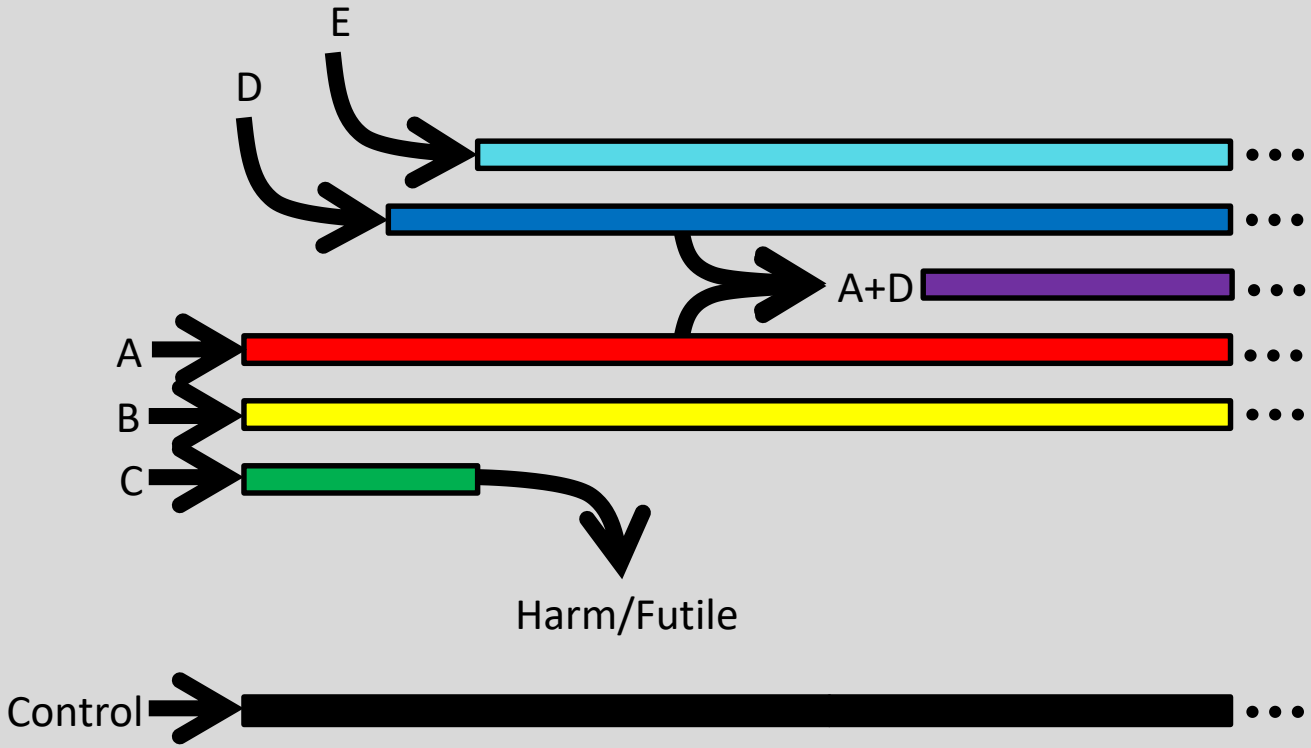
Potential Features of a Platform Trial



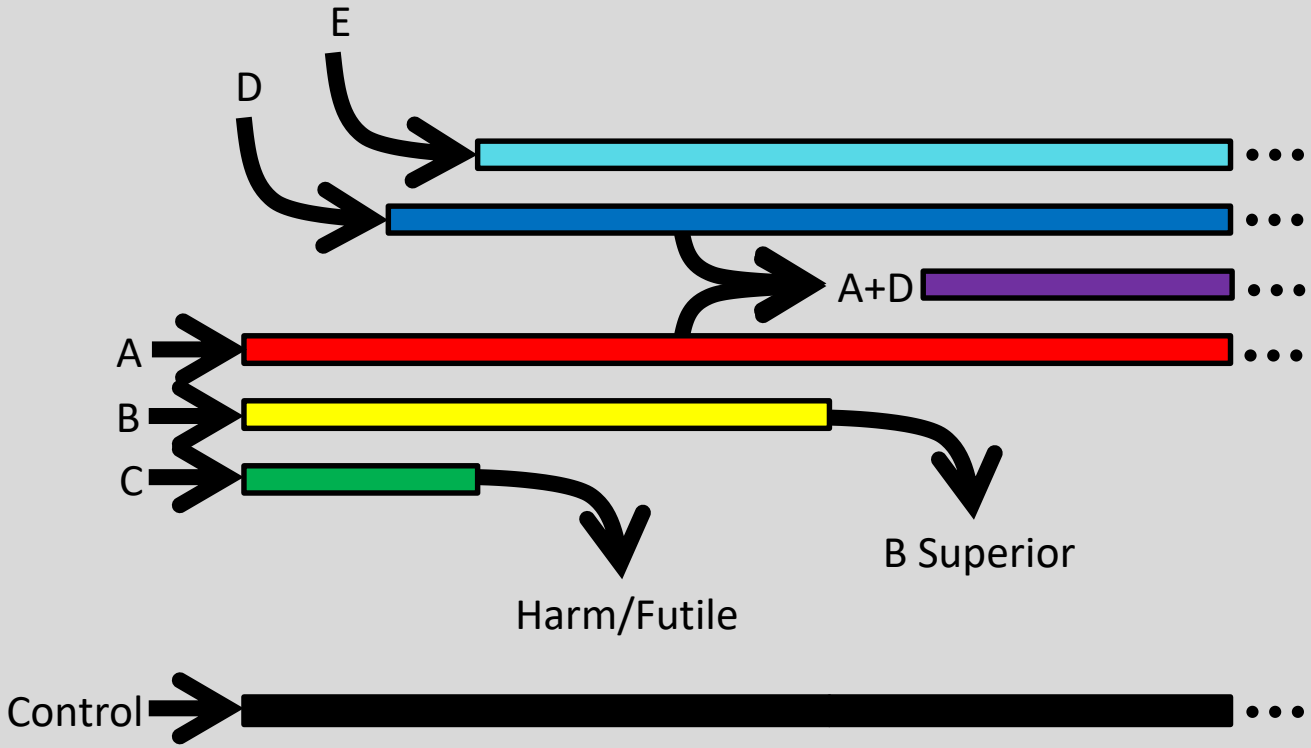
Potential Features of a Platform Trial



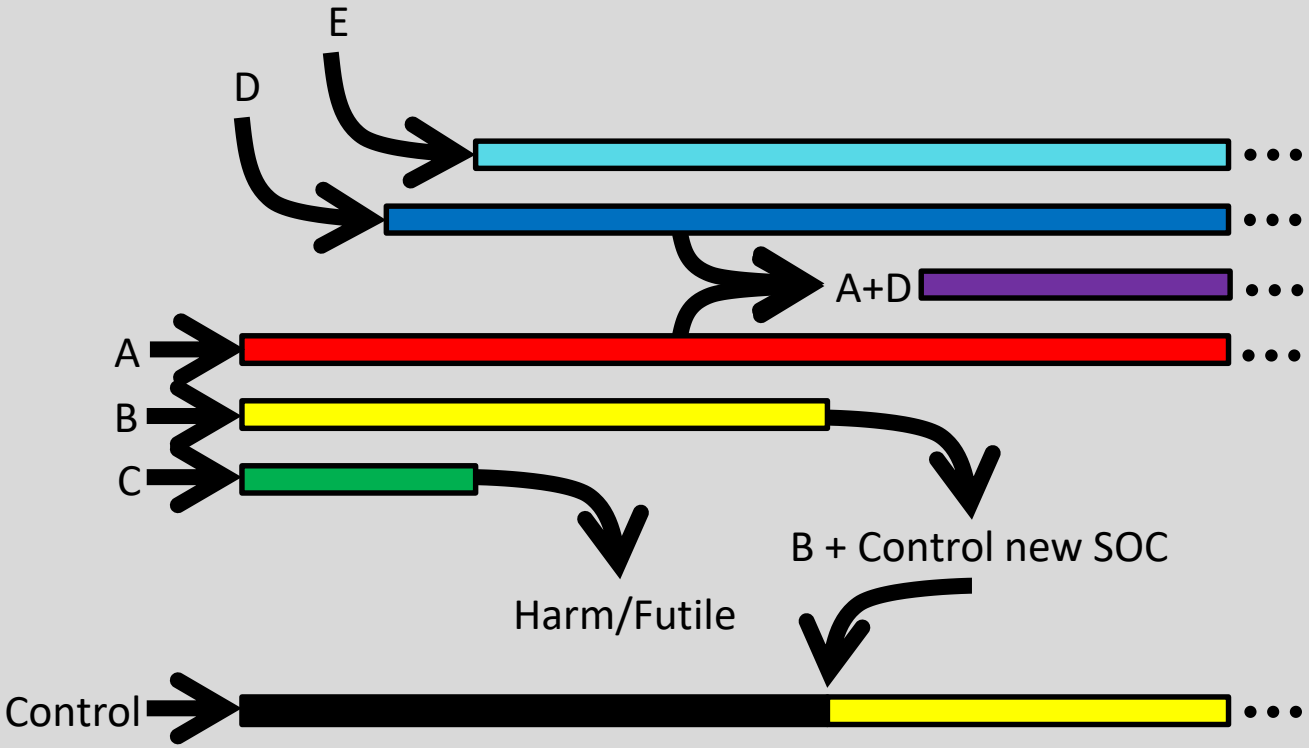
Potential Features of a Platform Trial



Potential Features of a Platform Trial



Potential Features of a Platform Trial



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Adaptive Platform Trials in COVID-19

- *PRINCIPLE: Mild non-hospitalized but higher risk populations in UK primary care*
- REMAP-CAP: Hospitalized ICU patients across 8 countries
- RECOVERY: UK-based trial in hospitalized patients not in ICU
- ACTT(NIAID), SOLIDARITY(WHO), ISPY COVID(UCSF), ACTIV(NIH)

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PRINCIPLE: COVID-19 in Primary Care

- Most people with COVID-19 are managed in the community
  - Community treatments may have the widest reach and impact
- PRINCIPLE objective: Evaluate whether re-purposed drugs can make a difference with early intervention
- Needed a rapidly initiated trial with adaptive features
  - Ability to evaluate treatments quickly (early superiority/futility)
  - Flexibility to add treatments
- Urgency: First patient randomized < 3 weeks from initial contact with Oxford collaborators!

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PRINCIPLE: COVID-19 in Primary Care

Participants:

- Aged ≥65 years OR ≥50-64 years with comorbidities, *or ≥18 with shortness of breath or comorbidity*
- Presenting **in primary care** within 14 days since onset of cough and/or fever during time of prevalent COVID-19 infections

Interventions:

- Multiple interventions, beginning with Hydroxychloroquine

Pragmatic open-label comparison:

- Usual care without study drug

Primary Endpoint

- Two co-primary endpoints
  1. Time to self-reported recovery within 28 days
  2. Hospitalization/Death (binary)
- Gate-keeping approach for primary analysis
- Compare interventions to Usual Care in open label, pragmatic trial
- Primary Analysis Population
  - SARS-CoV-2 positive swab
  - Trial enrolls participants with COVID symptoms, regardless of swab
  - Secondary analysis on overall population

Primary Analysis

1. Time to self-reported recovery
   - Bayesian piecewise exponential model
2. Hospitalization/Death (binary)
   - Logistic regression model

- Features of both models
  - Adjust for covariates: age, comorbidities, COVID swab result, vaccination status
  - Adjust for time trends (changing population/disease)

Primary Analysis: Time to Recovery

Model time to recovery T_{ij} as piecewise exponential with hazard λ_{ijs} for subject i in arm j at time interval s:

$$\lambda_{ijs} = \exp(\gamma_s + \theta_j + \boldsymbol{x}_i'\boldsymbol{\beta} + \eta_{t(i)})$$

- γ_s is intercept, θ_j is treatment effect, $\boldsymbol{x}_i$ are covariates for subject i
- $\eta_{i(t)}$ is a function of time of randomization from start of study
  - 2nd order normal dynamic linear model (NDLM)
  - Bayesian hierarchical smoothing over 2-week intervals
- Statistical model allows comparison of treatment arms to non-concurrently randomized controls
  - Gap bridged by overlap between multiple treatment arms

Adaptive Platform Design

- Expected accrual: 30-250 participants/week
- Weekly, bi-weekly, or monthly interims depending on speed of enrollment
- Interim analysis for superiority of intervention
  - Superiority time to recovery: Bayesian posterior probability of superiority ≥ 0.99
  - Superiority hospitalization/death: Bayesian posterior probability of superiority ≥ 0.975
- Interim analysis for futility
  - Drop intervention if Pr(Meaningful benefit) < 0.01

Participant Allocation

- Response adaptive randomization
  - Allocates more subjects to interventions with better outcomes
  - Fixed allocation to Usual Care (open label)
- If intervention X is superior to Usual Care on one or both co-primary endpoints, results announced
  – X is removed from trial and can be adopted into Usual Care
  – Future interventions compared to Usual Care (which may be evolving)

Virtual Trial Simulation

- Key to adaptive design is to pre-specify adaptations
- Simulations used as a tool for trial design
  1. Explore/calibrate adaptive algorithm on single example trials
  2. Evaluate/calibrate performance under a wide range of plausible scenarios
- Simulations completed and decision rules finalized prior to the first interim analysis

Virtual Trial Simulation

Simulated (Example) Interim data

Recovery Data

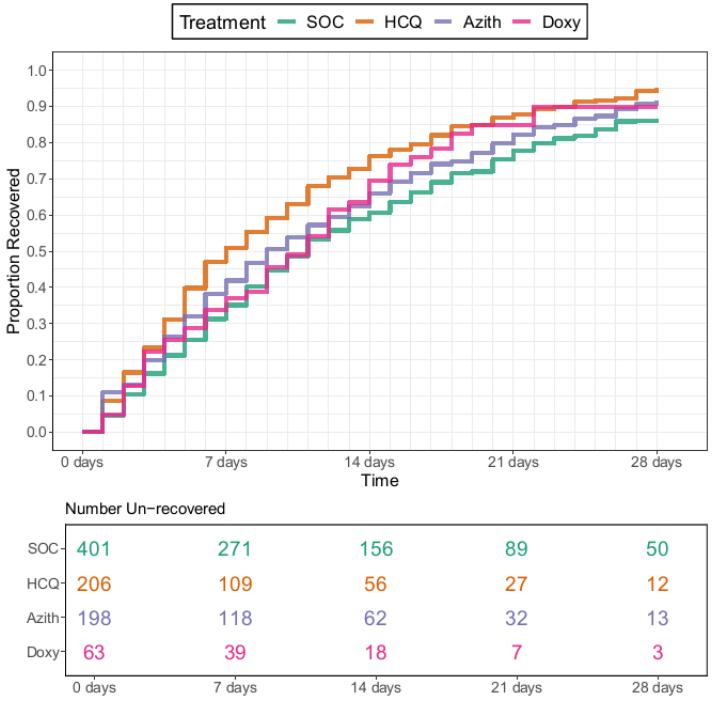
	Enrolled	Complete	Recovered	Exposure Days	Recoveries Per Day	Estimated Hazard	Estimated HR (95% interval)	Estimated Median Time to Recovery
SOC	401	383	334	4861	0.069	0.07	1	10.44
HCQ	206	206	196	1933	0.101	0.098	1.392 (1.182, 1.637)	7.63
Azith	198	177	165	2032	0.081	0.079	1.129 (0.949, 1.34)	9.28
Doxy	63	53	50	619	0.081	0.078	1.105 (0.836, 1.416)	9.48
Total	868	819	745	9445	0.079			

Hospitalization Data

Hospitalizations	28 Day Completers	Observed Hosp. Rate	Est. Hosp. Rate (95% interval)
17	356	0.0478	0.0443 (0.0268, 0.0679)
5	206	0.0243	0.0289 (0.0105, 0.0567)
2	142	0.0141	0.0151 (0.0032, 0.0362)
2	27	0.0741	0.0467 (0.0099, 0.1121)
26	731	0.0356	

Intervention Status
Enrolling
SuccessOnTTRFutilityOnHosp *Announced*
Enrolling
Enrolling

Observed Patient Recoveries



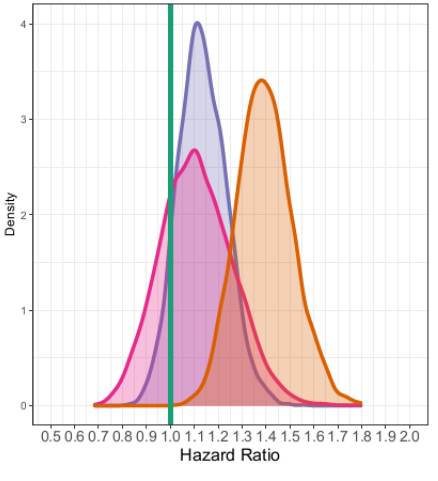
Recovery Inferences

	Pr(Superiority)	Pr(Meaningful Effect)	Pr(Best)	Randomization Probability
SOC				0.33
HCQ	1	0.9263	0	0
Azith	0.9153	0.2117	0.566	0.36
Doxy	0.7623	0.2397	0.434	0.3

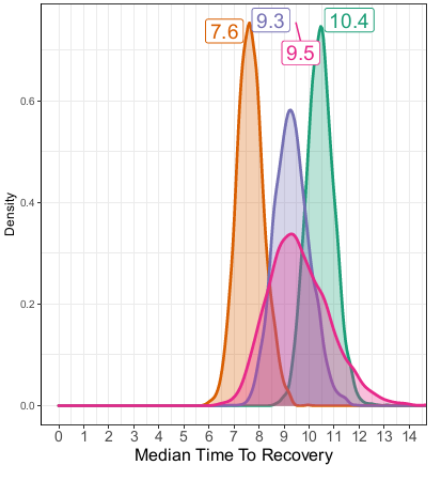
Hospitalization Inferences

Pr(Superiority)	Pr(Meaningful Effect)
0.8423	0.398
0.98	0.763
0.5267	0.2047

Hazard Ratio Estimates



Median Time To Recovery Estimates



Trial Implementation

- The implementation of platform trials requires several teams
  - *Statistical Analysis Committee (SAC)*: small unblinded group that performs the interim analyses
  - Results provided to a Data Monitoring Committee
  - Strict firewalls between unblinded & blinded individuals
- Emphasis on timely data collection & cleaning (Oxford data team)
- The primary analysis model incorporates data from all available treatment arms
  - Topline model results are provided to Trial Management Group
  - Caution needed to preserve integrity of ongoing interventions

Inverse care law

The Lancet · Saturday 27 February 1971

THE INVERSE CARE LAW

JULIAN TUDOR HART
Glyncorrwg Health Centre, Port Talbot, Glamorgan, Wales

Summary The availability of good medical care tends to vary inversely with the need for it in the population served. This inverse care law operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced. The market distribution of medical care is a primitive and historically outdated social form, and any return to it would further exaggerate the maldistribution of medical resources.

interpreted either as evidence of high morbidity among high users, or of disproportionate benefit drawn by them from the National Health Service. By piling up the valid evidence that poor people in Britain have higher consultation and referral rates at all levels of the N.H.S., and by
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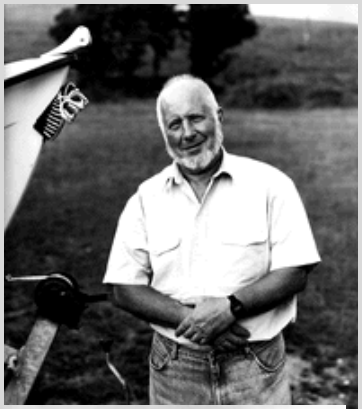


Inverse research participation law

Access to research is often inversely proportional to a participants' potential contribution and to where the research findings should be most applicable

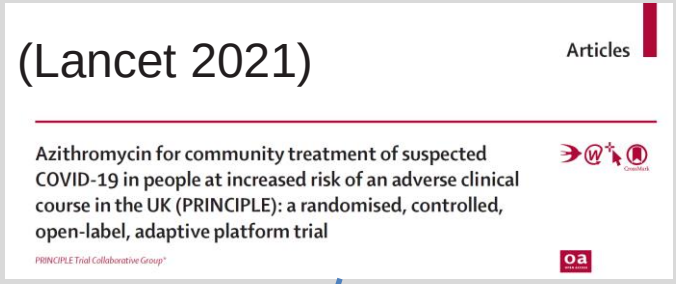
Innovation in Subject Recruitment

"Patient comes to the research"	"Research taken to the patient"
GP practices set up as sites: requires contract, GCP training	UK wide access through website: clinicians, NHS 111, care homes, patients themselves
Paper, face-to-face consent	Online consent
Study clinician confirms eligibility	Central eligibility check using summary care record or information form patient and GP
Medicine stored at every study site and issued to patient by study clinicians	Medicine and study materials couriered to patients home
Study clinician does sampling	Self swabbing
	Follow up by study team, online, telephone, trial partner, routinely collected data extract

The first truly 'democratic', nationally- inclusive, trial of an acute condition in the UK

Why no placebo?

- The study aimed to determine if there is an advantage to adding intervention into NHS care, rather than whether intervention is better than a placebo intervention
- As placebo intervention is not part of NHS care, adding it in would not have allowed us to answer the study question
- Pragmatic studies should ensure the comparator group is as close to usual care as possible
- We acknowledge that this trial design does not allow us to understand the mechanisms behind any observed effect, but is the best design to find out what would happen if the treatment was used in the real world.



Favipiravir

8 Apr 2021

Colchicine

4 Mar 2021

In. Budesonide

27 Nov 2020

30 March 2021

Doxy

24 Jul 2020

14 Dec 2020

Az

22 May 2020

30 Nov 2020

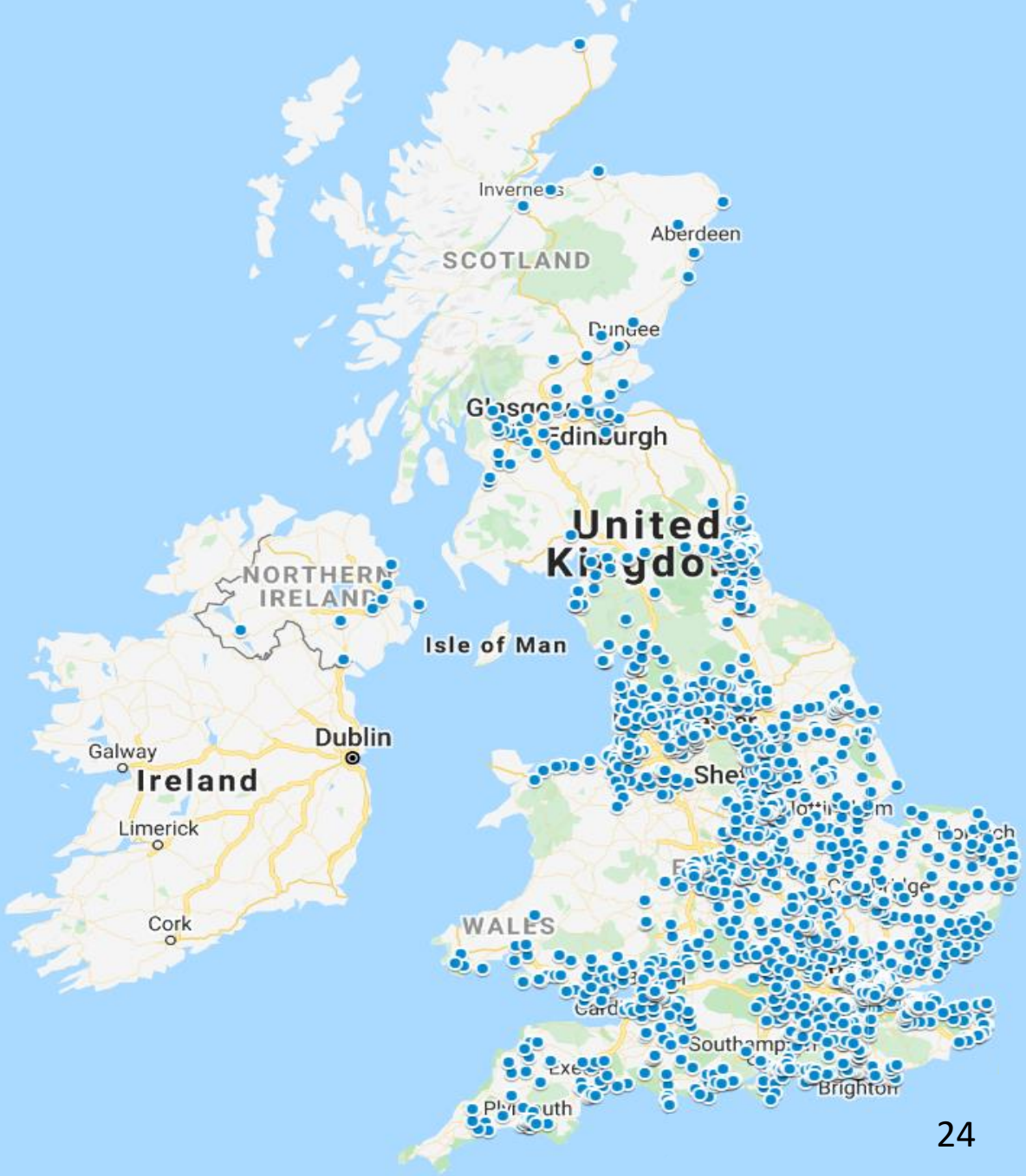
HCQ

2 Apr 2020

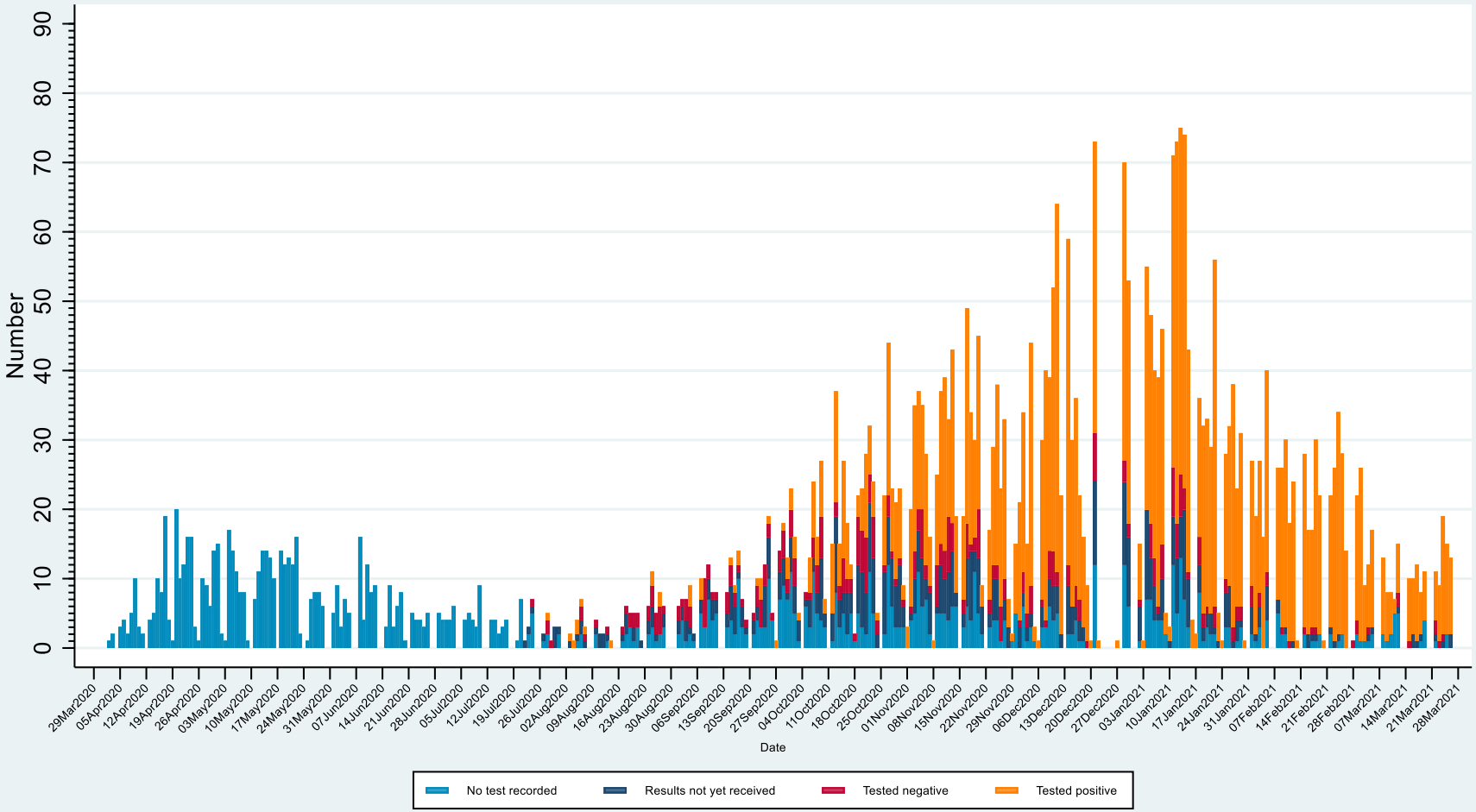
22 May 2020

Apr 2020 | Jun | Aug | Oct | Dec | Feb 2021 | Apr

Map of general practices that have recruited at least one participant to PRINCIPLE



Daily Randomisation Rate



Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2021/003 28 January 2021

Antimicrobials (azithromycin and doxycycline) Not Beneficial in the Management of COVID-19 (SARS-CoV-2) Positive Patients

Recommendation

It is recommended that:

Azithromycin should NOT be used in the management of confirmed or suspected COVID-19 infection either within primary care or in hospitalised patients, unless there are additional indications for which its use remains appropriate (see Product Details).

Doxycycline should NOT be used in the management of confirmed or suspected COVID-19 infection within primary care, unless there are additional indications for which its use remains appropriate (see Product Details).

Budesonide Results

Background:

- Budesonide arm stopped on 31 March 2021: evidence to be certain that budesonide improves time to recovery
- Results presented here and in preprint are using most recent data from 25th March 2021
- These results are not yet complete and not peer reviewed; final results May 2021

Numbers of participants in the interim analysis

- By 25th March 2021, PRINCIPLE trial had enrolled 4663 participants with suspected COVID-19.
- Of these, 2617 (56.1%) tested SARS-CoV-2 positive and contributed data to this interim budesonide primary analysis; 751 budesonide, 1028 usual care and 643 to other interventions

Budesonide Results

Primary SARS-CoV-2 Positive Population Analysis
Time To First Reported Recovery
Budesonide vs. Usual Care

Subgroup	Sample Size		Model Results	
	Inhaled Budesonide	Usual Care	Median Hazard Ratio (95% CI)	Prob(Superiority)
Overall	751	1028	1.208 (1.076, 1.356)	0.999

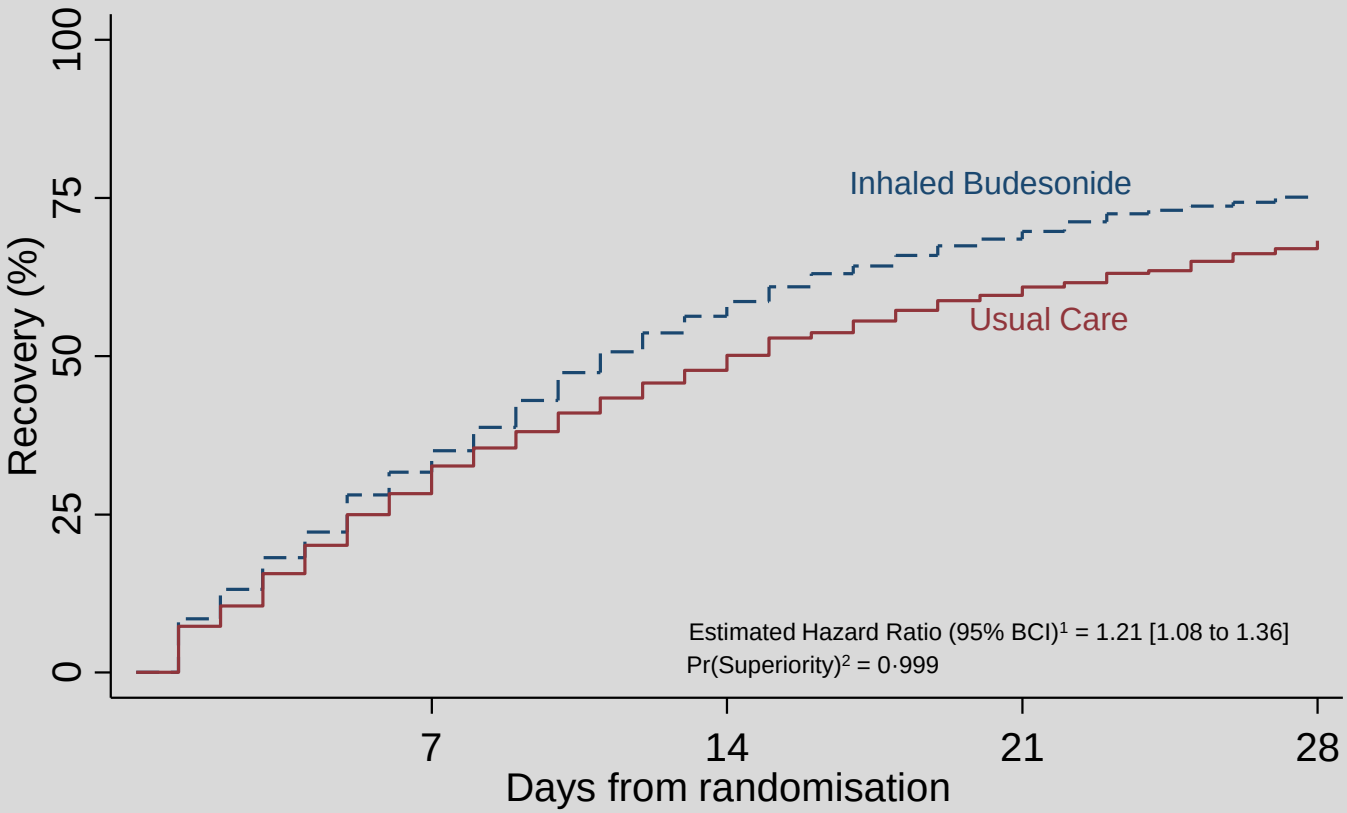
Subgroup	Median Estimated Benefit in Median Time To Recovery in Days* (95% CI)
Overall (Population−averaged)	3.011 (1.134, 5.410)

* Numbers are reported in terms of benefit – i.e. positive numbers represents amount of reduction

Primary SARS-CoV-2 Positive Population Analysis

Time To First Reported Recovery

Budesonide vs. Usual Care



	Inhaled Budesonide	Usual Care
Time to recovery (days) , median(IQR)	11.0 (5.0 to 27.0)	14.0 (6.0 to .)

[1] Estimated hazard ratio derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. Hazard ratio > 1 favors inhaled budesonide.

[2] Probability of superiority, treatment superiority is declared if Pr(superiority) ≥ 0·99 versus Usual Care

Summary

Those with COVID-19 and basically eligible for ‘flu vaccine and if given inhaled budesonde in addition to usual NHS care:

- Will recover around 3 days sooner
- Will feel less unwell while recovering
- Once recovered, will more often remain recovered
- Will have a greater sense of well-being at 14 days and at 28 days follow up
- About a quarter are still not recovered by 28 days

Trend favours reduced hospital admission, but caution with this preliminary finding

COVID-19 Therapeutic Alert

CEM/CMO/2021/011 12 April 2021

Inhaled Budesonide for Adults (50 Years and Over) with COVID-19

Recommendation

Inhaled budesonide is not currently being recommended as standard of care but can be considered (off-label) on a case-by-case basis for symptomatic COVID-19 positive patients aged 65 and over, or aged 50 or over with co-morbidities, in line with the published Interim Position Statement.

Supporting Evidence

After completing an interim analysis, the PRINCIPLE trial has reported that **inhaled budesonide (800 micrograms taken twice daily, for up to 14 days) can reduce recovery time by a median of 3 days in symptomatic COVID-19 positive patients aged 65 and over, or aged 50 or over with co-morbidities. A benefit in self-reported early sustained recovery at 28 days was also identified.**

The analysis has not established whether budesonide can reduce hospital admissions or reduce mortality.

The interim results from PRINCIPLE build on the findings of the STOIC trial Phase II study on inhaled budesonide. This study suggests that early administration of inhaled budesonide reduces the likelihood of needing urgent medical care and reduces time to recovery following early COVID-19 infection.

Eligibility

In summary, potentially eligible patients will:

- Have COVID-19 symptoms, with symptom onset within the last 14 days, AND
- Be COVID-19 positive, confirmed by a recent polymerase chain reaction (PCR) test, AND
- Be aged 65 or over, or aged 50 or over with one or more co-morbidities consistent with the long-term conditions referenced in the flu vaccine list

Please see the published Interim Position Statement for more details on the specific inclusion and exclusion criteria.

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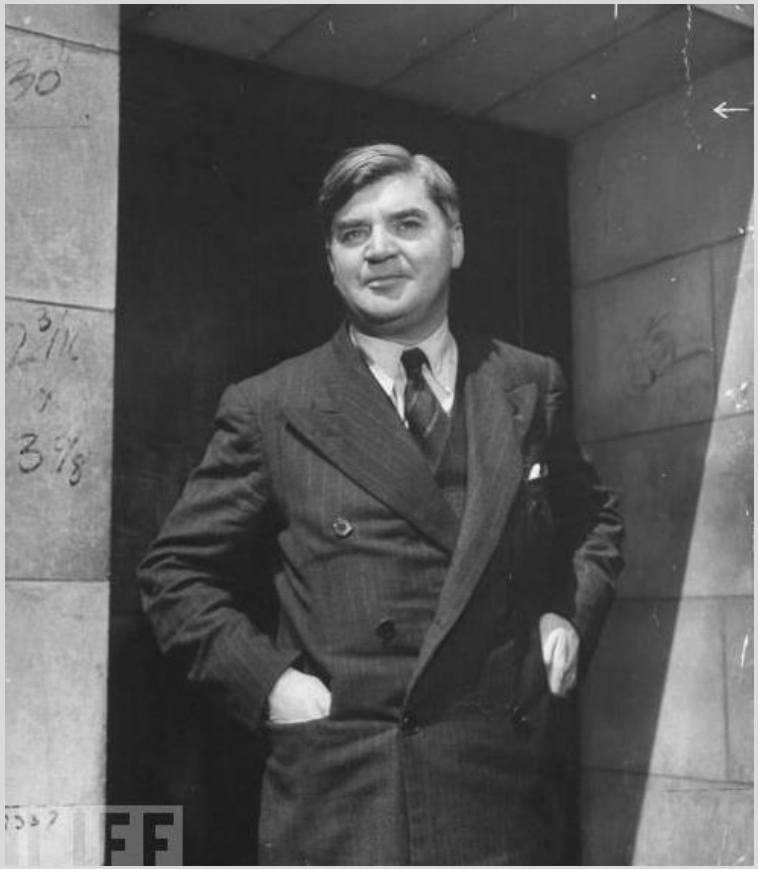
4956 Randomized, 2770 GP practices

Where to next for PRINCIPLE?

Need answers for:

- colchicine (recovery)
- favipiravir
- Further repurposed and viral specific drugs



https://www.principletrial.org
EudraCT number: 2020-001209-22
ISRCTN registry: ISRCTN86534580

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