NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

PRINCIPLE

Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

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Innovation in design and implementation of primary care clinical trials to generate evidence for community therapeutics for COVID-19: The UK National Urgent Public Health PRINCIPLE Trial example

Chris Butler
Professor of Primary Care, University of Oxford
Clinical Director, Primary Care Clinical Trials Unit

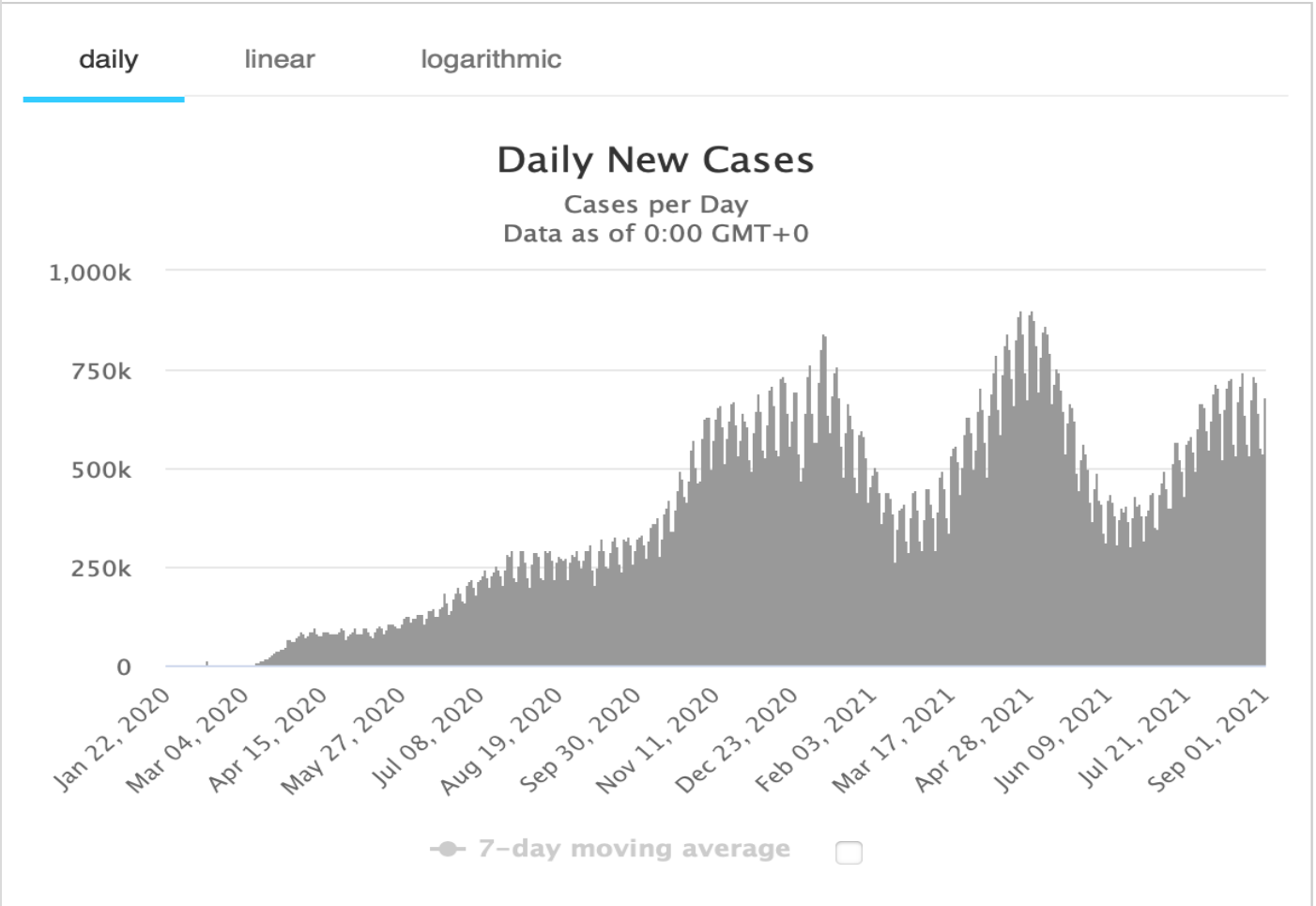
And PRINCIPLE Trial Team

Health Research Symposium 2021
Hong Kong

Background

Despite vaccination,
no room for complacency:
therapeutics still urgently needed

Therapeutics still urgently needed: Cases worldwide



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

Berry Consultants
Statistical Innovation

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

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Statistical Innovation

PRINCIPLE study outline: PICO

Participants:

- Aged ≥65 years OR ≥50-64 years with comorbidities, or ≥18 for ivermectin and favipiravir
- Presenting **in primary care** within 14 days since onset of illness, currently ill, with positive test SARS-Cov-2 test

Interventions:

- Multiple interventions, beginning with hydroxychloroquine

Comparisons:

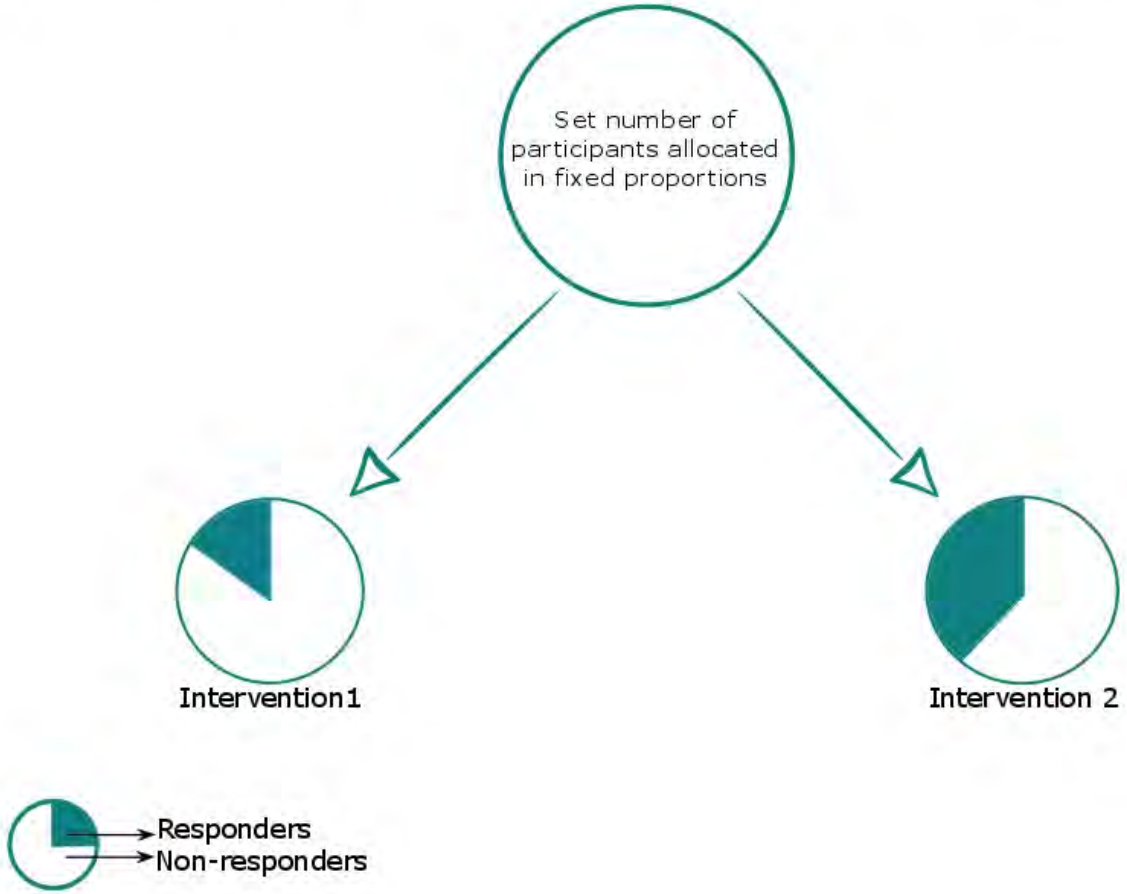
- Usual care without study drug

Innovation in primary care trail design

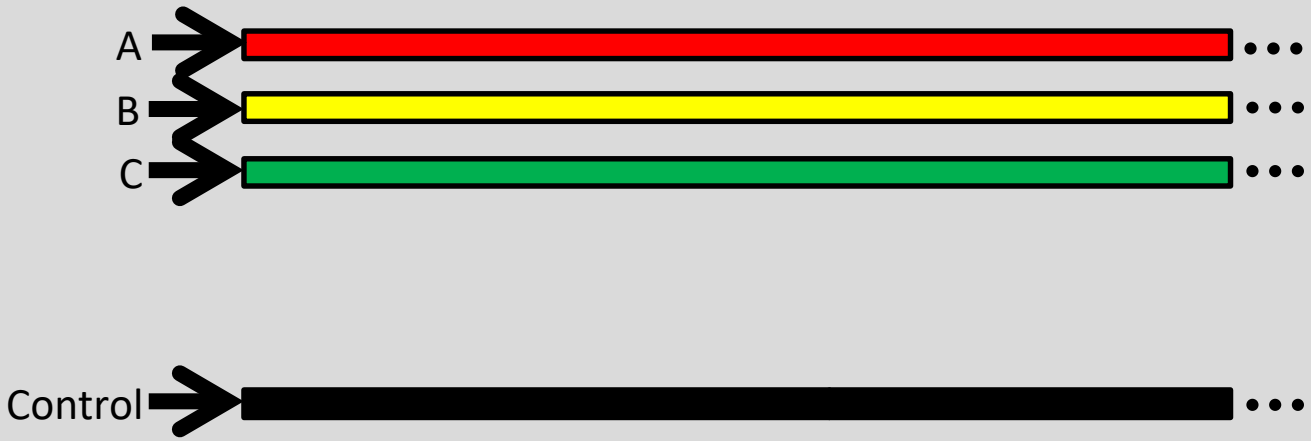
Design considerations

- Pragmatic
- Open
- Platform trial
- Response adaptive

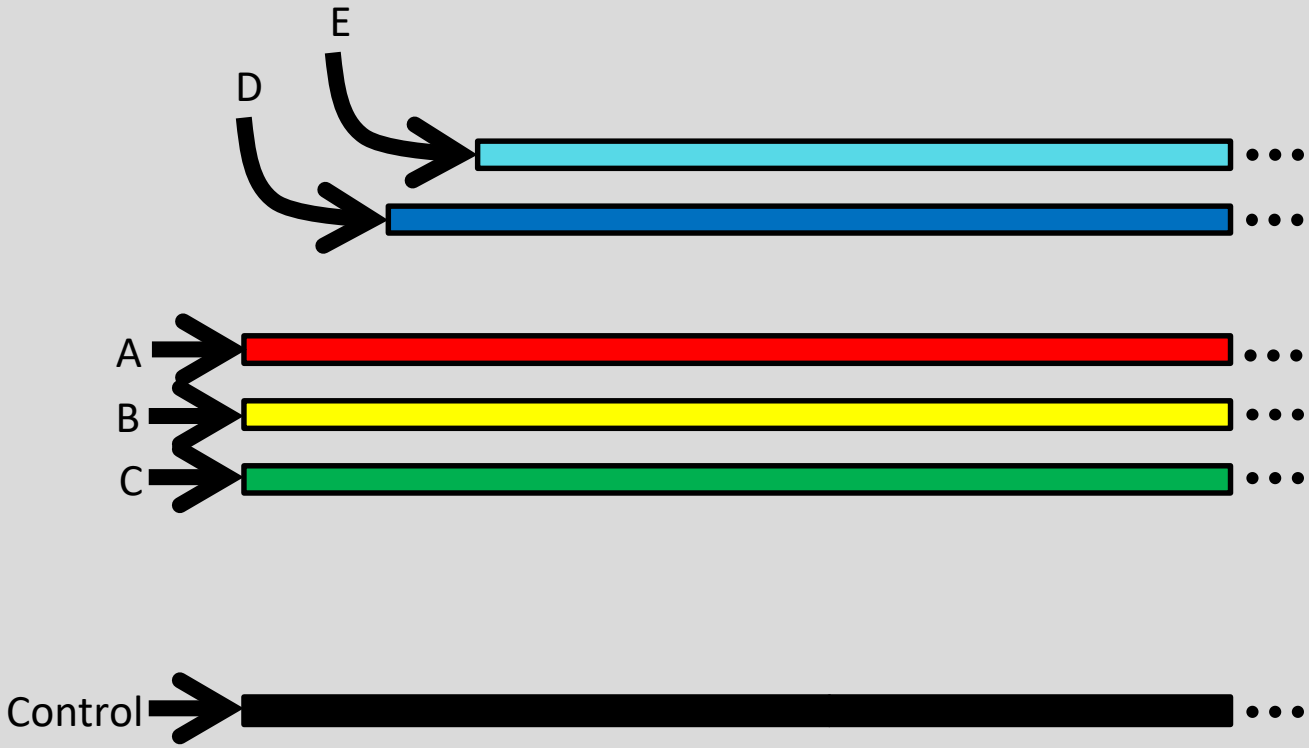
Figure 1: The two arm, fixed proportion allocation Trial: What is the average effect?



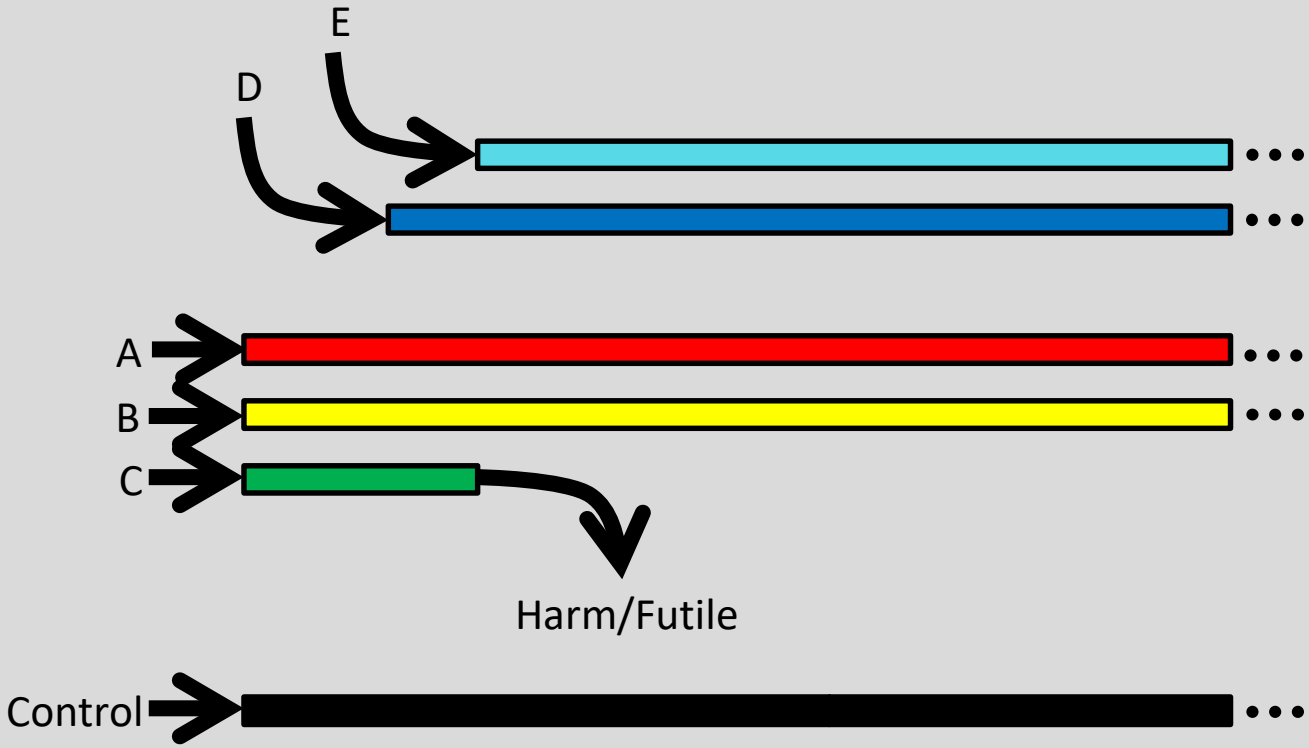
Potential Features of a Platform Trial



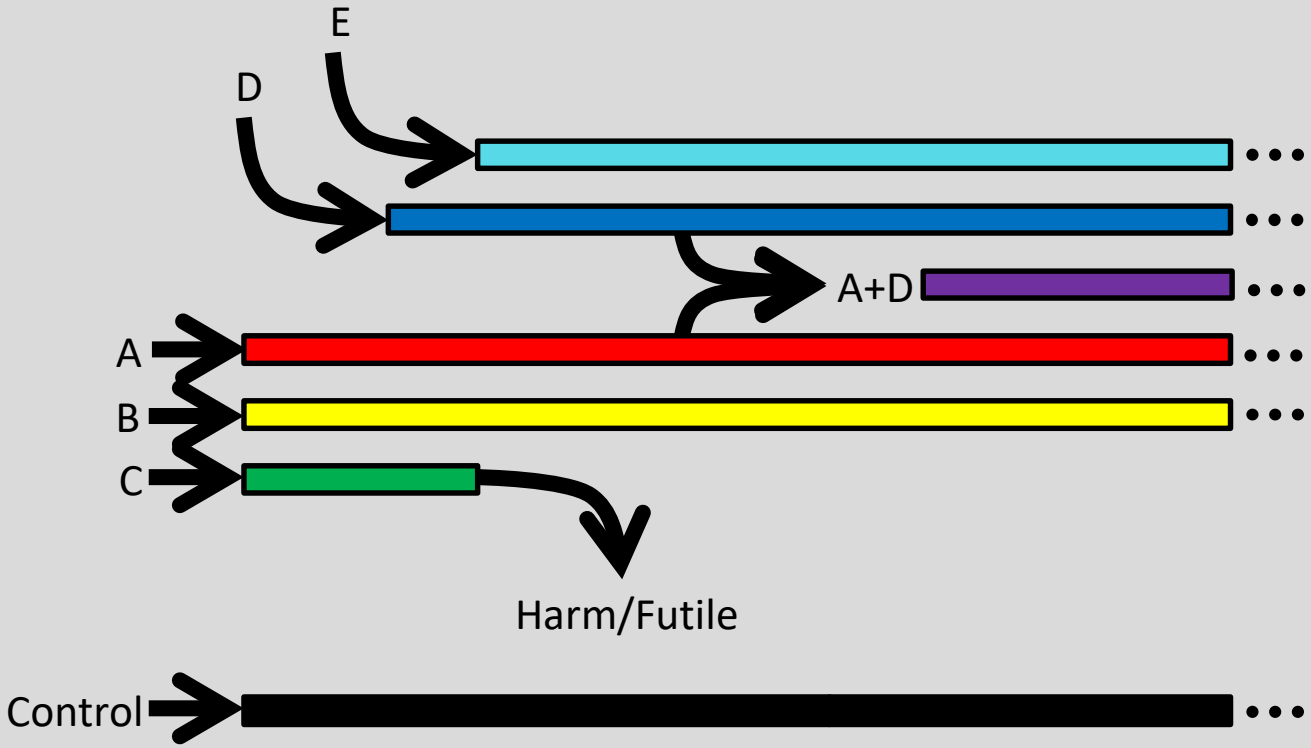
Potential Features of a Platform Trial



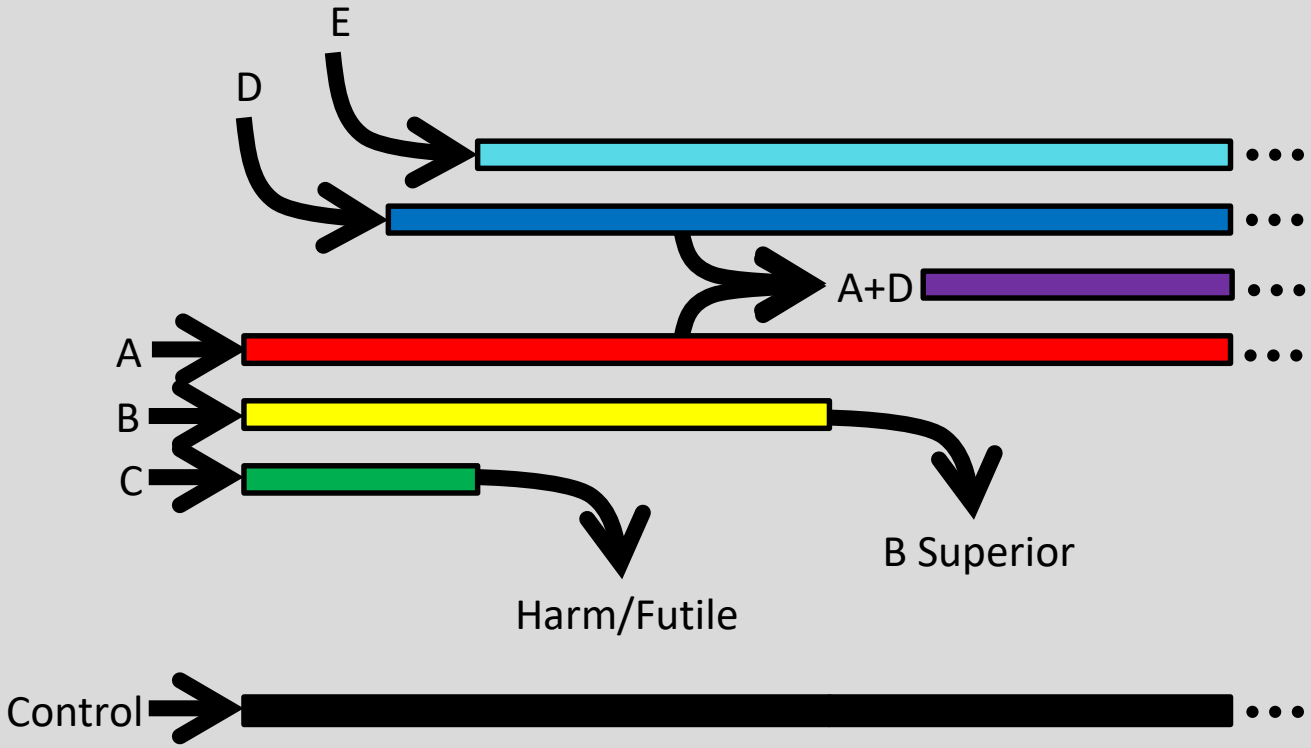
Potential Features of a Platform Trial



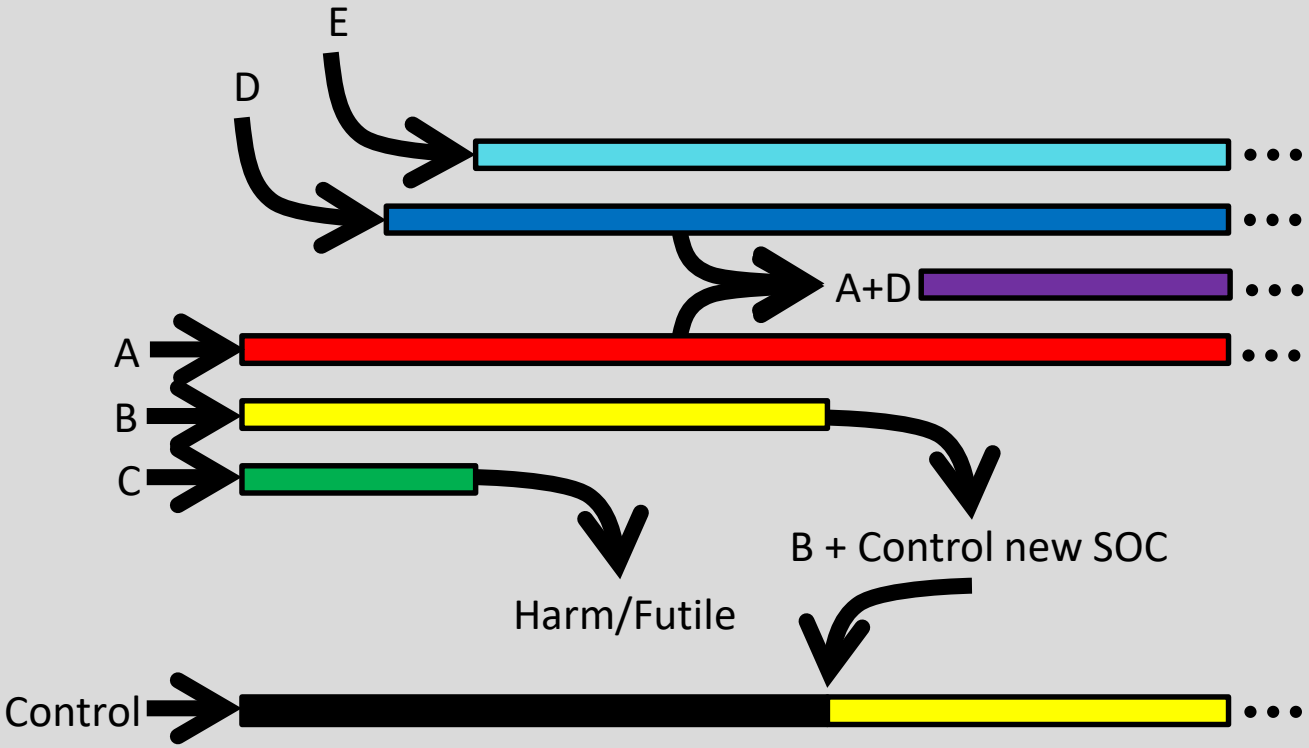
Potential Features of a Platform Trial



Potential Features of a Platform Trial



Potential Features of a Platform Trial



Innovation in trial delivery

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 differences in morb that Titmuss's opin no significant gradi of medical care in th

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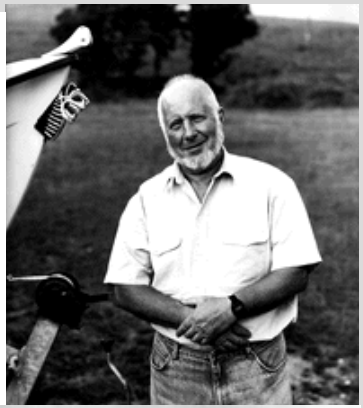

Inverse research participation law

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

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Innovation in Subject Recruitment

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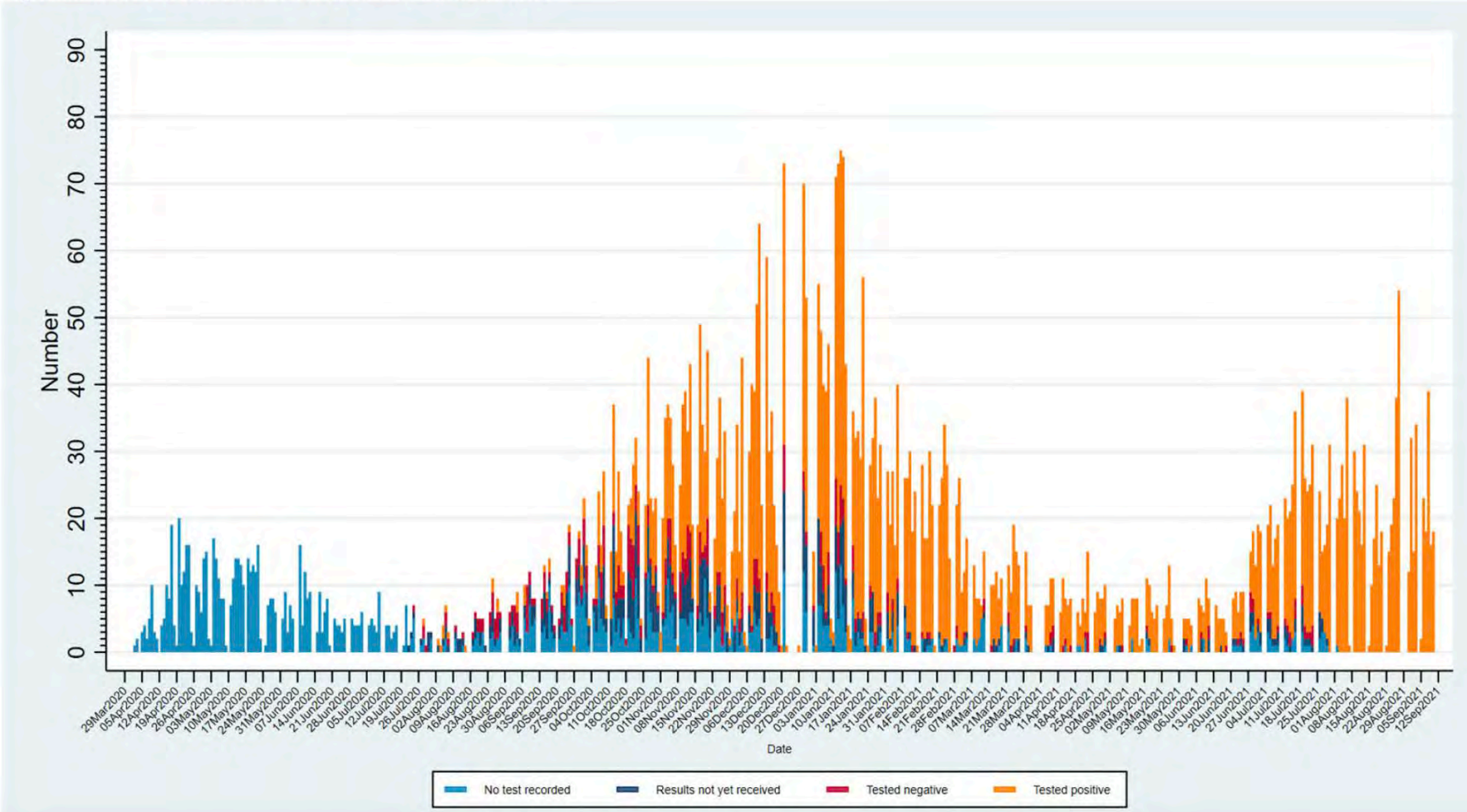
"Patient comes to the research"	"Research taken to the patient"
GP practices set up as sites: requires contract, GCP training	UK wide access through website: clinicians, NHS 111, care homes, patients themselves
Paper, face-to-face consent	Online consent
Study clinician confirms eligibility	Central eligibility 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

Daily randomisations (n=~7714)

Figure 3 DAILY RANDOMISATION AS OF 14-SEP-2021



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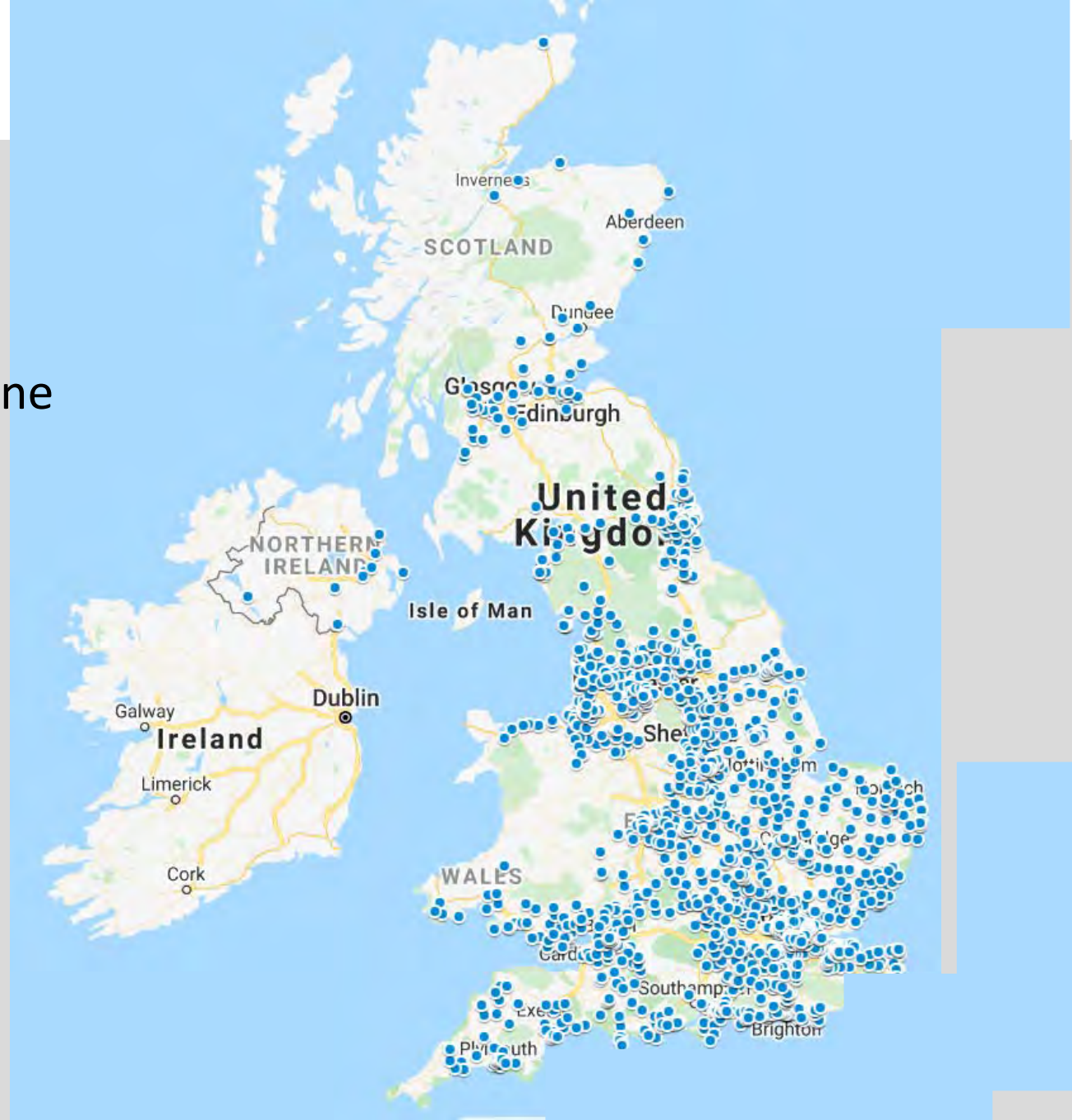
Map of general practices that have recruited at least one participant to PRINCIPLE

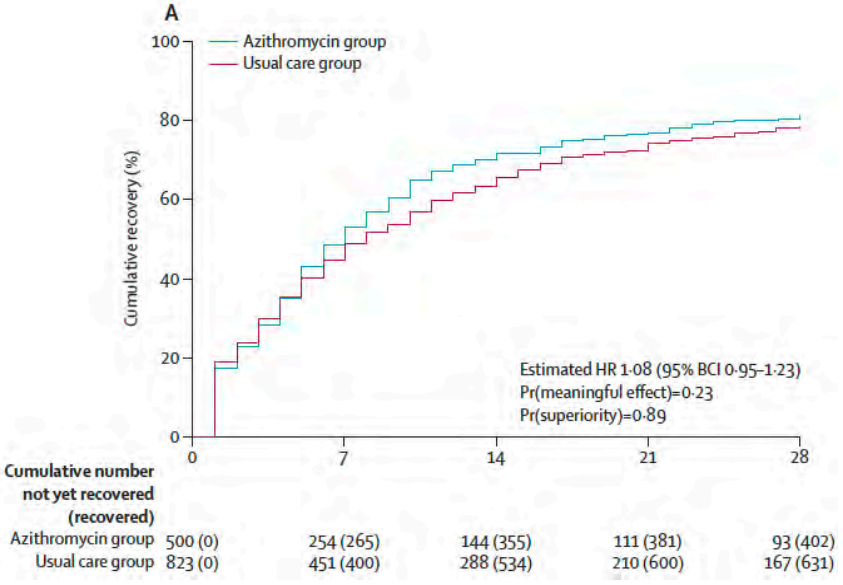


Innovation in evidence generation

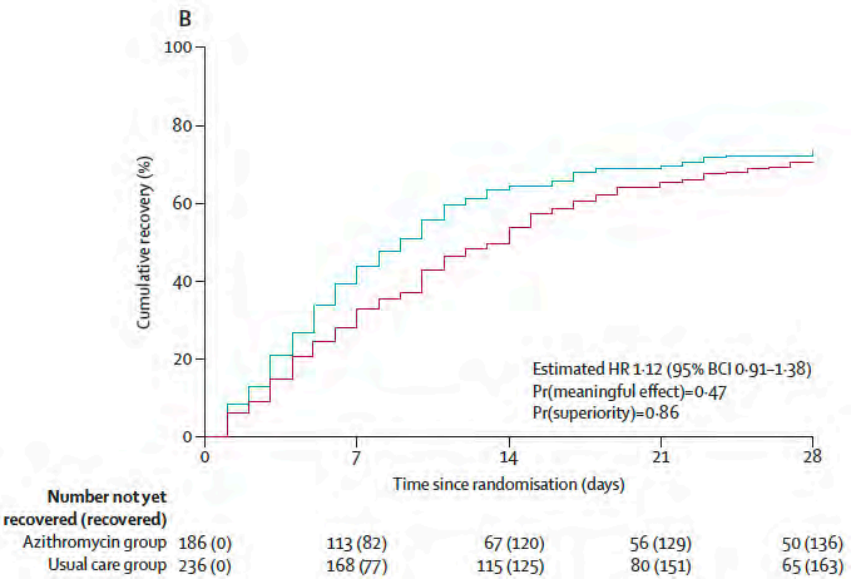
Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

PRINCIPLE Trial Collaborative Group*

Primary analysis population



SARS-Cov-2-positive analysis population



Futility: The probability that there was a clinically meaningful benefit of at least 1·5 days in time to recovery was 0·23.

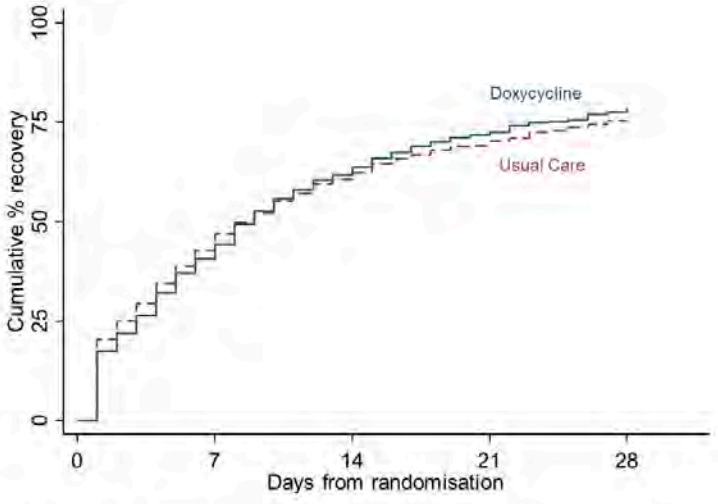
Hospitalision/death: 16 (3%) of 500 participants in the azithromycin plus usual care group and 28 (3%) of 823 participants in the usual care alone group (absolute benefit in percentage 0·3%, 95% BCI –1·7 to 2·2).

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Christopher C Butler, Ly-Mee Yu, Jienchi Dorward, Oghenekome Gbinigie, Gail Hayward, Benjamin R Saville, Oliver Van Hecke, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Ratko Djukanovic, Stephan Gadola, John Kirkpatrick, Simon de Lusignan, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, F D Richard Hobbs, on behalf of the PRINCIPLE Trial Collaborative Group

Figure 2 Summary and results of the time to first self-reported recovery

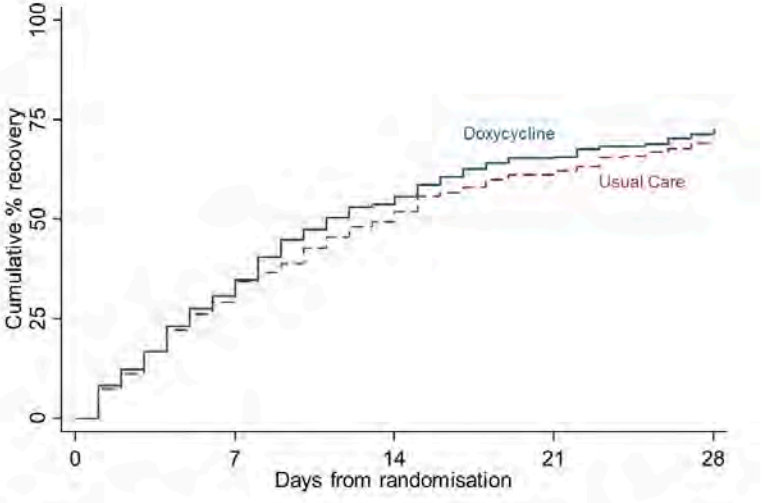
(a) Concurrent Analysis Population



Cumulative number not yet recovered (recovered)

Doxycycline	780 (0)	452 (343)	284 (488)	205 (553)	162 (596)
Usual Care	644 (0)	363 (302)	246 (398)	186 (447)	147 (477)

(b) Concurrent Randomisation Analysis population in participants with SARS-CoV-2 positive test



Cumulative number not yet recovered (recovered)

Doxycycline	435 (0)	292 (149)	189 (236)	140 (276)	114 (304)
Usual Care	321 (0)	225 (110)	159 (165)	118 (197)	93 (218)

Futility: Estimated benefit (95% BCI) in median time to first self-reported recovery was 0·5 [-0·99 – 2·04] days Probability of a clinically meaningful benefit ≥1·5 days was 0·1.

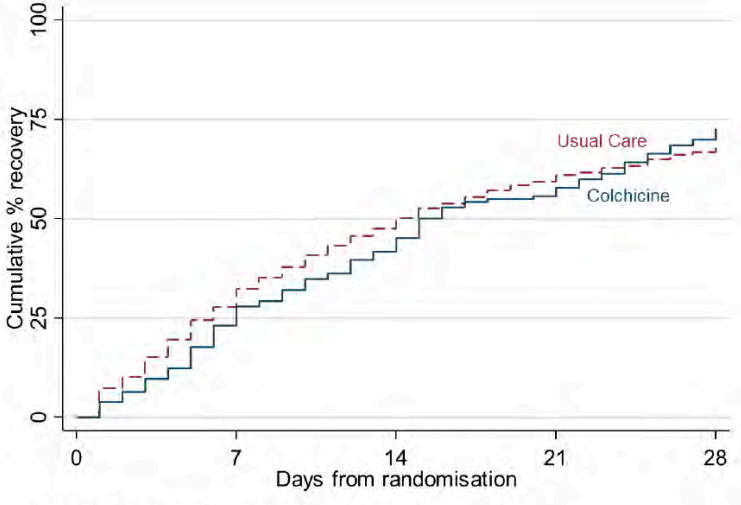
Hospitalision/death: 41 (5·3%) COVID-19 related hospitalisations/deaths in doxycycline group vs 43 (4·5%) in usual care group (absolute percentage difference, -0·5% [-2·6 – 1·4%]).

Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial

PRINCIPLE Trial Collaborative Group¶

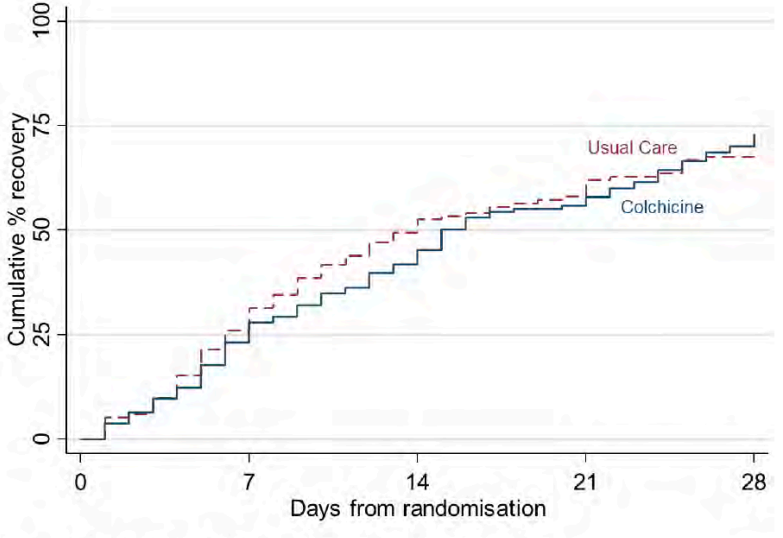
¶*Writing committee listed below on behalf of the PRINCIPLE Trial Collaborative Group. PRINCIPLE trial collaborators are listed in the appendix*

a) SARS-CoV-2 positive primary analysis population



Cumulative number not yet recovered (recovered)					
Colchicine	156 (0)	113 (42)	84 (67)	63 (85)	42 (106)
Usual Care	1145 (0)	811 (369)	581 (567)	443 (684)	355 (760)

b) Concurrent randomisation SARS-CoV-2 positive population



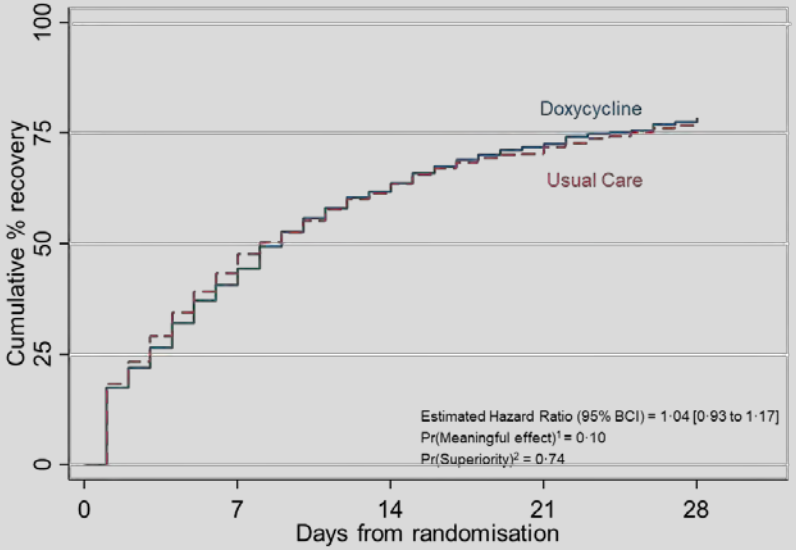
Cumulative number not yet recovered (recovered)					
Colchicine	156 (0)	113 (42)	84 (67)	63 (85)	42 (106)
Usual Care	133 (0)	95 (41)	65 (68)	53 (80)	39 (88)

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

*Christopher C Butler, Ly-Mee Yu, Jienchi Dorward, Oghenekome Gbinigie, Gail Hayward, Benjamin R Saville, Oliver Van Hecke, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Ratko Djukanovic, Stephan Gadola, John Kirkpatrick, Simon de Lusignan, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, F D Richard Hobbs, on behalf of the PRINCIPLE Trial Collaborative Group**

Figure 2 Summary and results of the time to first self-reported recovery

(a) Primary Population Analysis

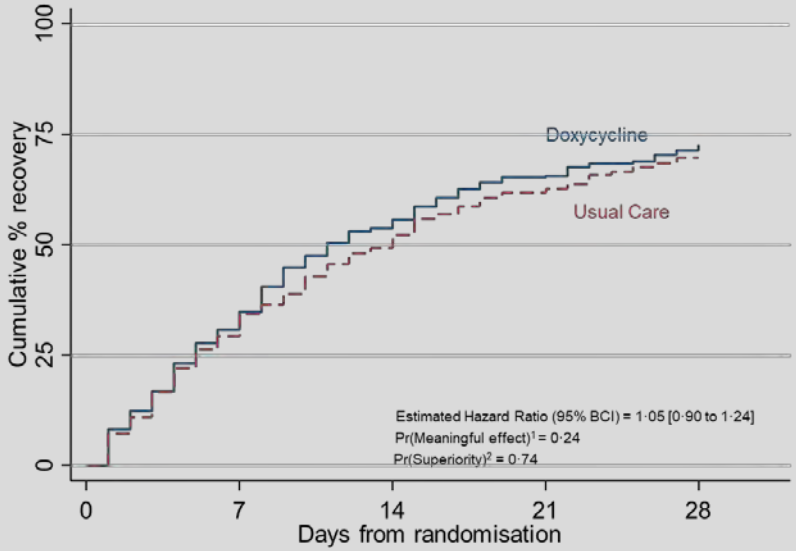


Cumulative number not yet recovered (recovered)					
Doxycycline	780 (0)	452 (343)	284 (488)	205 (553)	162 (596)
Usual Care	948 (0)	530 (451)	352 (597)	262 (672)	204 (717)

[1] Bayesian model-based estimated probability that the benefit in median time to recovery compared to Usual Care is at least 1·5 days

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

(b) SARS-CoV-2 positive analysis population



Cumulative number not yet recovered (recovered)					
Doxycycline	435 (0)	292 (149)	189 (236)	140 (276)	114 (304)
Usual Care	336 (0)	235 (115)	167 (174)	122 (208)	96 (230)

[1] Bayesian model-based estimated probability that the benefit in median time to recovery compared to Usual Care is at least

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

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).

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Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Ly-Mee Yu*, Mona Bafadhel*, Jienchi Dorward*, Gail Hayward, Benjamin R Saville, Oghenekome Gbinigie, Oliver Van Hecke, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, Duncan Richards, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Milensu Shanyinde, Simon de Lusignan, Monique I Andersson, Peter J Barnes, Richard E K Russell, Dan V Nicolau Jr, Sanjay Ramakrishnan, F D Richard Hobbs†, Christopher C Butler†, on behalf of the PRINCIPLE Trial Collaborative Group‡

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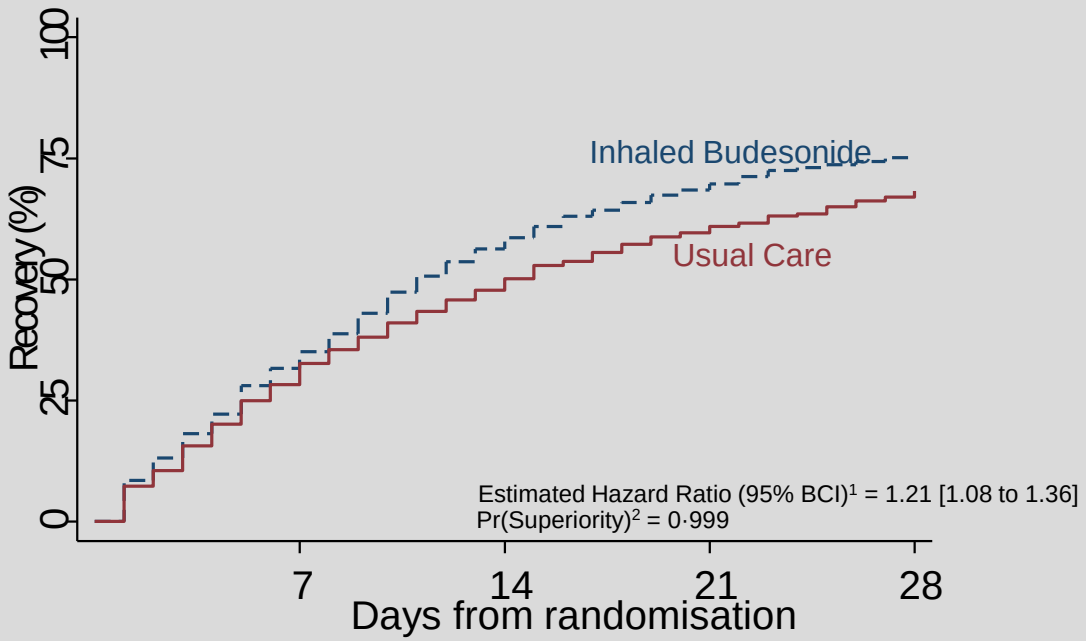
Primary SARS-CoV-2 Positive Population Analysis
Time To First Reported Recovery: Budesonide vs. Usual Care



	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

Budesonide results

Primary SARS-CoV-2 Positive Population Analysis

Time To First Reported Recovery

Budesonide vs. Usual Care

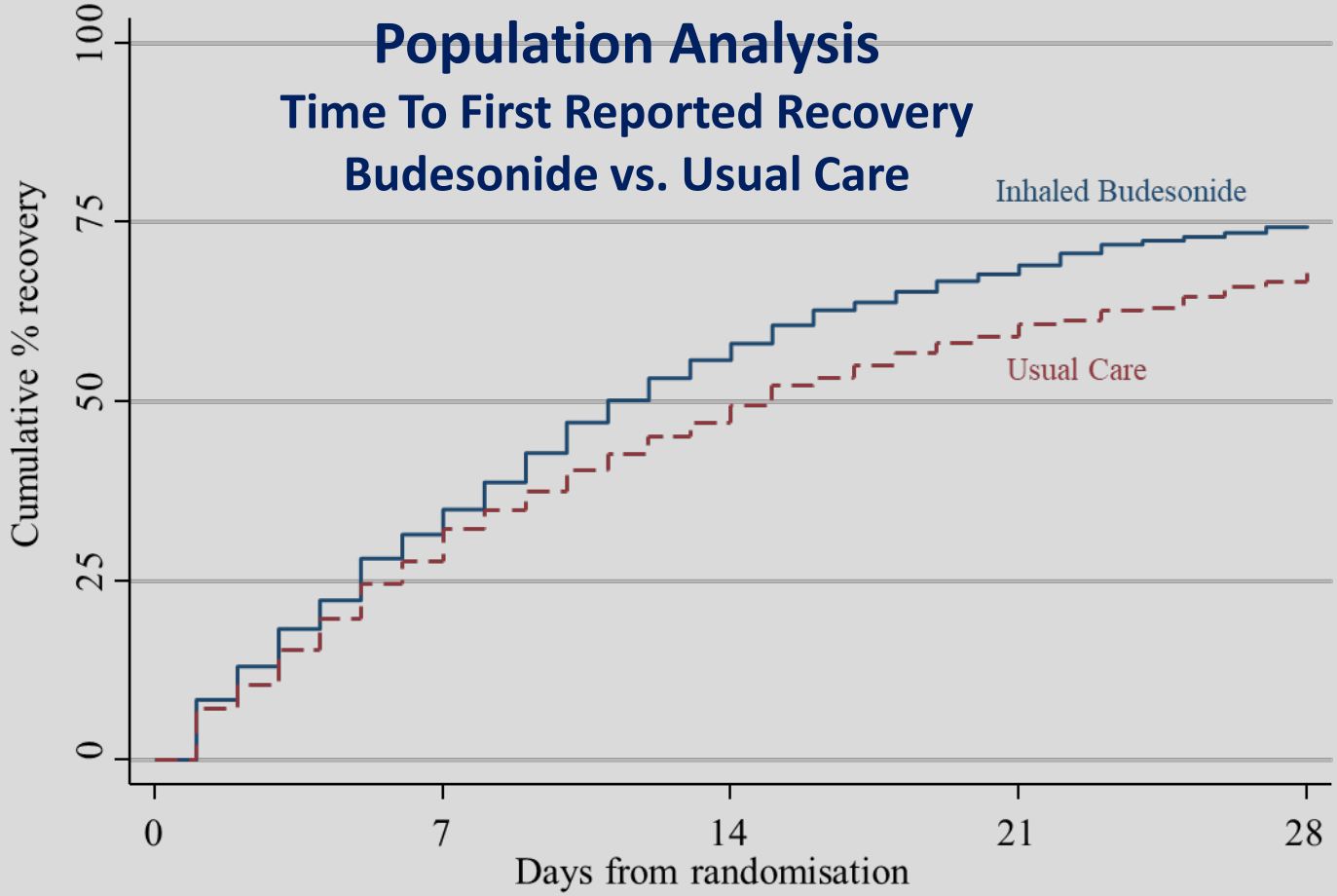
Sample Size		Model Results	
Inhaled Budesonide	Usual Care	Median Hazard Ratio (95% Bayesian credible interval)	Prob(Superiority)
787	1069	1.213 (1.084 to 1.357)	> 0.999

	Median Estimated Benefit in Median Time To Recovery in Days* (95% Bayesian credible interval)
Overall (Population−averaged)	2.941 (1.191, 5.115)

* 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



Model-based estimates	Inhaled Budesonide	Usual Care
Estimated median Time to first reported recovery (95% Bayesian credible interval), days	11.8 (10.0 to 14.1)	14.7 (12.3 to 18.0)

Budesonide results

Primary SARS-CoV-2 Positive Population Analysis

Hospitalisation/Death

Budesonide vs. Usual Care

n/N (%)		Model Results	
Inhaled Budesonide	Usual Care	Odds ratio (95% BCI)	Prob(Superiority)
72/787 (9.1%)	116/1069 (10.9%)	0.753 (0.548 to 1.028)	0.963

	Estimated benefit in Hospitalisation/Death rate* (95% Bayesian credible interval)
Overall (Population−averaged)	2.0% (-0.2%, 4.5%)

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

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Budesonide results

Concurrent Randomisation SARS-CoV-2 Positive Population Analysis

Hospitalisation/Death

Budesonide vs. Usual Care

n/N (%)		Model Results	
Inhaled Budesonide	Usual Care	Odds ratio (95% BCI)	Prob(Superiority)
72/787 (9.1%)	101/838 (12.1%)	0.727 (0.527 to 1.000)	0.975

	Estimated benefit in Hospitalisation/Death rate* (95% Bayesian credible interval)
Overall (Population−averaged)	2.2% (0.0%, 4.9%)

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

Secondary outcomes based on concurrent randomisation and eligible population in participants with SARS-CoV-2 positive

Secondary outcomes	Estimated treatment effect (95% CI)	P-value
Early sustained recovery, n/N (%)	1·48 (1·26 to 1·75)[1]	<0·0001
Time to sustained recovery (days), median (IQR)	1·39 (1·21 to 1·59)[2]	<0·0001
Time to alleviations of all symptoms (days), median (IQR)	1·07 (0·96 to 1·19)[2]	0·26
Time to sustained alleviation of all symptoms (days), median (IQR)	1·13 (1·01 to 1·27)[2]	0·037
Time to initial reduction of severity of symptoms (days), median (IQR)	1·19 (1·07 to 1·32)[2]	0·0019

[1] Adjusted relative risk adjusted for age, comorbidity at baseline, duration of illness, and vaccination status at baseline
[2] Adjusted hazard risk adjusted for age, comorbidity at baseline, duration of illness, and vaccination status at baseline

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Secondary outcomes based on concurrent randomisation and eligible population in participants with SARS-CoV-2 positive

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Secondary outcomes‡	Inhaled Budesonide	Usual Care	Estimated treatment effect (95% CI)	P-value
Rating of how well participant feels (1 worst, 10 best), mean (SD) [n]				
Day 7	7·0 (1·8) [747]	6·6 (1·9) [759]	0·33 (0·14 to 0·52)[1]	0·0001
Day 14	7·9 (1·7) [745]	7·5 (1·7) [763]	0·37 (0·17 to 0·57)[1]	<0·0001
Day 21	8·4 (1·5) [623]	7·9 (1·6) [612]	0·38 (0·15 to 0·61)[1]	0·0001
Day 28	8·4 (1·5) [759]	8·2 (1·5) [772]	0·19 (-0·07 to 0·44)[1]	0·16
Well-being (WHO5 Questionnaire), mean (SD)[n]				
Day 14	42·5 (25·0) [713]	39·4 (24·4) [724]	2·97 (0·64 to 5·30)[1]	0·013
Day 28	54·6 (25·1) [713]	52·0 (24·8) [721]	2·36 (0·03 to 4·69)[1]	0·047
Self-reported contact with ≥1 healthcare service, n/N (%)	416/778 (54)	466/787 (59)	0·90 (0·83 to 0·98)[2]	0·017
GP reported contact with ≥1 healthcare service, n/N (%)	305/602 (51)	351/607 (58)	0·87 (0·79 to 0·97)[2]	0·010
New infections in household, n/N (%)	197/772 (26)	214/782 (27)	0·93 (0·79 to 1·10)[2]	0·40
Prescription of antibiotics, n/N (%)	42/550 (8)	53/543 (10)	0·78 (0·53 to 1·15)[2]	0·24
Hospital assessment without admission, n/N (%)	22/786 (3)	22/797 (3)	1·01 (0·57 to 1·82)[2]	>0·99
Oxygen Administration, n/N (%)	50/774 (7)	73/785 (9)	0·69 (0·49 to 0·98)[2]	0·039
Mechanical ventilation, n/N (%)	13/776 (2)	14/784 (2)	0·94 (0·44 to 1·98)[3]	>0·99
ICU admission, n/N (%)	10/771 (1)	21/779 (3)	0·48 (0·23 to 1·01)[3]	0·068

[1] Mixed effect model adjusting age, comorbidity, duration of illness, vaccination status at baseline, and time. Participant was fitted as a random effect. WHO well-being score was also adjusted for the score at baseline

[2] Relative risks adjusted for age, comorbidity at baseline, duration of illness, and vaccination status at baseline.

[3] Unadjusted relative risks due to low event rate.

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Forest plot of subgroup analysis of time to first reported recovery (concurrent randomisation and eligible SARS-CoV-2 positive population)

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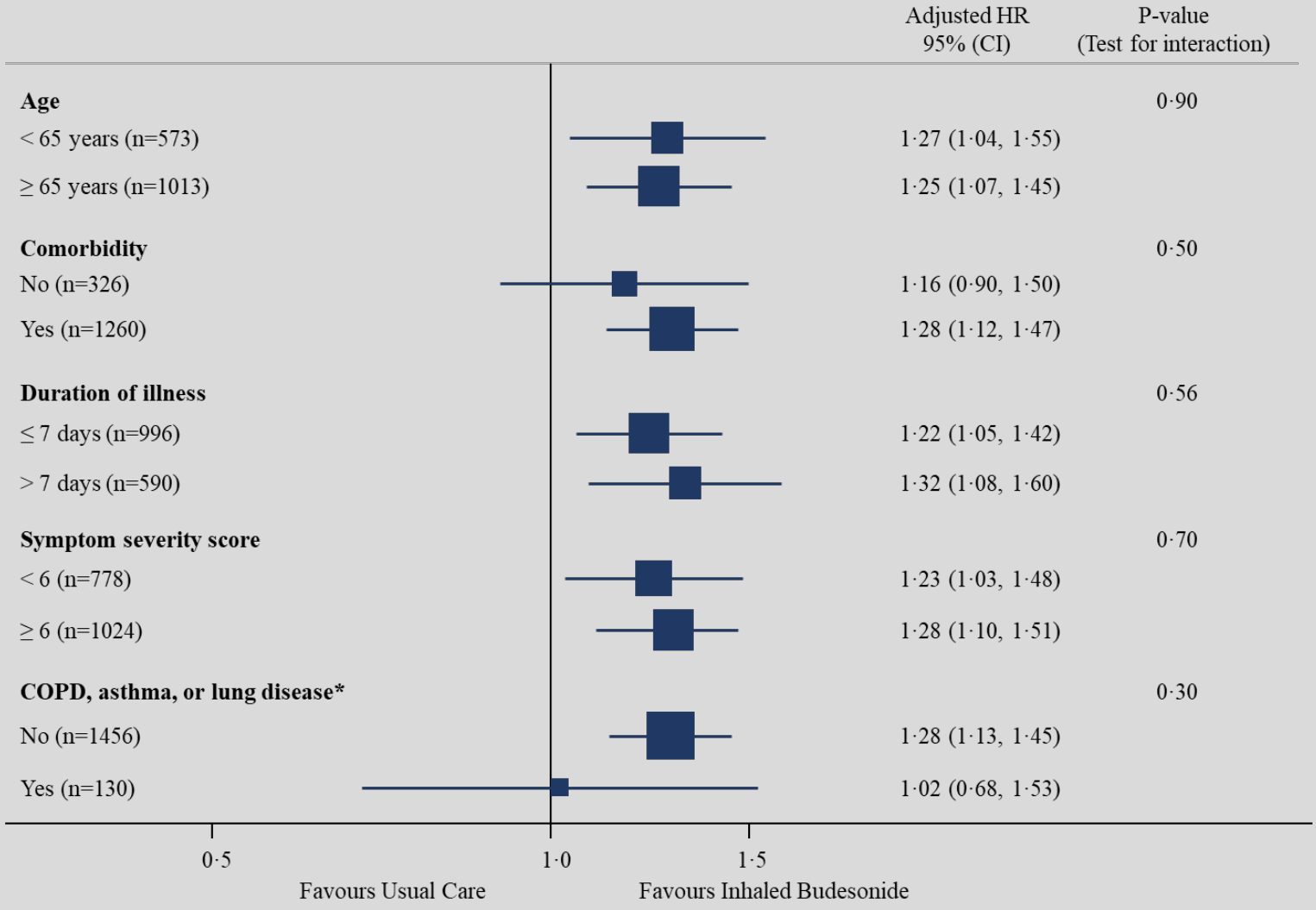

* Subgroup analysis not pre-specified

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Forest plot of subgroup analysis of COVID-19 related hospitalisation/death (concurrent randomisation and eligible SARS-CoV-2 positive population)

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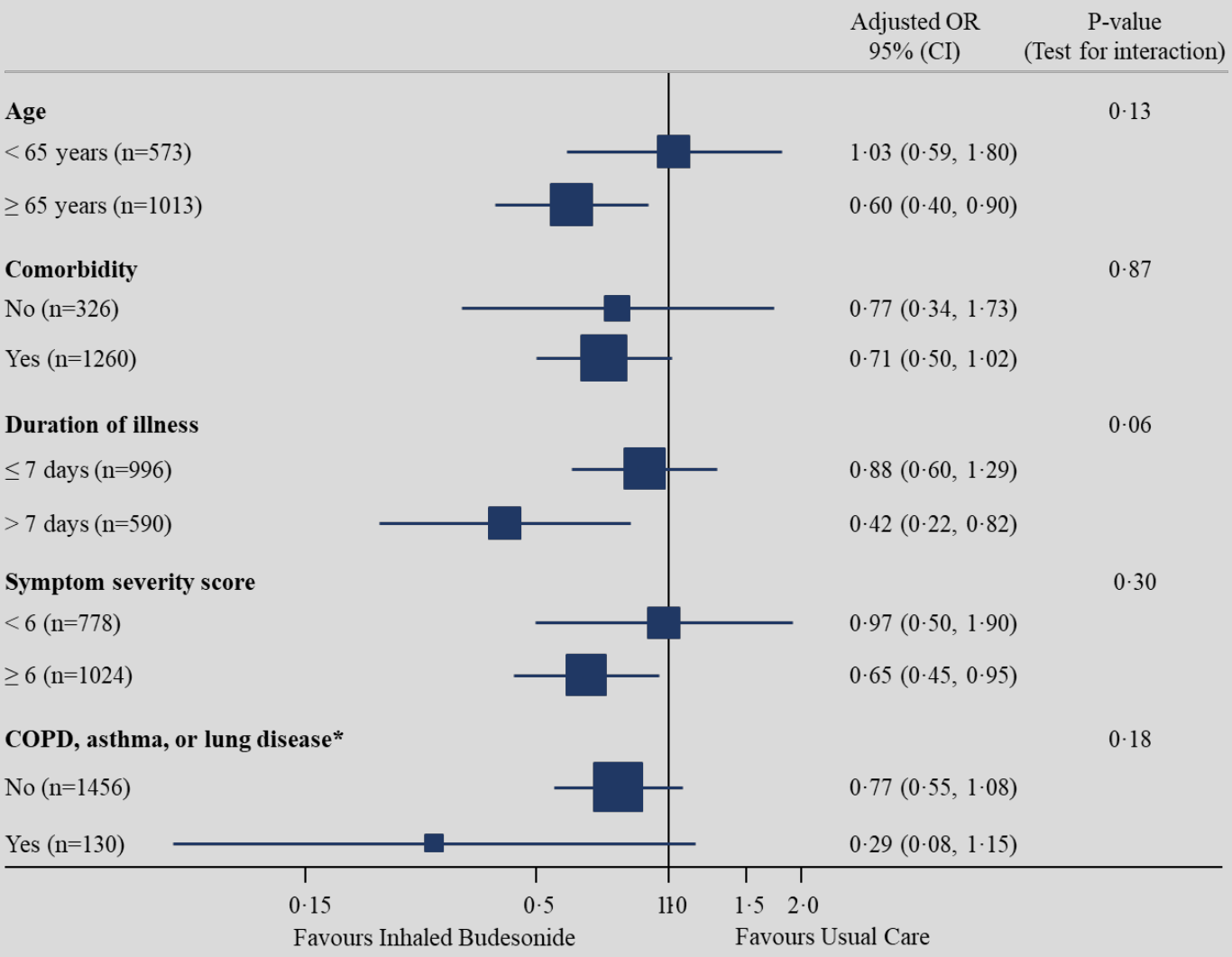

* Subgroup analysis not pre-specified

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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Summary

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Innovation in trial design:

- Platform, response adaptive, open, trial using Bayesian approaches

Innovation in trail delivery

- Largest trial of community therapeutics for COVID-19 word-wide
- Online consent; trial partner; central eligibility check; courier of medicine to home; online follow up; "Takes research to the patient"

Innovation in enhancing the evidence base

- Antibiotics not useful in the absence of other indications
- Colchicine does not speed recovery (preliminary)
- **Those on Inhaled budesonide:**
  - Recovered 3 days sooner
  - Felt less sick while recovering
  - Had greater, well being (WHO 5 Scale)
  - Once recovered, more often remained recovered (~50% relative benefit)
  - Consulted less often
  - Were hospitalized less often (Number Need To Treat = 50)

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

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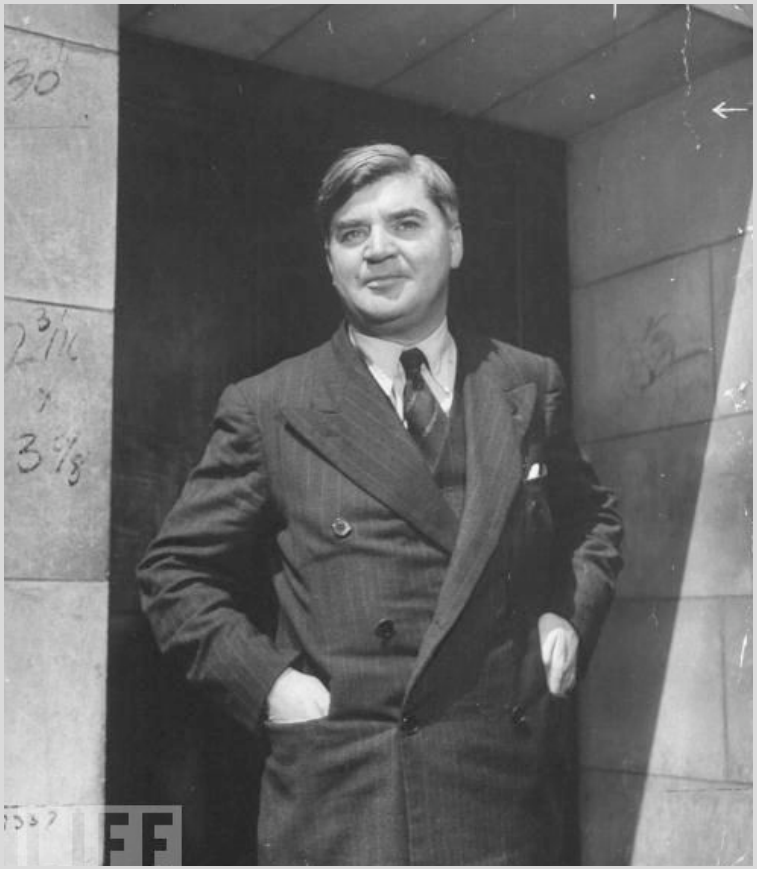
7714 Randomised, 2881 GP practices

Where to next for PRINCIPLE?

Need answers for:

- favipiravir
- Ivermectin
- Novel antivirals

People aged 18 years and over with comorbidity and/or shortness of breath now eligible



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

PRINCIPLE is funded by UK Research and Innovation & the Department of Health and Social Care through the National Institute for Health Research.

FUNDED BY NIHR | National Institute for Health Research

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