Adaptive Platform Trial Scientific Meeting

September 28 – 29 • Toronto, Canada

CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

Primary Care Clinical Trials Unit

UNIVERSITY OF OXFORD

Overcoming Practical Challenges in adaptive platform trials

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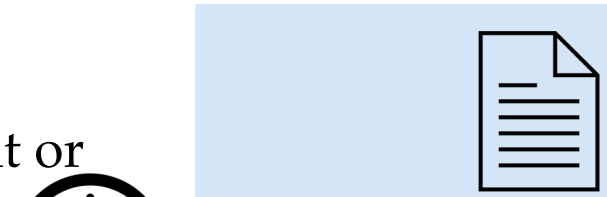
Deputy Director Academic and Lead Statistician
Oxford Primary Care Clinical Trials Unit, University of Oxford

Oxford Primary Care Clinical Trials Unit

Portfolio

16 in development or waiting for outcome

30 projects funded in 2021



63 NDPCHS projects across different research themes

80% of the submitted were funded by NIHR

38 trials completed since 2018

32 main papers published

21 in top journals such as Lancet, JAMA, NEJM and BMJ

114,558 participants randomised (March 2023)

14 trials currently in set up

Adaptive Platform Trials at PC-CTU

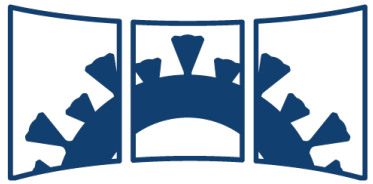
ecraid

Prime

PRINCIPLE

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

PRUDENCE



PANORAMIC

Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community

Adaptive Platform Trials

- There is an increasing awareness of using more efficient trials to
  - Be flexible answering multiple clinical questions faster
  - Maximise recruitment
  - Reduce trial set-up time

Challenges

- Methodology
- Trial team
- Protocol, submission, contracts, and agreement
- System development and data collection tool
- Statistics
- Oversight
- Recruitment and follow-up
- Drug delivery
- Safety considerations
- Communications
- Data sharing
- Etc…

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.

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

Population	• High risk population presenting in primary care within 14 days since onset of cough and/or fever during time of prevalent COVID-19 infections
Intervention	• Multiple interventions, beginning with Hydroxychloroquine
Control	• Usual care without study drug
Outcome	• Time-to-recovery from randomisation • Hospitalisation/death due to COVID-19 by 28 days

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

Key features

- Open label
- Decentralised
- Rapid recruitment
- 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
- Response adaptive randomsation

Trial Team

- Trial management
  - Sites initiation
  - Submission for approval, amendment
  - Contracts and agreement
  - Recruitment
  - Communication
  - NHS England
  - Call team
  - Notes review
  - PPI
  - On site A/B team
- Clinical Team (clinicians and nurses)
  - ISA preparation
  - Safety
  - Recruitment
- Statistics
  - Blinding
  - Unblinding
- IT and Data
- Pharmacy

Protocol, submission, contracts, agreement

- Master protocol with Intervention Specific Appendices.
- Engage with the Sponsor, MHRA, ethics committee, and contract office as soon as possible.
- A lot of meeting, phone calls!

System development and data collection tools

Sentry

- Participant screening
  - Consent
  - PIS
  - Trial Partner
- Clinical team confirmation
- Individual link to daily diary
- Able to send email reminders

OpenClinica

- Clinical database

Sortition

- No adding/dropping Rx capability
- No RAR capability
- Randomisation started with two treatment arms
- All or none?

Sortition A vs UC

Sortition B vs UC

Sortition A vs B vs UC

Statistics

- Allocation of tasks so heavy on statistician resource
- Clear and transparent allocation of roles

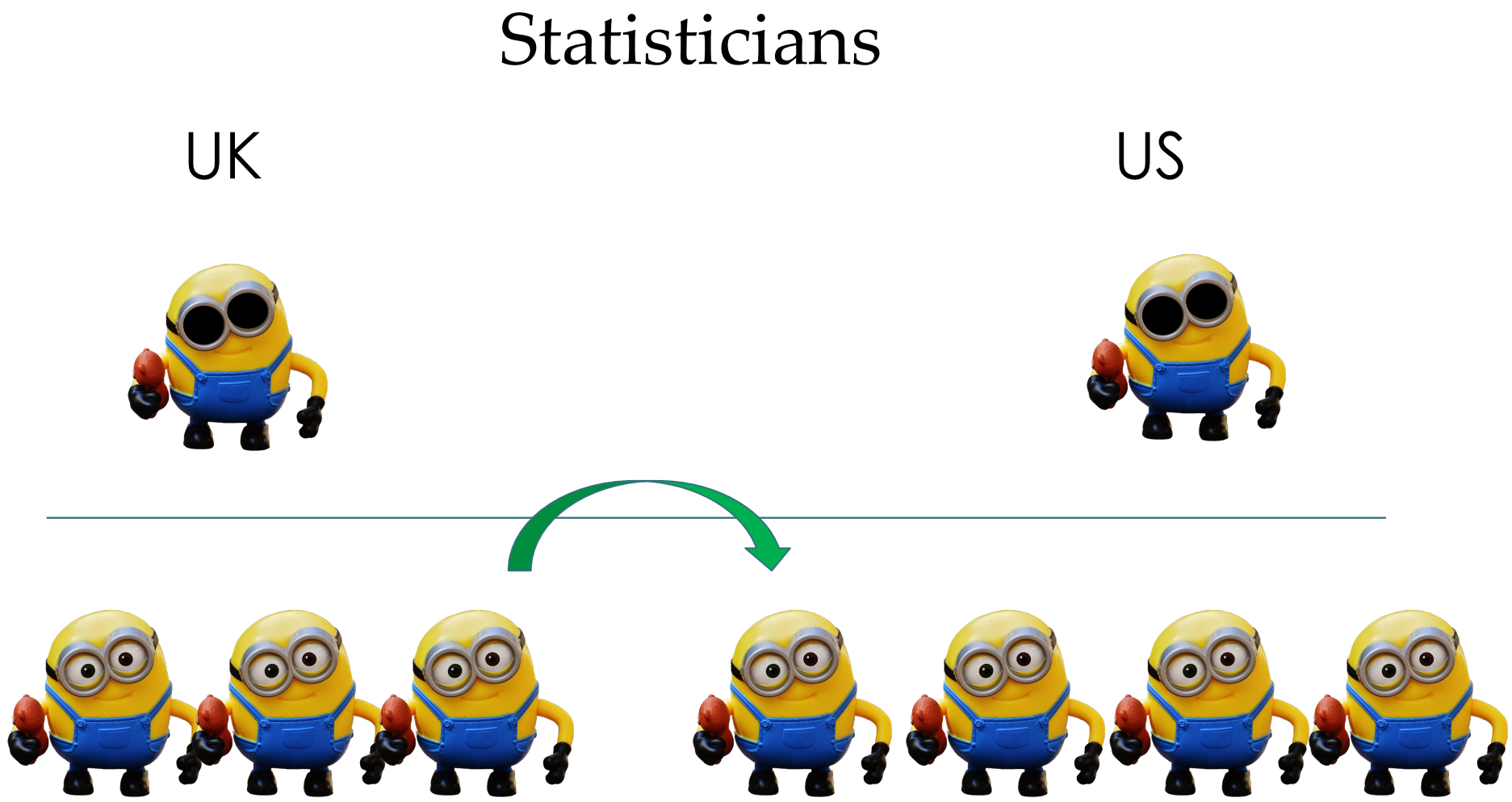
- Blinding team

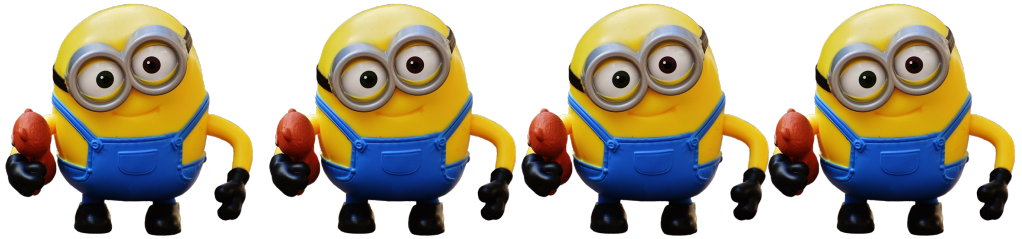
Berry Consultants (USA)	PC-CTU (Oxford)
○ Development of Adaptive Design Report (ADR)	○ Development of Master Statistical Analysis plan (M-SAP)

- Unblinding team

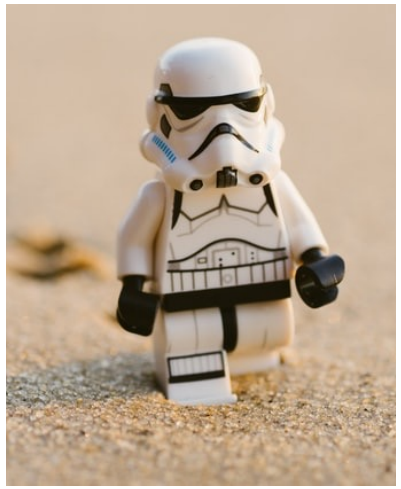
Berry Consultants (USA)	PC-CTU (Oxford)
○ Interim and primary analyses – Bayesian approach	○ Safety and secondary analyses – Frequentist approach

RAR + open label is a challenge!

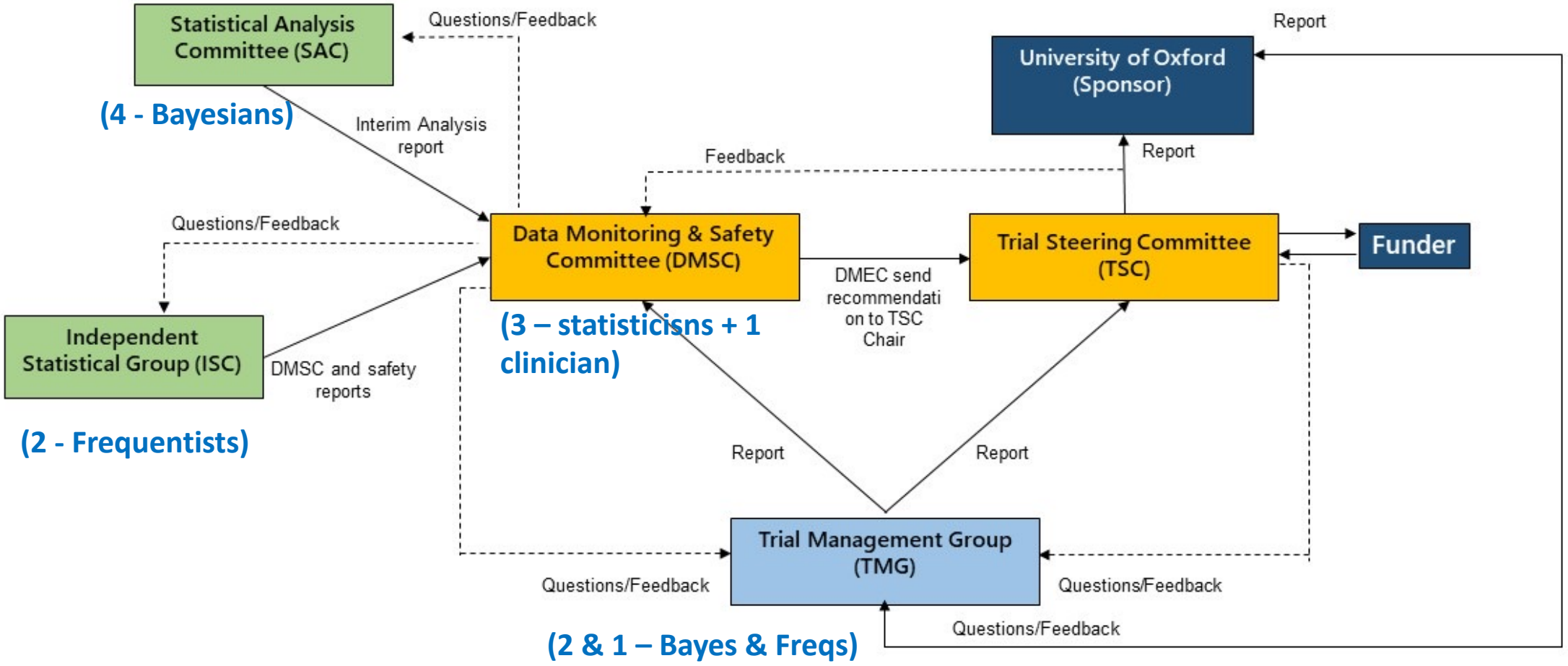




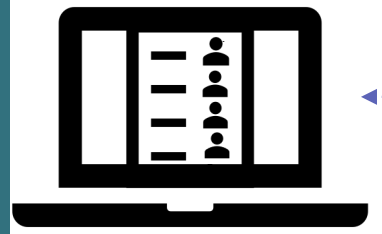
RAR allocation ratio



Oversight

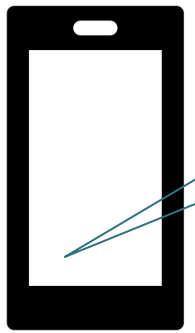

Statistical Analysis Committee (SAC)
Questions/Feedback
(4 - Bayesians)
Interim Analysis report
University of Oxford (Sponsor)
Report
Feedback
Report
Questions/Feedback
Data Monitoring & Safety Committee (DMSC)
Trial Steering Committee (TSC)
Funder
DMEC send recommendation to TSC Chair
(3 – statisticisns + 1 clinician)
Independent Statistical Group (ISC)
DMSC and safety reports
(2 - Frequentists)
Report
Report
Trial Management Group (TMG)
Questions/Feedback
Questions/Feedback
Questions/Feedback
(2 & 1 – Bayes & Freqs)

Recruitment and follow-up

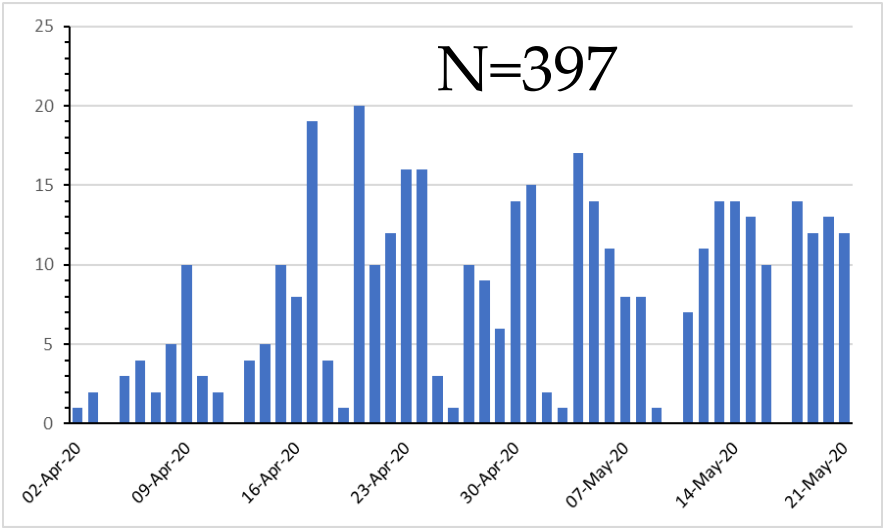


GP sites

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



Principletrial.org
☎0800 138 0880



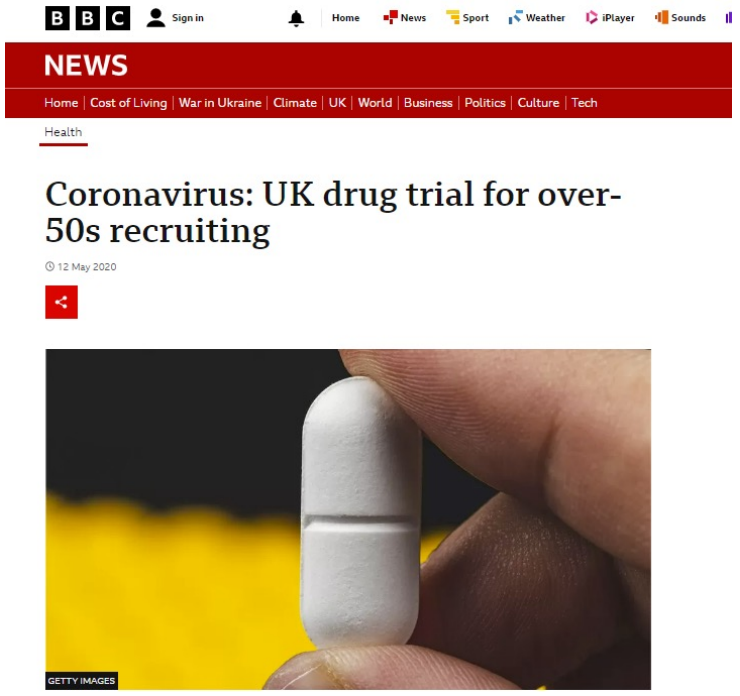
UK NHS England
Pillar 2
[Nov 2020]

Zoe App
[August 2020]

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

GP sites
[Mar 2020]

Online self-screening
[May 2020]



Ambulance service
(111/119)
[May 2020]

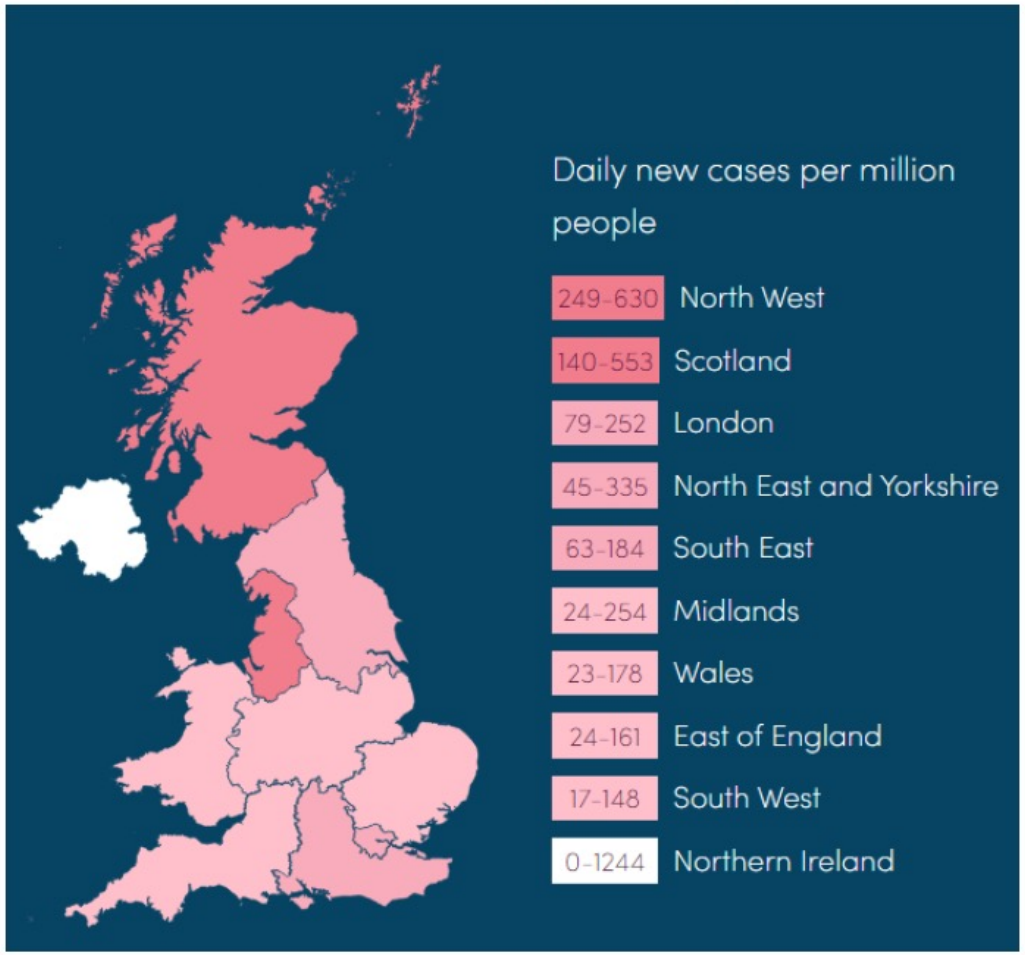
Trial signposting
[Oct 2020]

Tracking recruitment

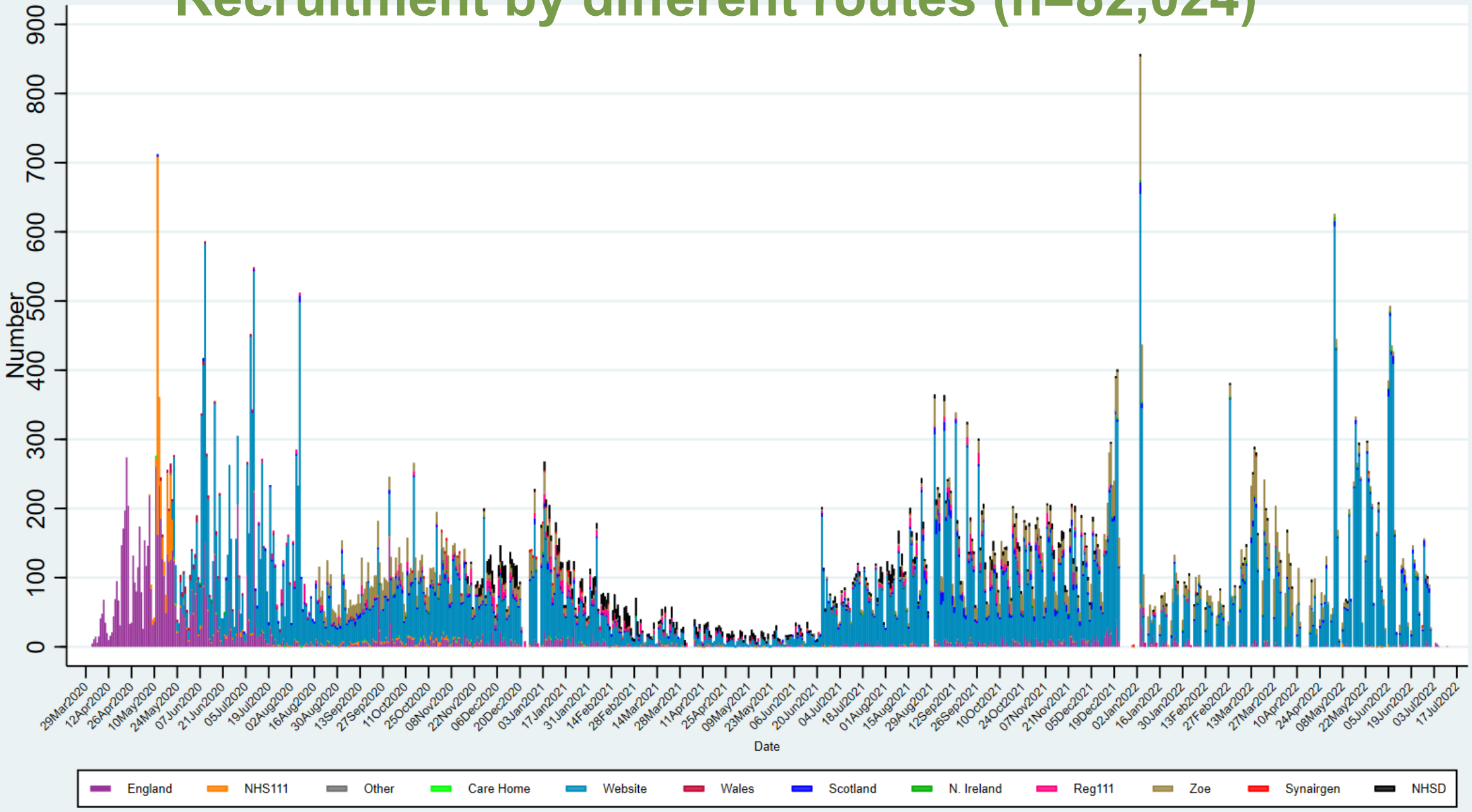
89 participants across 81 GP practices

Red = GP sites ; Blue = NHS unlinked sites; Orange = Zoe

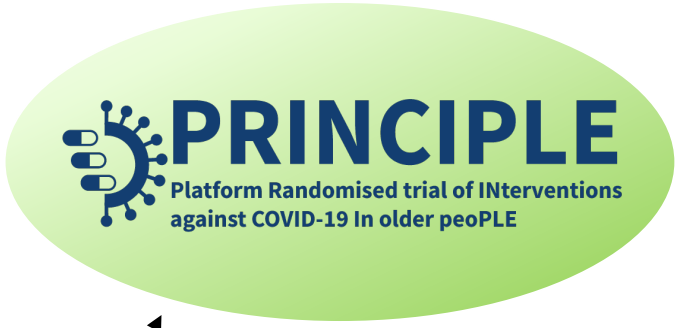
Daily new cases extracted from Zoe app (6 June 2021)



Recruitment by different routes (n=82,024)



Eligibility assessment



Contact GP practice

Queues

Refused to provide information

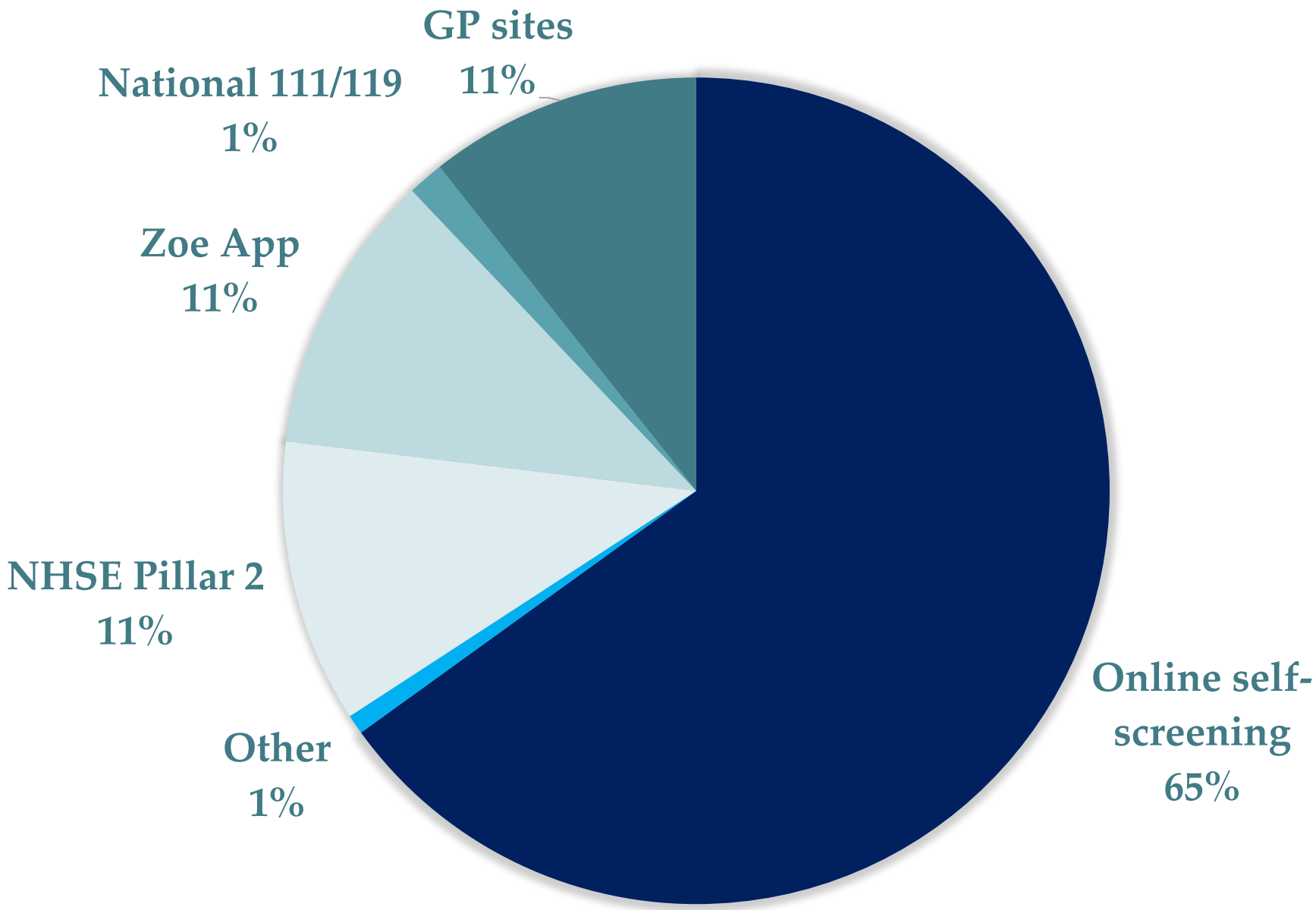
Not received the ICF

No answer/ response

NHSE SCR [Dec 2020]

- Summary Care Record
- Primary Care clinical record
- Patients in England
- Prescription information, allergies, long term conditions, key diagnosis, and recent notes
- Can be accessed remotely by authorised clinicians

Randomisation distribution by route (n=11,768)

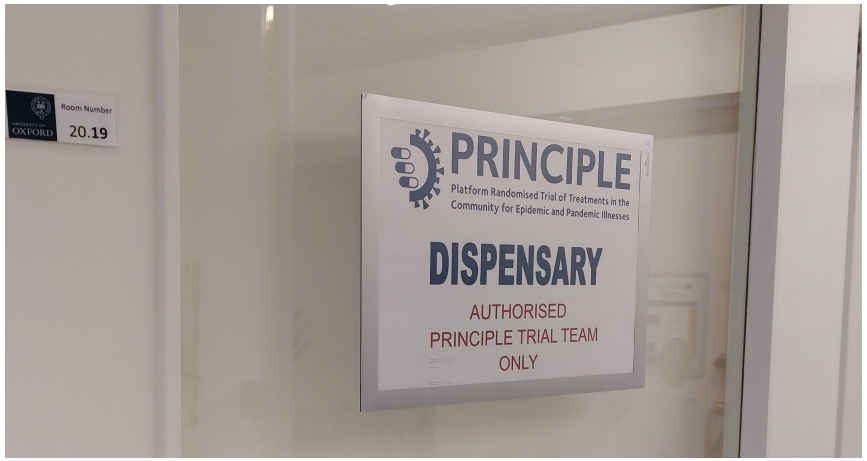


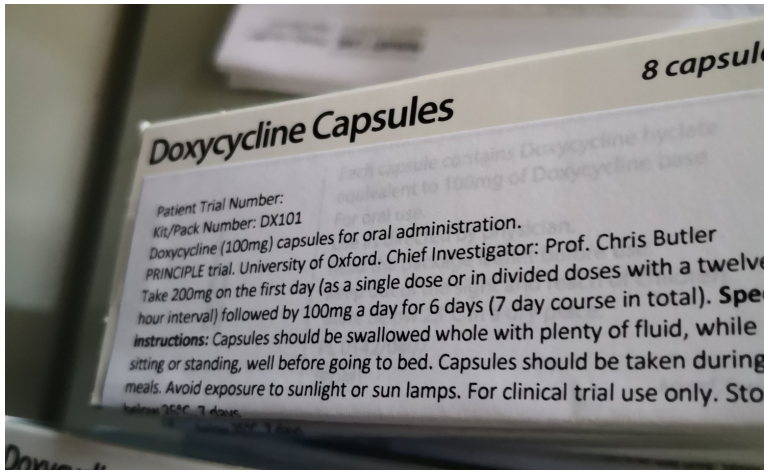
4,582 GP practices have recruited at least one participants to PRINCIPLE

IMP Delivery

- GP sites
- Local pharmacy
- CTU

- Over-labelling IMPs by clinicians
- Assembly and packaging
- Storage and handling (including distribution)
- Temperature controlled
- Need for exemption for each IMP within same trial
- MHRA exemption in place for over-labelling





Communications

- Patients
- Oversight Committees - what to share with who and how
  - Interim results
  - Co-primary outcome
- Re-stock of IMPs
- Dissemination of results
- MHRA, government, funder

Rapid Dissemination

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2020/040 15 December 2020

Azithromycin in the Management of COVID-19 (SARS-CoV-2) Positive Patients

Summary

Results of the RECOVERY trial, a randomised, controlled, open-label, adaptive platform trial, showed no significant clinical benefit of either oral or intravenous azithromycin in patients hospitalised with COVID-19. Compared with usual standard of care alone, azithromycin (administered once daily at 500mg either orally or intravenously, for up to 10 days) did not significantly decrease length of stay or 28-day mortality. In patients not receiving invasive mechanical ventilation at baseline, there was no difference between groups in the proportion of patients progressing to the composite endpoint of invasive mechanical ventilation or death.

It is therefore now recommended that azithromycin should NOT used in the management of confirmed or suspected COVID-19 infection in hospitalised patients unless there are additional indications for which its use remains appropriate (see Product Details). Within primary care the use of azithromycin and other antimicrobials, specifically in the treatment of COVID-19 infection, should be solely within the context of a trial.

The recommendation will be reviewed as further evidence becomes available, including from the PRINCIPLE trial.

Data Sharing

- Linkage data (NHS England)
- What can/can't share
- Data transfer

Expect the unexpected

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation m[illegible]ide, are b[illegible] widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Althoug[illegible]nerall[illegible]fe whe[illegible] used for approved indications such as autoimmune disease or malaria, the safety and bene[illegible]f th[illegible]treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine [illegible]oquine with[illegible]thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hospi[illegible]s in s[illegible]ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory [illegible]g for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagno[illegible]e included in [illegible]f four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor[illegible]ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed [illegible] control gr[illegible]. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or [illegible]ile they w[illegible]on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc[illegible]of int[illegible]t were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias ([illegible]tained or [illegible]ed ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) [illegible]OVID-19 were hospitalised during the study period and met the inclusion criteria. Of the[illegible] patie[illegible]were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with [illegible]macro[illegible]e, 3016 [illegible]eived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and [illegible]4 pati[illegible]in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple c[illegible]f four[illegible]ctors ([illegible] sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac[illegible], diabetes, [illegible]derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), w[illegible]mpared wi[illegible]ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95%[illegible]1·22[illegible]457), hydro[illegible]chloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, [illegible]18–1·531), [illegible]chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated [illegible]n an increased [illegible]f in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6[illegible]; 2·36[illegible]·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; [illegible]51, 2[illegible]0–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate[illegible]an inc[illegible]d risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretati[illegible] We w[illegible]unable[illegible]nfirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macro[illegible]on in[illegible]spital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospita[illegible]vi[illegible]reased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Funding William[illegible]vey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

[illegible]ed Online
[illegible]22, 2020
https://doi.org/10.1016/S0140-6736(20)31180-6

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See Online/Comment
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RETRACTED

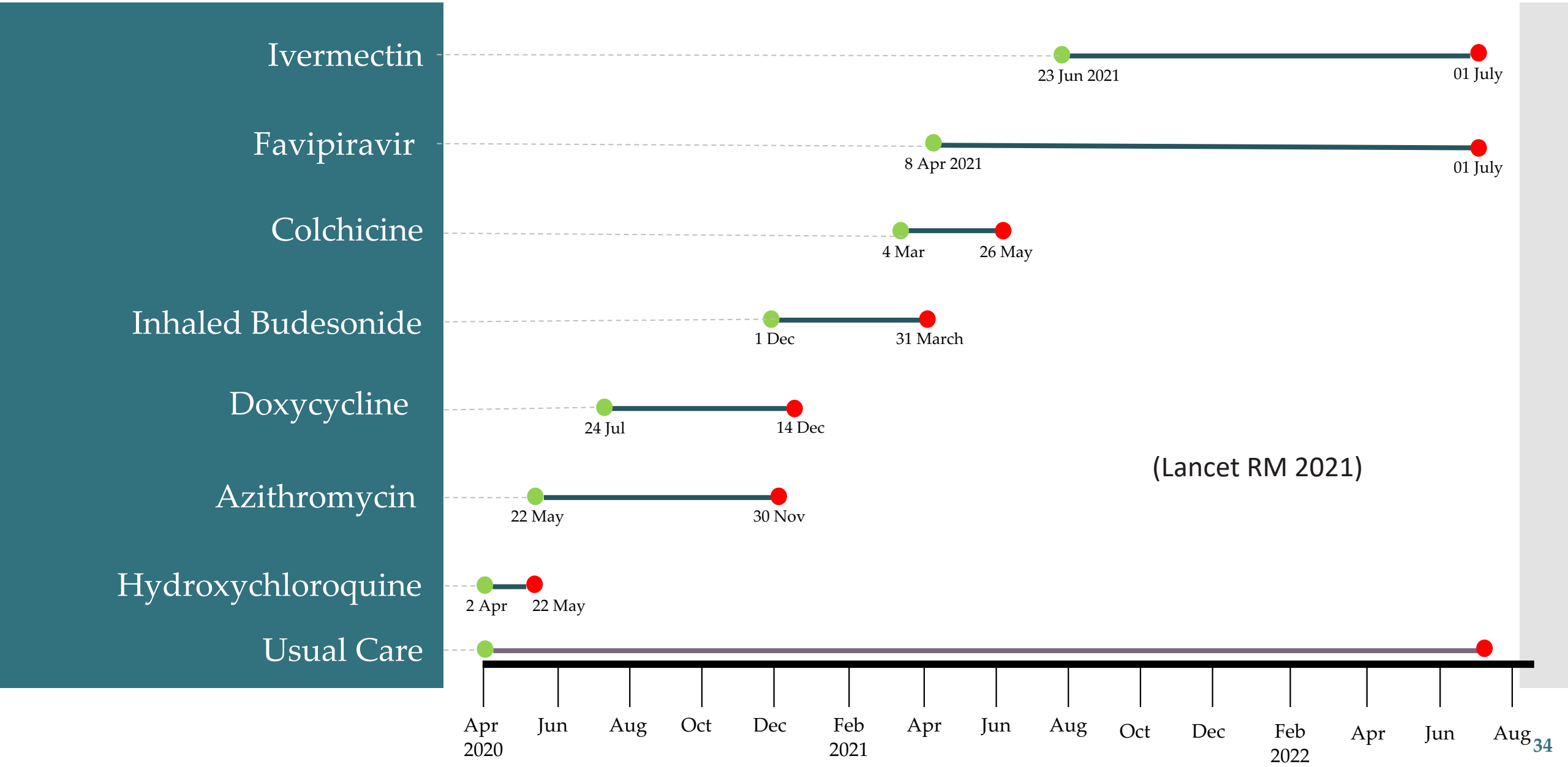
Expect the unexpected

GMP facility license

- MHRA reluctance to extend exemptions
- Desire to replicate/extend operations to other trials
- Lead to work on submission for an MIA(IMP) license in January 2021
- MHRA application submitted in November 2021, Full onsite inspection in August 2022, License approved January 2023

Treatment timeline in PRINCIPLE (n=11,768)

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



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HELP FIND EFFECTIVE EARLY TREATMENTS FOR COVID-19

Click to find out more

IF YOU WISH TO SIGN UP AS A PARTICIPANT:

Click to join the PANORAMIC Trial

Panoramic is a UK-wide clinical study sponsored by the University of Oxford and funded by the National Institute for Health and Care Research to find out in which people new antiviral treatments for COVID-19 in the community reduce the need for hospital admission and get better sooner.

We are recruiting volunteers, whether they have been vaccinated or not, to join PANORAMIC through this website, participating GP practices and other NHS sites across the UK.

PANORAMIC is open to everyone ***with ongoing symptoms of COVID-19 and a positive PCR or Lateral Flow test***, regardless of vaccination status.

You can participate in your own home from anywhere in the UK. No face-to-face visits are required.

Follow up will be by answering questions each day online and/or telephone calls with the study team, who will be there to support you throughout the study.

Recruitment

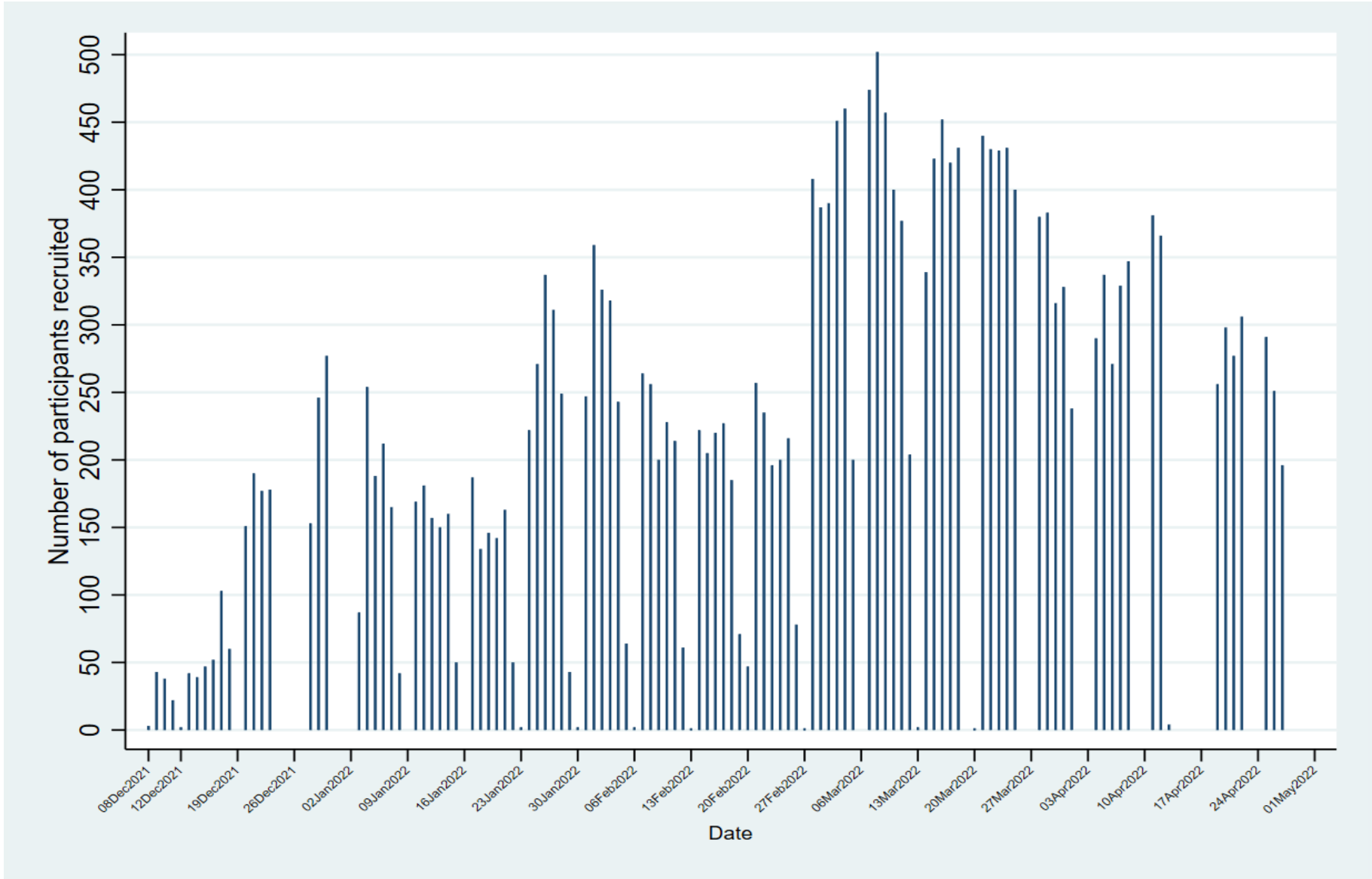
Participants: 27,930

Sites: 65

	PRINCIPLE https://www.principletrial.org/	PANORAMIC https://www.panoramictrial.org/
Recruitment	GP sites, Online self-screening, National 111, Zoe App, NHSE Pillar 2, Other	Hubs (GP sites, community trusts, other health service providers), Online self-screening
Screening	Medically qualified professional, research nurse	Medically qualified professional, prescribers, (research nurse)
Digital tools	In-house separate systems for eligibility, randomisation, database	External bespoke one single system
IMP delivery	CTU couriered to patients home	Pharmaceutical services company couriered to patients home
Data collection	28 days diary, 3, 6 and 12 months follow-up	28 days diary, 3 and 6 months follow-up. Virology data (self-swabbing) and HE data
Data linkage	NHS England only	All four devolved nations

Daily randomisation between December 2022- April 2023 (n=25,793)

PANORAMIC
Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community



> 6,500 GP practices have recruited at least one participants to PANORAMIC

Summary

- Learned a great deal!
- APT is not just about statistical methodology.
- Each intervention will have it's own challenges as well as the platform itself.
- Forward thinking
- Anything that can go wrong will go wrong - Murphy's Law!

Thank you!