COVER-ME Statistical Analysis Plan

1 Administrative information

Trial name:	Covid-19 vaccination coverage among underserved populations: Developing and Evaluating community-based interventions in East London minority ethnicity (ME) populations; underserved migrants and persons with low income (COVER-ME).
Trial registration number:	NCT05866237
SAP version:	0.8 (12-Sep-24)
Protocol Version:	5.0
SAP revisions:	
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Signatures:

2 Introduction

2.1 Background and rationale

This randomised controlled feasibility study was run to pilot a patient-engagement tool (PET) developed to increase COVID-19 and Flue vaccination uptake in underserved at-risk populations including migrants and persons with ethnic minority (EM) backgrounds in East London. The rationale was to assess acceptability and feasibility of the intervention: results will be used to plan a larger study to evaluate effectiveness.

2.2 Objectives

The primary objectives are to determine the feasibility, design, and implementation plan for a subsequent randomised controlled trial to evaluate the effectiveness of the PET for increasing uptake of COVID-19 and Flu vaccination.

The secondary objectives are to determine (i) an estimate of COVID-19 and Flu vaccination uptake, its variation by population group, and other parameters to design a subsequent randomised controlled trial; (ii) the feasibility and practicality of implementing the PET; and (iii) the appropriate level of support needed for health care providers at site-level to ensure successful implementation of the PET and to identify supporting activities needed to implement interventions for COVID-19 and Flu vaccinations.

3 Study Methods

3.1 Trial design

The PET was designed in qualitative work packages that preceded the feasibility trial. Eligible patients from six general practitioner (GP) practices from Tower Hamlets and Newham were individually randomised 1:1 to the intervention (PET) or control (routine care) during the study. The Appt-Health workflow tool was used, but patients in the control group did not receive additional (individual level) interventions outside routine; however some "cluster-level" interventions were used including posters in surgeries. Letter were used to invite patients with no device to receive sms invitation for flu vaccination.

To enable a comparison of the intervention to a control group at a practice level, we randomised GPs after they were recruited to the study. n=6 practices were randomised 1:1 to two groups of size n=3 vs. n=3. During a first study period, the first group of n=3 GPs received training, activation of the software, and patients were randomised. This happened for the second group of GPs in a subsequent study period.

A cluster-level analysis will use data from the first period in all n=6 GPs. The individual-randomisation comparison will use data from all GPs, with the second group contributing data from the second period only.

3.2 Randomisation

The practices were randomised in one block by the statistician, independent from the trial team. Individuals within each GP were randomised using simple randomisation in the practice software (reference: https://learn.microsoft.com/en-us/dotnet/api/system.random?view=net-8.0). This was done on the same day or shortly after the eligible list was determined. The randomised allocation was concealed to staff; patients were not told about arm beyond option to opt out – where they got the study information from a website.

3.3 Sample size

The sample size used was chosen based on calculations reported in the protocol (reference: COVID-19 vaccine uptake amongst underserved populations in East London protocol V5.0) and justified based on uptake.

3.4 Framework

- Primary analysis on uptake will report 95% CI, with no p-values to test superiority because this is a feasibility study that is not powered on superiority.
- Secondary analysis on other outcomes will use descriptive analysis.

3.5 Timing of final analysis

Final analysis will be done by September 2024 using a database with updated follow up (to >180 days for all).

4 Statistical Principals

4.1 Confidence intervals and P values

For the primary outcomes two-sided 95% confidence intervals will be used for uptake in each arm, and for the comparison between arms. For secondary outcomes confidence intervals (CIs) will be presented with no adjustment for multiplicity. For all other outcome point estimates, 95%CIs will be reported and no a priori statistical significance or decisions based on cut points for p-values will be used.

4.2 Adherence and Protocol deviations

The main protocol deviations to be summarised are patients who were randomised but did not meet inclusion / exclusion criteria (we expect this to be zero, as eligibility was determined prior to randomisation). The number and percentage of patients in each arm with this type of protocol deviation will be reported, as well as the number (%) of all other protocol deviations per patient; and in total.

4.3 Analysis populations

4.3.1 Intention to treat

This is all patients randomised, including withdrawals, with comparisons on the basis of randomised allocation.

4.3.2 Per-protocol population

This is all patients who consent, are randomised, do not withdraw, and receive the intended intervention.

5 Trial Population

5.1 Screening data

Public data on GP practice profiles will be collated (Fingertips), as will be the number of potential participants invited and opted out.

5.2 Eligibility

Eligible participants will be those aged 18 years or older and registered at study site (GP surgery), who are eligible for COVID-19 vaccination (i.e., are aged 75 years old or over, or live

in a care home for older adults, or are aged 6 months old or over and have a weakened immune system and have not received COVID-19 vaccination that season) or Flu vaccination (i.e., are aged 65 or over, or have certain long-term health conditions, or are pregnant, or live in a care home, or are the main carer for an older or disabled person or receive a carer's allowance, or live with someone who has a weakened immune system and those who have not received the seasonal Flu vaccination). This study is designed for underserved populations in East London, the underserved population group is defined as (i) non-white ethnicity; or (ii) resident in a postcode in the bottom 20% of index of multiple deprivation; or (iii) those receiving little or no income. Underserved population will be identified using (i) and (ii) as it is unable to assess (iii) in practice.

Patients were ineligible if they were unable or unwilling to consent (including those who did not consent to text messaging; those who opted out from taking part in research studies; and those who opted out from data sharing with NHS Digital national opt out).

5.3 Recruitment

Information to be included in the CONSORT flow diagram:

- The location (site),
- Vaccination group (COVID-19, Flu),
- Invitation method (COVID-19: sms; Flu: sms and letter), and
- Study period of each site.

Information on patients assessed for eligibility will not be recorded.

5.4 Withdrawal/ Follow-up

The number of withdrawals is expected to be very small. The number of participants who withdraw from the study after (opt-out) consent will be reported, and thereafter withdrawals separated by randomised allocation on an intention-to-treat basis. Timings of withdrawal will be the number (reporting only categories >0):

1. Between enrolment to 3 months follow-up, after receiving vaccination
2. Between enrolment to 3 months follow-up, not vaccinated
3. Between 3-6 months, after receiving vaccination
4. Between 3-6 months, not vaccinated
5. Between 6 months to end of study, after receiving vaccination
6. Between 6 months to end of study, not vaccinated

5.5 Baseline patient characteristics

The following baseline characteristics will be summarised:

- Demographics
  - Age (y)
  - Sex (male/female)
  - Ethnicity (all groups with >5 participants separately, <5 will be grouped as others)

- Index of multiple deprivation (decile)
- Comorbidities (yes/no)
- Indication for vaccination (recommended for COVID, FLU, or both)
- GP

Characteristics will be presented on an intention to treat basis. Categorical data will be shown with number and percentage. Continuous data will be shown as median and inter-quartile range, range. Some numerical data will be categorised (age, index of multiple deprivation, income) and shown as continuous and categorical summaries using cut points defined in this SAP. No p-values will be presented to compare baseline characteristics between the two groups. The summaries will be presented using a table (see appendix for dummy table).

6 Analysis

6.1 Outcome definitions

6.1.1 Primary outcome

The primary outcome is vaccination uptake in patients individually randomised. This will be measured as the number (percent) of relevant SNOMED codes in eligible patients. Uptake will be measured from the time that the eligible group in each practice is identified (and randomised) until 6 months follow-up (>180 days since randomisation).

6.1.2 Secondary outcomes

1. Vaccination uptake in patients after 3- and 9-months follow-up (>90 and >270 days). This will be measured as the number (percent) of relevant SNOMED codes in eligible patients identified during the period.
2. Mean vaccination rate after 3-, 6- and 9-months follow-up. This will be measured as the number of patients vaccinated divided by the follow-up time. Time is defined as time from randomisation until the earliest of vaccination, leaving the GP, withdrawal the consent of use of data, or death.
3. Acceptability of the intervention
    a. To patients: Proportion of patients randomised to the intervention who engage with the PET and / or linked patient resources, as determined by user statistics logged on the software for
        i. The SMS messaging tool (number of SMS sent)
        ii. Number (percent) of patients who view the linked patient awareness resources
        iii. Usage of the patient work list tool
    b. To staff: Number and proportion of eligible patients randomised to the intervention processed using the patient work list tool
4. Feasibility of the intervention and randomisation
    a. Number and proportion of eligible patients randomised
    b. Clinical capacity: number of slots available for vaccination bookings for each GP surgery and each day, by appointment time
5. Feasibility of the study design for a subsequent trial

a. Number and proportion of patients with all inclusion / exclusion data available on the electronic health records
b. Number and proportion of patients eligible for the intervention
c. Number and proportion of patients randomised who are sent material from the intervention (letter / sms)
d. Number and proportion of patients eligible by vaccination status (none, first, second, with booster or without booster)
e. Number and proportion of patients who opt out for their data to be used or withdraw from the study
f. Number and proportion of patients who consent for further questionnaires
g. Number and proportion of patients who are booked for a vaccination appointment
h. Number and proportion of patients who are categorised a “failed encounter” (not booked, no more action taken)

This list only includes quantitative endpoints in the protocol. There will be additional qualitative analysis of other points in the protocol.

6.2 Timing of outcome assessments

6.2.1 Timing of primary endpoint

Consent and uptake to vaccination will be determined based on patients having the vaccination done. The window to record this will be from the time that the eligible patient in each practice is identified and randomised until 6 months (180 days) follow-up. Follow begins when practices became live, and is the same time for each patient included from the same GP.

6.2.2 Timing of secondary endpoints

The number of patients having the vaccination done since randomisation until 3- (90 days) and 9-months (210 days) follow-up.

6.3 Analysis methods

6.3.1 Primary analysis

For the primary analysis, uptake of COVID-19 and Flu vaccination will be presented in each arm on an intention to treat basis. The Flu vaccination trial will have both sms and letter group combine as one trial.

We will assess the individual-level-randomised component. This analysis will include all patients who are eligible for the intervention, and who were randomised to receive one of two workflows on an individual basis (standard of care or the PET). All patients from first group of GPs (n=3) in both study periods, and only patients from second group (n=3) who are eligible in the second period (i.e., any eligible patient from first period in the second group of GPs who was vaccinated in the first period would not be part of the analysis sample) will be included. Uptake (from time of randomisation) will be estimated overall. Uptake 95% CIs will be obtained

based on binomial assumption, as well as from a mixed-effects model that allows for hierarchical (random effects) variation by GP. Logistic regression with adjustment described below will be used to estimate the marginal odds ratio of the PET compared with standard of care, and a profile-likelihood ratio confidence interval for the odds ratio will be reported.

6.3.2 Adjustments

Adjusted estimates will use:

- GP (categorical)
- Age (continuous)
- Sex (male/female)

6.3.3 Analysis of secondary outcomes

All outcomes will be reported as point estimates with 95% CIs as appropriate. Summary statistics for each outcome by arm will be presented on an intention-to-treat basis. Categorical data will be shown with number and percentage. Continuous data will be shown as median and inter-quartile range, or mean, standard deviation if approximately normal.

6.3.4 Subgroup analysis

Analysis of the primary and secondary endpoints and potential heterogeneity in uptake by subgroups specified below will be undertaken.

- GP
- Deprivation (decile)
- Age group (≥18-<65, 65-<75, ≥75y)
- Sex (Male/Female)
- Ethnicity (White, Black, South Asian, Other Asian, Mixed)
- Communication methods for Flu trial (sms, letter)

6.3.5 Exploratory analysis

We will explore vaccination uptake in patients after 9-months follow-up. We will explore the cluster-randomised component of this study. The population of analysis is those identified as eligible in both groups in the first study period, from the same calendar time. Analysis of uptake will take clustering in the design into account by using generalised linear models with (normal) random intercepts, and the model will also be used to obtain an estimate of the intra-class correlation coefficient. There are several methods to analyse cluster randomised trial data and we will also explore different models and assumptions in order to propose methods for the larger trial.

We will also explore whether a per-protocol analysis would be possible, by determining feasibility to define compliance / contamination from individual randomised allocation using process data. We will explore an analysis that makes use of the comparison between period 1 and period 2 in the n=3 GPs who are activated in the second period. This analysis may be

confounded by temporal effects so is treated as an exploratory analysis.

We will also adjust estimates using additional variables ethnicity and deprivation as an exploratory analysis.

6.4 Missing data

Most of the data will be complete by design, and data capture maximised where feasible. If the level of missing data is likely to affect reported point estimates and estimates of effect size then imputation will be used for analyses when appropriate (method chosen based on data), as well as complete-case analysis.

6.5 Additional analyses

No further analyses are pre-planned; but other exploratory analysis may be undertaken for example to assess robustness or help to explain findings.

6.6 Harms

Due to the nature and design of this study, safety reporting of adverse events will not occur and are not reported.

6.7 Statistical software

The analysis will be undertaken using the statistical software R (4.0 or greater) or STATA (17 or greater).

References

1. Randomisation software: https://learn.microsoft.com/en-us/dotnet/api/system.random?view=net-8.0
2. COVID-19 vaccine uptake amongst underserved populations in East London protocol V5.0
3. This statistical analysis plan is prepared following the SOPs:
    - Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337–2343. doi:10.1001/jama.2017.18556
    - SOP Barts CTU GEN ST01_Statistical Analysis Plan_V5.0_29_06_2021
    - SOP Barts CTU GEN TM06 Data Management V4.0 31032022

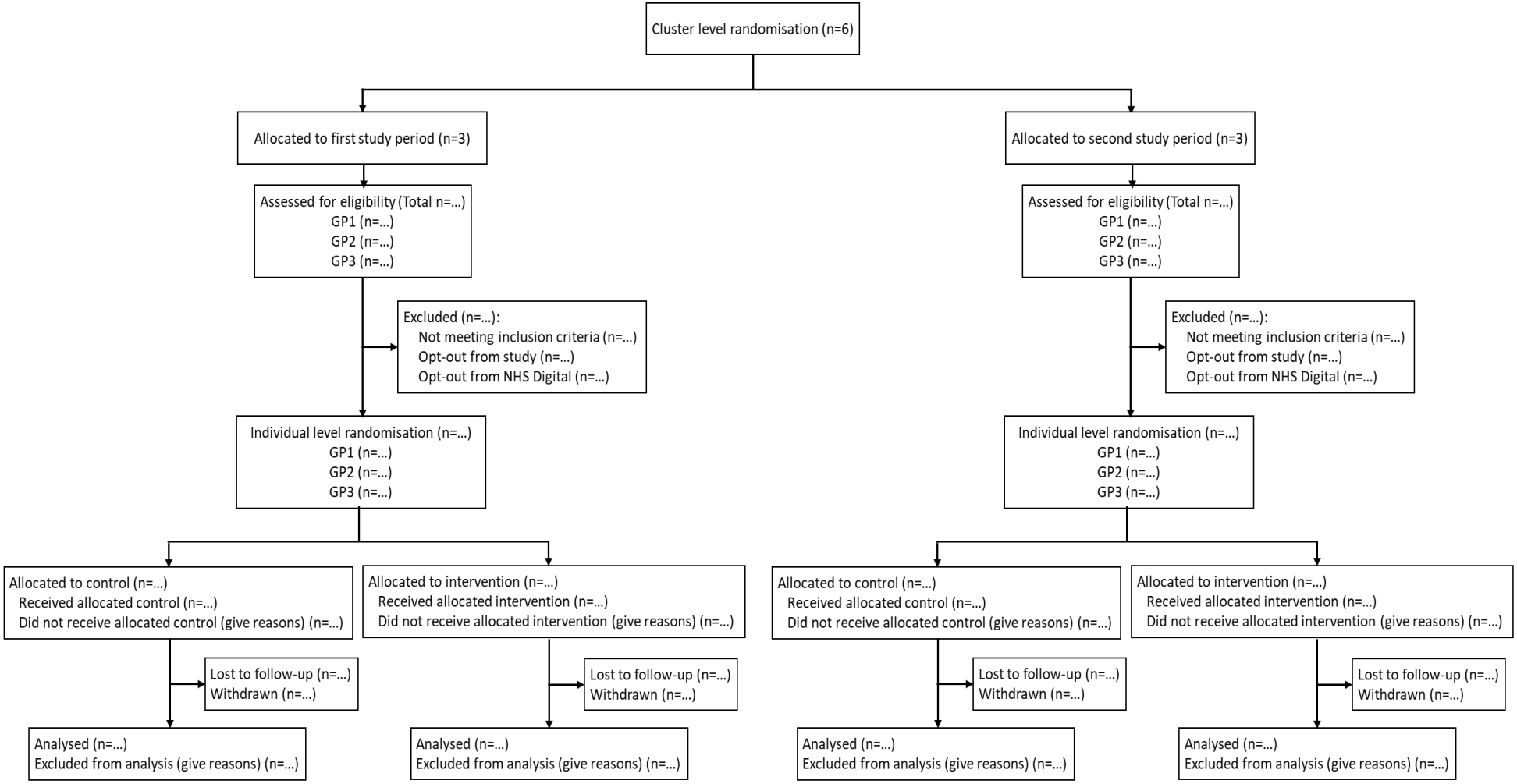
Appendix

1. Dummy tables

(a) Baseline characteristics

Variable	Overall	Control	Intervention
Age (years) (median, IQR, Range)			
Age group (n,%) – ≥18-<65 – 65-<75 – ≥75y			
Sex (n,%) – Male – Female			
Ethnicity (n,%) – White – Black – South Asian – Other Asian – Mixed			
Index of multiple deprivation (n,%) – 1 – 2 – 3 – 4 – 5			
Comorbidities (n,%) – Yes – No			
Indication for vaccination (n,%) – COVID – COVID & Flu – Flu			
GP (n,%) – GP1 – GP2 – GP3 – GP4 – GP5 – GP6			

2. Dummy Figures
   (a) CONSORT diagram


Cluster level randomisation (n=6)
Allocated to first study period (n=3)
Allocated to second study period (n=3)
Assessed for eligibility (Total n=...)
GP1 (n=...)
GP2 (n=...)
GP3 (n=...)
Assessed for eligibility (Total n=...)
GP1 (n=...)
GP2 (n=...)
GP3 (n=...)
Excluded (n=...):
Not meeting inclusion criteria (n=...)
Opt-out from study (n=...)
Opt-out from NHS Digital (n=...)
Excluded (n=...):
Not meeting inclusion criteria (n=...)
Opt-out from study (n=...)
Opt-out from NHS Digital (n=...)
Individual level randomisation (n=...)
GP1 (n=...)
GP2 (n=...)
GP3 (n=...)
Individual level randomisation (n=...)
GP1 (n=...)
GP2 (n=...)
GP3 (n=...)
Allocated to control (n=...)
Received allocated control (n=...)
Did not receive allocated control (give reasons) (n=...)
Allocated to intervention (n=...)
Received allocated intervention (n=...)
Did not receive allocated intervention (give reasons) (n=...)
Allocated to control (n=...)
Received allocated control (n=...)
Did not receive allocated control (give reasons) (n=...)
Allocated to intervention (n=...)
Received allocated intervention (n=...)
Did not receive allocated intervention (give reasons) (n=...)
Lost to follow-up (n=...)
Withdrawn (n=...)
Lost to follow-up (n=...)
Withdrawn (n=...)
Lost to follow-up (n=...)
Withdrawn (n=...)
Lost to follow-up (n=...)
Withdrawn (n=...)
Analysed (n=...)
Excluded from analysis (give reasons) (n=...)
Analysed (n=...)
Excluded from analysis (give reasons) (n=...)
Analysed (n=...)
Excluded from analysis (give reasons) (n=...)
Analysed (n=...)
Excluded from analysis (give reasons) (n=...)