Statistical analysis protocol for an evaluation of COVID Oximetry @home using a Generalised Synthetic Control approach

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PICOT

Population: individuals registered with a GP practice falling under the remit of a CCG in England and testing positive for COVID-19 who are either 65 years of age or older, or classed as clinically extremely vulnerable.

Intervention: delivery by a CCG in England of a COVID Oximetry @home (either pre-hospital or* step-down) pathway to its eligible population.

Comparison: CCGs in England which do not offer a COVID Oximetry @home (either pre-hospital or step-down) patient pathway.

Outcomes: CCG-level rates of occurrence within 28 days of a first positive COVID-19 test of: A&E attendance; emergency admission; critical care admission; mortality; hospital stay (in bed days).

Timings: subject to feasibility considerations† the study period is set to start on 19 October 2020 and end on 29 November 2020. The pre-intervention period lies between 23 March 2020 and the start of the study period. Depending on how long it takes for the pulse oximetry technology to become embedded into practice, a 'bedding-in' period of 1–3 weeks may be introduced following the start of the study period.

* Since interest for an evaluation was originally in the pre-hospital, rather than step-down, model of service delivery, the analysis will only focus on outcomes attributable to the former should available data permit.

† Outlined timings are based on the final (as of 31 December 2020) Academic Health Science Network onboarding returns from 135 CCGs in England implementing a CO@h pathway.

Background

Overview

Coronavirus disease 2019 (COVID-19) has led to many individuals in England suffering from severe health degradation, complications and deaths. One issue lies with people presenting to hospital with low oxygen saturation levels, often without accompanying breathlessness (silent hypoxia). Delayed presentation at secondary care of individuals with the infection can lead to prolonged hospital stay, invasive treatment in intensive care units (ICUs) being required and an increased risk of death.

Remote home monitoring models, some prescribing the use of pulse oximeters to monitor a patient's oxygen levels, have been implemented in several countries. The aim of these models is twofold:

- avoid unnecessary hospital admissions ('appropriate care in the appropriate place')
- escalate cases of health deterioration earlier to avoid invasive ventilation and ICU admission.

A systematic review of 17 remote home monitoring models implemented across seven countries found that most (15/17) were led by secondary care teams, with only two by primary care teams; 9/17 operated a pre-hospital service, 3/17 a step-down model and 5/17 both.[1] A pilot of remote home monitoring models, including the use of pulse oximeters, was launched in eight settings in England during the first wave of the pandemic. This showed variation in study design and implementation between sites.[2]

National roll-out of CO@h

National roll-out in England of the COVID Oximetry @home (CO@h) programme, consisting of the remote monitoring of oxygen saturation levels of people diagnosed with COVID-19 and at risk of health deterioration due to silent hypoxia, was originally planned for completion by the end of December 2020. In practice the introduction of the service was staggered over time and geography, with some delays being reported for several Clinical Commissioning Groups (CCGs) in ordering and allocating the technology across the population under their remit. On the other hand, since CO@h is not a mandatory intervention it need not be rolled out across a whole CCG but may only be offered within some of its sites.

According to the standard operating procedure,[3] individuals eligible for onboarding along a CO@h pathway are those symptomatic to and diagnosed with COVID-19, either clinically or via a positive test result, and (i) either 65 years of age or over, or (ii) clinically extremely vulnerable (CEV) to COVID-19. It is understood that the model of CO@h delivery is primarily implemented in primary care; referrals may additionally be received from the NHS111 COVID Clinical Assessment Service, NHS Test and Trace and Accident & Emergency (A&E) hospital departments. After referral (ideally on the same day) [Stage 1] patients will undertake a standard assessment [Triage – Stage 2], including where possible a baseline pulse oximetry reading. Patients entering the CO@h pathway [Onboarding – Stage 3] will then be provided

with a pulse oximeter and supporting information. This should be done immediately if the assessment takes place face to face or within 12 hours of presentation if a patient is assessed remotely. Patients are encouraged to record three oximeter readings a day; patients should receive text or email prompts or check-in calls [Monitoring – Stage 4]. If patients do not show signs of health deterioration within 14 days of onset of symptoms, they are discharged from CO@h [Recovery and Discharge – Stage 5]. This period can be extended (if a patient remains symptomatic and after further clinical assessment) or shortened (if a patient's COVID-19 test comes back negative).

It is estimated that 4% of the population in England are CEV, and that approximately 2.4% of the population are CEV and 65 years of age or under. The Chief Medical Officer (CMO) for England, working with the devolved administrations and other senior clinicians, asked NHS Digital (NHSD) to produce a list of vulnerable people at high risk of health complications from COVID-19. The CMO may request at any time that a new high-risk category (for instance people with end-stage kidney disease or adults with Down's Syndrome) be added to the list. NHSD will then add a flag to patient records of individuals falling into the category. Separately, hospital specialists may review this list and identify additional patients falling into high-risk categories. These data are submitted to NHSD and then automatically included into patient records. In addition, GPs are required to periodically review the list to identify registered patients to be added to or removed from it. These additions and subtractions are managed through SNOMED CT codes.

Patients are normally added to the CEV to COVID-19 list through an automated process, based on information from patient records. However, since reviews by GPs and hospital specialists may lead to patients being included into or excluded from the list, clinical judgement may also influence the process, thus bringing into consideration multiple additional COVID-19 risk factors. As long as these patients are flagged as CEV in the General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR) data set, they can be identified from the data.

CO@h is also available to care home residents; the CO@h diary for recording oxygen readings has been tailored for care home usage.

Other related interventions

Vaccinations

The roll-out of COVID-19 vaccinations in England started on 8 December 2020.[4] The order of priority for vaccination is, as of 11 February 2021:

1. Residents in a care home for older adults and their carers
2. Individuals 80 years of age or over and front-line health and social care workers
3. Individuals 75 years of age or over
4. Individuals 70 years of age or over and CEV individuals
5. Individuals 65 years of age or over
6. Individuals 16 to 64 years of age with underlying health conditions which put them at higher risk of serious complications and mortality
7. Individuals 60 years of age or over
8. Individuals 55 years of age or over
9. Individuals 50 years of age or over

The target is to vaccinate everyone in the four highest priority groups by mid-February 2021.[5]

COVID virtual wards

COVID virtual wards, providing additional support at home (including, but not limited to, pulse oximeters) to patients hospitalized with COVID-19 were introduced at the end of December 2020 – the first pulse oximeters were sent on 23 December 2020 to West Berkshire Community Hospital – and are rapidly being rolled out across the country. The Academic Health Science Network (AHSN) has already started to map this implementation across the country. The COVID-19 Daily Patient Discharge SitRep is being amended by NHSD to include numbers of people discharged to a COVID virtual ward and should become operational by the end of January 2021.

CO@h is a complementary but separate programme to COVID virtual wards, which will therefore not fall within the scope of the present evaluation. COVID virtual wards target emergency hospital patients with higher acuity or complex conditions in a hospital supervised setting, and aim for early supported hospital discharge and safe admission avoidance.[6] At present it is not anticipated that sites offering a CO@h pathway will run out of pulse oximeters due to competing demand from COVID virtual wards.

PRINCIPLE trial

The PRINCIPLE trial is a national clinical study from the University of Oxford to find COVID-19 treatments for individuals of 50 years of age or over that can be taken at home. It is designed to contrast the effect among its participants of usual care with that of usual care combined with inhaled budesonide (a commonly used inhaled corticosteroid). Patients eligible for

enrolment are individuals either symptomatic to or testing positive for COVID-19 within the previous 14 days, who are either 65 years of age or over or are 50 to 64 years of age with predefined underlying health conditions, in part overlapping with those populating the CEV to COVID-19 list. Enrolment to PRINCIPLE started on 17 April 2020; as of 11 February 2021, 4,053 patients had been recruited to the trial.

Aim of the evaluation

The IAU will carry out two separate impact evaluations: one informed by patient-level data, and another exploring the impact of CO@h at CCG level. The latter is the subject of the remainder of this document.

More specifically, this evaluation aims to quantify the impact during the second wave of the COVID-19 pandemic of the roll-out by CCGs in England of pulse oximeters for the early detection of silent hypoxia and rapid health deterioration signs among eligible patients diagnosed with COVID-19. This will be achieved by contrasting differences in hospital activity and mortality within 28 days of a positive COVID-19 test, recorded weekly throughout the evaluation study period, between CCGs providing either a pre-hospital or a step-down CO@h pathway and CCGs which do not.

A population-level approach to evaluation

The use of pulse oximeters for remote monitoring of high-risk individuals with a COVID-19 diagnosis is taking place in a growing number of GP practices and community teams in England.[7] More specifically, a clinical pathway using pulse oximetry technology for remote monitoring is being rolled out by CCGs in England not only in primary and community health care settings (primary care remote home monitoring model), but also to patients being discharged from A&E departments (secondary care model) or from hospitals (step-down model).[1] Originally, interest in a CO@h programme evaluation was confined to a pre-hospital model of service delivery; however limitations expected in the collection of onboarding patient-level data will likely prevent (reliable) identification of the type of pathway entered by CO@h service recipients. As such, the present evaluation will encompass both the pre-hospital and step-down models of delivery, unless robust data enabling their separation are made available: in this event, the evaluation will focus on the pre-hospital model of CO@h delivery as originally intended.

A programme evaluation at CCG level may proceed by comparing on a range of outcomes CCGs offering their eligible patient population a CO@h pathway (treated or intervention units) over a pre-fixed period of time (the study or follow-up period) with those CCGs not concurrently providing the technology (untreated or control units). The start and length of the follow-up period should be suitably chosen to ensure that by its end there remains a large enough pool of control CCGs in England from which to carry out a meaningful outcome comparison. Outcomes chosen to inform this comparison would comprise selected secondary care and mortality indicators, which will be retrospectively collected from national

administrative data – notably the Secondary Uses Services (SUS) database[8] and Office for National Statistics (ONS) data[*] – and suitably aggregated from patient-level records to CCG-level rates.

The effect on a given outcome of the CO@h intervention implemented in a treated CCG at a given time following its introduction (post-intervention or study follow-up period) can be quantified by the change (if any) detected in the CCG at that time between, on one hand, the outcome rate that was actually recorded and, on the other, what would have been hypothetically observed had the CCG not implemented a CO@h pathway (the counterfactual). As is invariably the case in programme evaluation assessments relying on retrospectively collected data, the counterfactual cannot be observed in practice; as such it needs estimating. A variety of statistical strategies have been proposed in comparative effectiveness research to estimate a counterfactual; the present evaluation will rely for this purpose on the Generalised Synthetic Control (GSynth) method.[9] This was chosen due to its generality: it builds and improves on traditional approaches (notably Difference in Difference) relying on somewhat restrictive assumptions; its ability to flexibly accommodate time-varying observed as well as unobserved effect confounders; and for yielding estimates of the uncertainty around the counterfactual it produces.

Once a counterfactual is derived for each CCG implementing a CO@h pathway during the evaluation follow-up period, an estimate of the impact at a given time of the CO@h initiative across treated CCGs (the average treatment effect among the treated, or ATT) will be obtained by averaging across treated CCGs the effect estimates obtained for the corresponding period. Lastly, an overall estimate of the impact of CO@h in CCGs where it is implemented can be obtained by averaging previously derived impact estimates over the evaluation follow-up period.

Methods

Study design

The choice of follow-up period will be instrumental in identifying the treated and control CCGs whose outcome comparison will inform the CO@h impact assessment. Up-to-date details on the stage of service operation reached by CCGs in England will be collected and used to determine an intervention start and end date enabling reasonably sized sets of comparator CCGs. The final start and end date will be determined from the latest, most reliable data available at the start of the analysis.

According to the latest available onboarding information on the CO@h roll-out across the country, there are 12 CCGs offering a fully operational CO@h pathway to the eligible population across their patch between 19 October 2020 and 29 November 2020[†]. Of these, three will not be retained in the analysis as their CO@h service was established before the onset of the second pandemic wave (ie prior to September 2020), thus leaving nine treated CCGs[‡] to inform the evaluation. Setting the start and the end of the evaluation follow-up

* Source: Office for National Statistics (www.ons.gov.uk).

† Source: Academic Health Science Network data on CCGs in England implementing a CO@h pathway. 31 December 2020.

‡ As of 31 December 2020 these are identified as: Oldham CCG; Heywood, Middleton and Rochdale CCG; Cheshire CCG; Salford CCG; Southampton CCG; West Hampshire CCG; Dorset CCG; North Hampshire CCG; and South Eastern Hampshire CCG.

period at those dates would correspondingly result in 98 other CCGs in England being documented as not providing their patients with the intervention before or during those respective time periods.* This in turn results in a pre-intervention period of 30 weeks and a study follow-up of 6 weeks. In addition, depending on information available on the friction that the introduction of pulse oximetry technology into common practice may encounter, a 'bedding-in' period of 1–3 weeks may be assumed following the start of the study period, whose data will be discarded from the evaluation.

For the purpose of the evaluation, a CCG will be considered as an intervention unit once it offers a fully operational CO@h pathway to its eligible population. Conversely, only CCGs that by a given point in time have not yet implemented a CO@h service will form part of the control pool of CCGs at that time. As mentioned in the National roll-out of CO@h section, CO@h is not a mandatory intervention at primary or secondary care level; as such, it might not be rolled out across an entire treated CCG. Should this classification of a CCG as a treated or control unit lead to the exclusion of too many CCGs to meaningfully inform an evaluation, the analysis will be limited to the areas within a CCG offering a CO@h service or, if needed, will be conducted at an appropriately lower level than CCG (eg by GP practice).

The period of time preceding the national roll-out of the CO@h intervention (the pre-intervention period), over which data on a variety of CCG-level characteristics will be sourced, is assumed to start on 23 March 2020 and will end at the chosen intervention start date. Data on preselected secondary care outcomes and other prognostic, socio-economic and demographic characteristics (covariates) will be collected at patient level from the population eligible for the intervention at each week spanned by the evaluation†. Hospital activity and mortality recorded within 28 days of a positive COVID-19 test will be allocated to the week of the positive COVID-19 test in the follow-up period. Covariates will then be aggregated to weekly counts at CCG level for each examined treated or control CCG in England, and in turn converted to rates (per 1,000 or 10,000 people as appropriate) over the size of the eligible CCG population to inform the subsequent counterfactual analysis. The final analysis data set will thus report longitudinal CCG-level outcome and covariate rates for all treated and control CCGs, spanning on a weekly basis the chosen evaluation follow-up period.

A formal comparison of outcome rates between treated and control CCGs will proceed by applying the GSynth approach to regression-based adjustment for observed time-varying differences in patient case-mix, CCG characteristics and pre-intervention outcome trends to obtain a counterfactual (the 'synthetic control') for each treated CCG at each post-intervention week for each outcome. Risk adjusted counterfactual outcomes will then be compared to the actual CCG-level outcome correspondingly recorded at each week of the post-intervention period to obtain an estimate of the weekly ATT for that outcome at that CCG. These estimates will then be aggregated across all treated CCGs in England, and finally averaged over the post-intervention period, to derive an overall estimate of CO@h impact at national level on the eligible population over the study follow-up.

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* The sizes of the treated and untreated CCG pools corresponding to the proposed intervention start and end dates were determined from the earliest dates in the Academic Health Science Network returns, based on respectively a fully operational and go-live implementation of locally established CO@h services.

† The evaluation aims to produce impact estimates on each examined outcome for all treated CCGs on a weekly basis, contingent on a sufficient rate of occurrence of outcomes events at CCG level; failing this requisite, coarser timescales (eg bi-weekly) will be attempted.

Study cohort

In line with the CO@h standard operating procedure,[3] the target population for the evaluation consists of individuals registered with a GP practice in England, testing positive for COVID-19* and either 65 years of age or over or classed by a clinician as CEV. Individuals in the target population are eligible for receipt of a pulse oximeter for home monitoring of silent hypoxia and health deterioration attributable to COVID-19. The evaluation excludes individuals not registered with a GP practice, not in possession of an NHS number, or any other unlinked records.

The study cohort consists of individuals in the target population whose CCG has provided either a pre-hospital or a step-down CO@h pathway throughout the follow-up period (ie up to and including 29 November 2020), or did not implement such an initiative during the pre- and post-intervention periods (ie from 23 March 2020 to 29 November 2020). CCGs that ceased to exist (typically as a result of mergers), or either initiated or halted delivery of the intervention during the study period, are excluded from the analysis. Given that the evaluation uses hospital activity data for continuous inpatient spells (CIPS) and A&E attendances, the study cohort is drawn from the entire target population regardless of whether individuals actually attended hospital for treatment. This allows the capture of variations in secondary care utilisation as well as changes in the composition of hospital resources being utilised during the study follow-up period.

Sources of data

The following pseudonymised, linked data sources will be used:

- **General Practice Extraction Service (GPES) data.**† Data for pandemic planning and research (GDPPR). Provides baseline data on patients registered in 97.5% of all GP practices in England.
- **Second Generation Surveillance System (SGSS) data.** SGSS is the national laboratory reporting system used in England to capture routine laboratory data on infectious diseases and antimicrobial resistance. Data on a first COVID-19 serologically positive test will be used to identify the study cohort.
- **Academic Health Science Network roll-out progress data.** This details information (final as of 31 December 2020) around dates, stage of operation and model of delivery of CO@h service implementations in CCGs across England. An updated data sheet is expected from the AHSN by March 2021.

* Although individuals eligible for onboarding to a CO@h pathway are technically required to be either clinically or serologically diagnosed with COVID-19, the evaluation adopts a stricter definition due to the unavailability of reliable dating information on clinical diagnoses.

† Source: General Practice Extraction Service (GPES) Data for Pandemic Planning and Research - Management Information (MI). September 2020 (https://digital.nhs.uk/binaries/content/assets/website-assets/coronavirus/gpes-data-for-planning-and-research/gdppr-data-coverage-sept2020.xlsx).

- **CO@h onboarding data.** This includes the date for each patient onboarding to a CO@h pathway. Onboarding data was to be collected across all CCGs from 1 December 2020; for those CCGs that implemented the intervention earlier, data may be collected retrospectively from 1 October 2020. A descriptive analysis will be carried out, notably around establishing the source of referral based on a comparison between onboarding date and date of hospital activity, to examine, if possible, the distribution of CO@h delivery models within a CCG.
- **Secondary Uses Services (SUS) data.** This is the national collection of individual-level health care data required by hospitals and used for planning health care, supporting payments, commissioning policy development and research data. This will provide patient-level records on hospital activity outcomes like emergency admissions and hospital bed days.
- **Emergency Care Data Set (ECDS) data.** This will provide information about A&E attendances.
- **ONS statistics on COVID-19 mortality.** This will provide individual-level records on mortality within 28 days of a COVID-19 diagnosis.
- **Care home residency identifiers.** These individual-level data are derived from patients' GP registration data; they will help informing a subgroup analysis of the study cohort residing in a care home during the study follow-up.
- **CCG reference data.** These data describe key characteristics of CCGs in England, collected from publicly available sources. They are used to profile both treated and control CCGs in England to build the respective synthetic control CCGs and/or to carry out risk adjustment. Data sources are:
  - NHS Digital. Number of patients registered at a GP practice. March 2020 to November 2020.
  - Office for National Statistics. Census 2011.
  - Office for National Statistics. Mid-year population estimates. 2020.
  - Office for National Statistics. Lower Layer Super Output Area (LSOA) population density. Mid-2019.
  - Ministry of Housing, Communities and Local Government. English indices of deprivation. 2019.
  - Care Quality Commission. CQC Care Directory. 23 March 2020 and 29 November 2020.

Variables are recorded at either GP practice or LSOA level. Variables available at LSOA level will be mapped to GP practice level according to the LSOA of each patient registered at the GP practice. Variables available at GP practice level will be aggregated to CCG level and rescaled according to the average size of the population registered to each GP practice testing positive for COVID-19 in a given week. Missing data will be imputed using the latest available value in time or, where appropriate, more suitable imputation methods. Hospital activity data will be obtained from de-identified (ie anonymised in line with the Information Commissioner's Office code of practice on anonymisation) SUS extracts.

A&E attendances referring to patients who left before being visited or declined treatment, or for whom there is a duplicate visit record, will be excluded. Inpatient data are structured into CIPS which may consist of several consultant episodes (since patients may be under the care of multiple consultants during a hospital stay) and stays at multiple hospitals (if patients are transferred). Spells that are missing an admission date, or where the discharge date preceded the admission date due to data quality problems, will be excluded. A&E visits and spells with gender not recorded as either male or female will also be excluded: although these records (where not missing altogether) may be considered valid, their disambiguation causes technical difficulties at a data set linkage level as well as for counterfactual modelling purposes.

Study endpoints

- A&E attendance rates within 28 days of a first positive COVID-19 test
- Emergency admission rates within 28 days of a first positive COVID-19 test
- Critical care admission rates within 28 days of a first positive COVID-19 test
- Hospital bed days rate following an emergency admission within 28 days of a first positive COVID-19 test
- Mortality within 28 days of a first positive COVID-19 test

Statistical methods

Selecting treated and control CCGs

As of 1 April 2020 there are 135 CCGs in England.[10] Once those offering a CO@h pathway throughout the designated study follow-up have been identified from AHSN data, a selection process aimed at determining a list of most similar control CCGs to each given treated CCG on a range of key characteristics will be conducted. This is recommended to avoid synthetic control CCGs, which will be estimated via the GSynth approach, from being unduly influenced by spurious heterogeneities caused by unlikely comparable untreated CCGs. In comparative effectiveness analyses it is generally advisable, when building a counterfactual, to only retain potential control units that are sufficiently similar on pertinent aspects to a treated unit. As such, unless in practice it turns out that by the intervention start date there are relatively few CCGs delivering a CO@h pathway compared to those not offering it, a method to identify untreated CCGs that are most comparable to the set of treated ones on broad characteristics is required. In this case, to assess similarity between treated and control CCGs an adaptation of the method used in NHS England's RightCare Similar 10 CCG Explorer Tool* will be adopted. This method measures similarity by computing the squared Euclidean distance (SED) between each pair of treated and control units across a set of variables, with a lower SED indicating

* The Similar 10 CCG Explorer Tool calculates the 10 most similar CCGs in England for a given CCG. See www.england.nhs.uk/publication/similar-10-ccg-explorer-tool.

greater similarity.* In brief, selected variables are first standardised, using inter-decile range standardisation, by subtracting the median and dividing by the difference between the 90th and 10th percentiles.† The SED is then calculated as the sum of the squares of the differences between these corresponding standardised variables. The RightCare method assesses similarity across 12 demographic indicators derived from publicly available reference sources: these include indicators relating to deprivation, population size and density, age structure and ethnic mix. To these, additional publicly available variables will be added as well as variables derived from SUS data which characterise the hospital activity, disease prevalence and comorbidity of patients with hospital use over time for the whole CCG population (Table 1).

The described method will be applied to compute the SED between all pairs of treated and control CCGs and use these values to order the control units in terms of decreasing overall similarity. Depending on an inspection of the distribution of SED values across the pool of candidate CCGs, a cluster of appropriate size of untreated CCGs most similar to a given intervention CCG will be retained to inform the counterfactual building process for the latter. The final set of control CCGs to be used as a comparator to the set of treated CCGs in the evaluation of a given outcome will thus be formed by the deduplicated union of the lists of most similar untreated CCGs separately derived for each treated CCG. Separate sensitivity analyses may be performed to assess the robustness of ATT estimates ensuing from the selection of at most 50% more and fewer most similar candidate control CCGs for each treated CCG, subject to the availability of a large enough pool of untreated CCGs for every CCG rolling out a CO@h pathway.

Hospital activity trends aggregated over time, as well as socio-economic and demographic characteristics of either treated or control CCGs in England, will be inspected in order to detect anomalous patterns. Such anomalous CCGs will be discarded from the analysis, together with CCGs which:

- have inconsistently implemented a CO@h pathway during the post-intervention period
- did not provide full service coverage of their geography, or
- onboarded a low number of patients to a CO@h pathway (subject to the availability of this information).

Moreover, to avoid introducing biases in the subsequent synthetic control-based outcomes comparison, CCGs known to be implementing a remote monitoring programme other than, but comparable to, pulse oximetry will be excluded from the evaluation.

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* Suppose there are I units and K baseline variables. Let $\tilde{x}_{ki}$ represent the standardised version of x_{kj} where x_{kj} is the kth, baseline variable in unit i, i=1, …I, k=1,…,K. Then the SED between unit i and unit j is calculated across K baseline variables as $SED_{ij} = \sqrt{\sum_{k=1}^{K}(\tilde{x}_{ki} - \tilde{x}_{ki})^2}$ for i, j<I, i≠j.

† The standardised value of baseline variable x_{kj} is calculated as

$$\tilde{x}_{kj} = \frac{x_{kj} - median(x_{1j}, x_{2j}, \dots, x_{Kj})}{90th\ percentile(x_{1j}, x_{2j}, \dots, x_{Kj}) - 10th\ percentile(x_{1j}, x_{2j}, \dots, x_{Kj})}$$ §

Creating synthetic control CCGs

The GSynth approach will be applied to model aggregate CCG-level outcome rates in the treated and control groups (of most similar or potentially all CCGs), after adjusting for differences in time-varying characteristics (eg CCG characteristics, patient case-mix and pre-intervention trends in outcomes). The GSynth method will provide an estimate of counterfactual (risk adjusted) outcome rates for each CCG rolling out a CO@h pathway during the post-intervention period. Time-varying (observed) characteristics whose inclusion in the model is warranted by their significant influence on a given outcome will be identified by graphical inspection of longitudinal trends.

For the examined outcomes, two possible groups of risk adjustment variables can be devised:

- **A&E attendance, emergency admissions and mortality outcomes (Table 2).** When looking at A&E attendances, emergency admissions or deaths, all patients in the target population are relevant for risk adjustment purposes. Characteristics adjusted for could include age, gender, ethnicity and education degree, which are all derived from publicly available information at CCG level.
- **Hospital bed days following emergency admission (Table 3).** Here only the characteristics of those patients from the target population with an emergency admission on record are relevant for risk adjustment purposes. These could include age, gender and ethnicity, as well as prevalence indicators for a range of health states typically assessed in primary care among patients experiencing an emergency admission.

Subgroup analyses

The following subgroup analyses will be carried out, subject to feasibility considerations relating to adequate sample sizes and outcome rates being available:

Care home residents. This subgroup may be of interest within the wider older population in that the handling of pulse oximeters and submission of oxygen saturation readings from individuals in this subgroup is expected to be facilitated by care home staff.

Individuals 75 years of age or older not residing in a care home. Unlike in the case of care home residents, it is expected that individuals in this subgroup may find the operation of an allocated pulse oximeter technically challenging. The age threshold may be altered to meet minimal data availability requirements or in recognition of early findings for the concurrent qualitative assessment of CO@h evidence.

CEV patients, according to the definition set by Public Health England.*

* See www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19.

Sensitivity analyses

- Expanding and shrinking by at most 50% the list of most similar potential control CCGs – provided there is a sufficient number of them available – to be used for impact estimation on each outcome of interest. This analysis is intended to shed light on whether any impact estimate produced by the main evaluation is sensitive to the composition of the control CCG pool underpinning it.
- Setting an earlier intervention start date and/or later end date, contingent on adequate CCG sample sizes and outcome rates considerations. This approach is aimed at detecting whether anticipatory effects exist ahead of a CO@h implementation by some CCGs or if the impact assessment derived from the main evaluation is affected by incorporating additional data from a longer follow-up.
- Reporting effect estimates from crude analyses (no risk adjustment). This modelling approach sets out to explore the influence of relevant covariates on impact estimates obtained from the main analysis.

Limitations and sources of bias

Limitation	Implication	Mitigation
Threats to internal validity		
Known interventions concurrently influencing outcomes among individuals eligible for a CO@h pathway: specifically the PRINCIPLE trial COVID virtual wards.	PRINCIPLE participants allocated to the treatment arm are administered inhaled budesonide. This may lead to this population subgroup showing different outcomes than those instead receiving usual care, leading to potentially biased impact estimates. Both CO@h and the COVID virtual wards programmes are expected to impact in particular on length of hospital stay outcomes; as such, corresponding intervention effects may not be discernible from patients in receipt of both.	Findings from the evaluation need to be interpreted by keeping in mind that PRINCIPLE participants cannot be distinguished from non-participants from available evaluation data. The study period of this evaluation was chosen to end before the start of the roll-out of COVID virtual wards, which therefore could have not yet shown an impact.
Control CCGs have fundamentally different outcome and/or covariate values to the treated ones.	Unable to identify a suitable synthetic control that provides a sufficiently good fit in the pre-intervention period. Unsuitable synthetic control may lead to extrapolation biases.	Ensuring adequate similarity between treated and control CCGs, provided sufficient numbers especially for the latter are available. Checking sensitivity to number and mix of CCGs in control group.
Available data do not allow distinguishing between outcomes of patients entering the pre-hospital and step-down models of CO@h pathway.	The analysis will not yield estimates specifically around the impact of the pre-hospital CO@h service type, which was originally intended to be the sole focus for an evaluation.	Findings from the evaluation – in particular on length of hospital stay – need to be interpreted with caution as they cannot be decoupled by type of delivery model.

The risk adjustment model does not accurately account for differences between treated and control CCGs.	Inability to control for observed and unobserved confounders will lead to biased estimates.	Ensuring adequate similarity between treated and control CCGs, provided sufficient numbers especially for the latter are available. Checking sensitivity to variables included for risk adjustment.
Eligibility for a CO@h pathway may be correlated with time-varying unobserved confounders.	Inability to account for unobserved confounders will lead to biased estimates. For example, attendance at A&E may depend on which local support services are available at the time and in the area where a patient lives (time-varying confounder), which in turn correlates with which GP practice the patient is likely to be registered with (in turn relating to whether a CO@h pathway is available or not).	GSynth can infer unobserved time-varying confounders with time-varying effects; these are reported as additional factor loadings. If detected by plotting them, these will be examined for plausibility and sensitivity to their inclusion.
The synthetic control is unduly capturing noise in outcomes, rather than underlying trends.	Credence is removed from the key assumption that similarity in pre-intervention outcome trends will also persist in the post-intervention period. It is documented that when the number of pre-intervention periods increases, the bias of synthetic control estimates shrinks towards zero. However, a criterion to determine a sufficient length for the pre-intervention period is not available.	Using a sufficiently long pre-intervention. Checking sensitivity to changes in the study start date (see the Sensitivity analyses section). Checking sensitivity to changes in the number of pre-intervention periods.
Interventions that influence outcomes among untreated CCGs but not in treated CCGs may have occurred in the pre-intervention period.	Key assumption that pre-intervention similarity among CCGs will also persist post-intervention will be implausible.	Checking sensitivity to using a different set of controls.
Interventions that influence outcomes in control CCGs may have occurred in the post-intervention period.	Key assumption that control CCGs reflect patterns of 'usual care' and that treated CCGs would have implemented policies with the same average effects on outcomes may be unwarranted.	Checking sensitivity to using a different set of control CCGs, subject to their availability in sufficient numbers.
The evaluation retains information only pertaining to first COVID-19 positive diagnoses.	The analysis omits hospital activity generated from subsequent COVID-19 tests, leading to a loss of information on the potential effectiveness of CO@h onboarding following an initial COVID-19 episode.	Validity of any findings derived from the evaluation is limited to the first instance of a positive COVID-19 test.
The time span between COVID-19 symptoms onset and a positive test varies in the target population.	Delays in undertaking and reporting of positive COVID-19 tests may apply inconsistently and be unreliably recorded between CCGs, potentially leading to spurious alteration of hospital activity observed over time.	It is assumed that delays in patient presentation to COVID-19 testing and in reporting do not apply systematically between CCGs or over time.

There is some evidence of false positive COVID-19 swab tests prevalence of between 0.8% and 4%.[11]	A proportion of the population may be receiving the intervention with no need, hence showing spuriously positive impact on hospital outcomes (by not attending A&E departments or having no hospital admissions).	While it is unlikely that false positive CO@h recipients will differentially bias findings across CCGs or over time, it is worth noting that the evaluation unavoidably retains a proportion of individuals falsely testing positive to COVID-19.
Threats to external validity		
SUS data may not fully reflect the hospital use of the target population within a CCG, for example if relevant information in SUS is missing or incomplete.	Estimates of the impact of CO@h may be biased.	Missing data in SUS is assumed to be missing at random, so all CCGs should be affected similarly.
SUS data may not reflect the population if GP registration data are not up to date, eg if patients moved in or out of the area but did not change GP.	Estimates of the impact of CO@h may be biased.	Missing patient registration data is assumed to be missing at random, so all CCGs should be affected similarly.
Impact of CO@h may not have been fully realised within the post-intervention period or may fluctuate over time.	Too short a post-intervention period may lead to misleading results. Extrapolating the estimated impacts beyond the post-intervention period may be inappropriate.	Have long post-intervention period; evaluate the effect over several time periods to understand if and how any discerned impact varies over time.
The evaluation measures the effect of the particular roll-out, rather than the effect of CO@h more generally.	Estimates of the impact of CO@h may be biased.	Assume that variations in service delivery do not affect intervention impact. CCGs associated with unusual patterns to be scrutinised more closely.
The evaluation is restricted to individuals testing positive for COVID-19.	The population eligible to enter a CO@h pathway additionally comprises individuals diagnosed positive for COVID-19 through a clinician's assessment.	Findings from the evaluation may not generalise to COVID-19 patients clinically but not serologically diagnosed.
Threats to construct validity		
Estimates may include the impact of other changes or initiatives that occurred during the study period.	Estimates of the impact of CO@h and concurrent initiatives may be biased.	Quantitative findings will be interpreted in the light of available qualitative analyses describing other initiatives occurring at CO@h practices.
The outcomes analysed do not capture all facets of the potential impact of CO@h.	Due to constraints with national data sets, some of the potential impacts of CO@h (eg on financial efficiency, patient satisfaction, staff morale and improvement in quality of care) will not be reflected in the set of outcomes included here.	The proposed analysis is intended to provide a broad snapshot of the clinical impact of CO@h and concurrent initiatives on key secondary care outcomes.

Appendix

Table 1: List of variables used to identify most comparable CCGs. Rates of hospital activity indicate number of events per 1,000 or 10,000 people in the specified age band registered in the CCG, calculated across the pre-intervention period (from 23 March 2020 to 27 September 2020).

Variable	Source	Target cohort	Date of collection
Percentage of females	ONS	Whole population	2020
Percentage of persons aged 0 to 4 years	ONS	Whole population	2020
Percentage of persons aged 5 to 14 years	ONS	Whole population	2020
Percentage of persons aged 15 to 44 years	ONS	Whole population	2020
Percentage of persons aged 45 to 64 years	ONS	Whole population	2020
Percentage of persons aged 65 to 74 years	ONS	Whole population	2020
Percentage of persons aged 75 to 89 years	ONS	Whole population	2020
Rural/Urban Indicator 2011	Census	Whole population	2011
Rate of care home beds available according to CQC (per 1,000 or 10,000 registered population)	CQC	Whole population	2020
Rate of GPs (FTE) (per 1,000 or 10,000 registered population)	NHS Digital	Whole population	2020
Population density – number of people per square kilometre	ONS	Whole population	2020
Percentage of ethnicity recorded as White	Census	Whole population	2011
Percentage of ethnicity recorded as Black	Census	Whole population	2011
Percentage of ethnicity recorded as Asian	Census	Whole population	2011
Percentage of ethnicity recorded as Mixed	Census	Whole population	2011
Percentage of ethnicity recorded as Other	Census	Whole population	2011
Individuals' day-to-day activities limited a lot or a little (standardised illness ratio)	Census	Whole population	2011
Index of multiple deprivation (IMD) quintile	IMD	Whole population	2011
Health deprivation and disability score	IMD	Whole population	2011
Income Deprivation Affecting Older People Index (IDAOPI) score	IMD	Whole population	2011
Rate of yearly emergency admissions	SUS	Population of 65+ years of age	Pre-intervention period
Rate of yearly A&E attendances	SUS	Population of 65+ years of age and testing positive for COVID-19	Pre-intervention period
Rate of yearly emergency admissions	SUS	Population of 18–64 years of age	Pre-intervention period
Rate of yearly A&E attendances	SUS	Population of 18–64 years of age and testing positive for COVID-19	Pre-intervention period
Rate of yearly emergency admissions	SUS	Population of 0–17 years of age	Pre-intervention period
Rate of yearly A&E attendances	SUS	Population of 0–17 years of age	Pre-intervention period

Table 2: Variables used for risk adjusting A&E attendances, emergency admissions and mortality for the target cohort testing positive for COVID-19 patients. Variables describe key reference characteristics of CCGs and are calculated across the pre-intervention period. If level of collection is other than CCG, then variables will be aggregated to CCG level.

Variable	Description	Date of collection	Level of collection	Source
Population size per CCG	Number of patients registered with a GP practice	Quarterly 2020	CCG	NHS Digital
Size of population testing positive for COVID-19	Number of registered patients testing positive for COVID-19	Weekly from 23 March 2020 to 29 November 2020	CCG	SGSS
Age	Proportion of registered patients 18–24, 25–64, 65–74 years of age and 75 years of age or over	Annually 2020	CCG	NHS Digital
Gender	Proportion of registered male patients	Annually 2020	CCG	NHS Digital
Ethnicity	Proportion of registered patients with self-reported White, Black, Asian and Mixed ethnicity	29 March 2011 (census day)	CCG	Office for National Statistics
Education	Proportion of registered patients with at least third-level education (ie two or more A levels or equivalent)		CCG	
Population density	Rate of persons per hectare in the nearest electoral ward		CCG	
Socio-economic deprivation	Weighted average of LSOA IMD scores according to the LSOA of patients	2020	LSOA	Ministry of Housing, Communities and Local Government
Health deprivation	Weighted average of LSOA level IMD scores on health deprivation according to LSOA of CCG registered patients		LSOA	
Number of full-time equivalent GPs	Rate of full-time equivalent GPs per 1,000 or 10,000 people in the registered CCG population	2020	GP practice	NHS Digital
Proportion of GDPPR conditions	Proportion of registered COVID-positive tested population with positive flags for 36 health states[12] which would be available in GDPPR data: • Alcohol problems • Other psychoactive substance misuse • Anorexia or bulimia • Asthma (currently treated) • Atrial fibrillation • Blindness and low vision • Bronchiectasis • Chronic kidney disease • Chronic liver disease	2020	Patient	GDPPR

Proportion of GDPPR conditions	• Chronic obstructive pulmonary disease (COPD) • Constipation (currently treated) • Coronary heart disease • Dementia • Depression, anxiety and other neurotic, stress-related and somatoform disorders • Diabetes • Diverticulosis • Epilepsy • Hearing loss • Heart failure • Hypertension • Inflammatory bowel disease • Irritable bowel syndrome • Learning disability • Migraine • Multiple sclerosis • New diagnosis of cancer within last 5 years • Painful condition (on prescription-only pain medication) • Parkinson's disease • Peripheral vascular disease • Prostate disorders • Psoriasis or eczema • Rheumatoid arthritis, other inflammatory polyarthropathies and systematic connective tissue disorders • Schizophrenia (and related non-organic psychosis) or bipolar disorder • Stroke and transient ischaemic attack • Thyroid disorders • Viral hepatitis	2020	Patient	GDPPR

Table 3: Variables used for risk adjusting hospital bed days rates following an emergency admission. These relate to patients testing positive for COVID-19 with hospital activity in the week and to the target population and they are calculated across the pre-intervention period.

Variable	Description	Date of collection	Level of collection	Source
Age	Total number of emergency admission CIPS for patients 18–24, 25–64, 65–74 and 75 years of age or over per 1,000 or 10,000 patients admitted as an emergency to hospital	Weekly during the pre-intervention period	Activity	SUS or GDPPR
Gender	Total number of emergency admission CIPS for male patients per 1,000 or 10,000 patients admitted as an emergency to hospital	Weekly during the pre-intervention period	Activity	SUS or GDPPR
Ethnicity	Total number of emergency admission CIPS for patients with self-reported race (White, Black, Asian, Mixed, Other) per 1,000 or 10,000 patients admitted as an emergency to hospital	Weekly during the pre-intervention period	Activity	SUS or GDPPR
Proportion of inpatient admissions by GDPPR health state	Total number of emergency admission CIPS for patients with positive flags for 36 health states which would be available in GDPPR data as Table 2	Weekly during the pre-intervention period	Activity	GDPPR

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