RECAP (Remote COVID-19 Assessment in Primary Care): a learning system approach to develop an early warning score for use by primary care practitioners

Version 11. Date: 13.07.22

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STUDY COORDINATION CENTRE: Department of Surgery and Cancer
IRAS Project ID: 283024
REC reference: 20/NW/0266

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<thead>
<tr>
<th>Name &amp; Role</th>
<th>Date</th>
<th>Signature</th>
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</thead>
<tbody>
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<td>Professor Brendan Delaney</td>
<td>2 May 2020</td>
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</tbody>
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Funder Community Jameel Imperial College COVID-19 Excellence Fund, NIHR Oxford Biomedical Research Centre, NIHR Imperial Biomedical Research Centre, NIHR Imperial Patient Safety Translational Research Centre, Economic and Social Research Council, UKRI
The Delphi process used existing internal funding from NIHR Oxford BRC
This protocol describes the ‘RECAP (Remote COVID-19 Assessment in Primary Care): a learning system approach to develop an early warning score for use by primary care practitioners’ and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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## GLOSSARY OF ABBREVIATIONS

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<th>Description</th>
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<tr>
<td>API</td>
<td>Application Programming Interface</td>
</tr>
<tr>
<td>BRC</td>
<td>Biomedical Research Centre</td>
</tr>
<tr>
<td>CAG</td>
<td>Confidentiality Advisory Group</td>
</tr>
<tr>
<td>CCAS</td>
<td>Covid Clinical Assessment Service</td>
</tr>
<tr>
<td>CCG</td>
<td>Clinical Commissioning Group</td>
</tr>
<tr>
<td>COPI</td>
<td>Control of patient information</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus disease 2019</td>
</tr>
<tr>
<td>CPR</td>
<td>Clinical Prediction Rule</td>
</tr>
<tr>
<td>CTRG</td>
<td>Clinical Trials and Research Governance</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic Health Record</td>
</tr>
<tr>
<td>EMIS</td>
<td>Egton Medical Information Systems</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GDPR</td>
<td>General Data Protection Regulation</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GSTT</td>
<td>Guy’s and St Thomas’ NHS Trust</td>
</tr>
<tr>
<td>HES</td>
<td>Hospital Episode Statistics</td>
</tr>
<tr>
<td>HL7 FHIR</td>
<td>Health Level 7 Fast Healthcare Interoperability Resources</td>
</tr>
<tr>
<td>HRA</td>
<td>Health Research Authority</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IRAS</td>
<td>Integrated Research Application System</td>
</tr>
<tr>
<td>LHS</td>
<td>Learning Health System</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NEWS2</td>
<td>National Early Warning Score 2</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>PPI</td>
<td>Patient and Public Involvement</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>RECAP</td>
<td>Remote COVID-19 Assessment in Primary Care</td>
</tr>
<tr>
<td>RSC</td>
<td>Research and Surveillance Centre</td>
</tr>
<tr>
<td>RCGP</td>
<td>Royal College of General Practitioners</td>
</tr>
<tr>
<td>SARS-CoV2</td>
<td>Severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>SNOMED</td>
<td>Systematized Nomenclature of Medicine</td>
</tr>
<tr>
<td>TPP</td>
<td>The Phoenix Partnership</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WSIC</td>
<td>Whole Systems Integrated Care</td>
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STUDY SUMMARY

TITLE  RECAP (Remote COVID-19 Assessment in Primary Care): a learning system approach to develop an early warning score for use by primary care practitioners

DESIGN  Primary care data linkage study: Cyclical ‘learning system’ validation and revision/revalidation of a predictive risk score. Nested qualitative study.

AIMS  To validate the RECAP V0 early warning score for use in GP-patient consultations (mainly by phone or video) in the context of COVID-19, as quickly as possible, followed by development and validation of a data-driven score (RECAP V1).

Research questions:
1. What is the sensitivity, specificity, and positive and negative predictive value of the RECAP score as used in the primary care assessment of COVID-19 patients?
2. How feasible and safe is the use of this score in this context?
3. Does the RECAP score add value over clinical judgement, and is it more accurate than other early warning scores e.g. NEWS2?
4. What is the performance and validation of a revised RECAP score?
5. How was GP experience using of the revised RECAP score?

OUTCOME MEASURES  Primary outcome measure: Admission to hospital.
Secondary outcome measures: Admission to ITU and Death.

POPULATION  The main cohort will include patients with clinically diagnosed COVID-19 in primary care and being managed as part of primary care-based remote monitoring for the management of clinical deterioration. Additional cohorts will include a) patients clinically diagnosed with COVID-19 who are sent immediately to hospital, and b) patients clinically diagnosed with COVID-19 who are given self-care advice.

Nested qualitative study will include 30 General Practitioners who have used the RECAP score.

ELIGIBILITY  SETTING: Being seen in a primary care setting where COVID-19 cases are occurring and either a practice-based triage system or a COVID-19 remote monitoring service, or local equivalent, is running.

CONSENT TO DATA LINKAGE: Patients locally recorded as being willing and able to give informed consent for data linkage either at a GP contact (entered on a template) or as part of a ‘platform service’ (checked by the patient on a template or via chatbot). Patients recruited through Covid Clinical Assessment Service
(CCAS) will be asked to provide verbal consent for data linkage for prospective data but access to retrospective data will be an automated process under the Control of Patient Information (COPI) notice, for which we have been granted REC approval. REC approval of COPI notice will also apply to the Doctaly research site.

Please note: COPI notice is due to expire on 31.3.22 and provisions are currently in progress to transition to Regulation 5 to allow continued access to patient free-text data (CCAS) and Doctaly data previously under COPI notice.

ABLE TO CAPTURE THE DATA: Part of a local data integration and care quality analysis service such as a clinical effectiveness group that are managing a local COVID-19 remote monitoring pathway and can deploy data collection tools (templates or a platform) to recruit a cohort. We will also plan to extend to EMIS users who have opted into a national resource publishing service, Doctaly platform and Adastra users at CCAS.

ABLE TO LINK DATA WITH OUTCOMES: Able to provide a linked data set for analysis relating defined cut points on the RECAP scores to the following outcomes: hospital admission, confirmed SARS-CoV-2 test result, ICU admission, hospital outcome (discharge date and/or cause of death).

DURATION

We will pilot the process in Southwark CCGs, North West London’s Whole Systems Integrated Care CCG Collaborative (WSIC), RCGP Research and Surveillance Centre, CCAS (set up to support NHS 111) and the patient facing platform Doctaly.

EXCLUSION CRITERIA: Not using a compatible electronic record system or using a remote monitoring system that cannot provide an output that is at least mapped to the appropriate SNOMED concepts.

26 months (study end 31st December 2022)
1. INTRODUCTION

1.1 BACKGROUND

LITERATURE REVIEW
As clinical academic GPs, we were at the forefront of the UK’s COVID-19 response, publishing rapid clinical guidance in the British Medical Journal which has so far been accessed by over 200,000 people and translated into 12 languages. This guidance formed the basis of key sections of the NICE Rapid Guideline on management of COVID-19 pneumonia in the community. It contained a flow chart, presented as an infographic, to guide GPs’ decision-making.

There is pressure on clinical services and emerging evidence that a small percentage of patients experience precipitous deterioration (usually on about day 7). For this reason, there is a growing clinical need to develop and validate early warning scores – that is, clinical prediction models designed to identify patients who need urgent escalation of care. Such scores need to be both sensitive (i.e. detect all patients who need hospital referral) and specific (i.e. exclude all or most patients who do not). In the clinical setting, the trade-off between false positives and false negatives should lie towards false positives, since the cost of misallocating a deteriorating patient to remain at home is higher than an unnecessary hospital review. In other words, sensitivity is favoured over specificity.

Most early warning scores have been developed for use in hospital inpatients using routinely collected vital sign data. The National Early Warning Score 2 (NEWS2), for example, is calculated from the patient’s temperature, pulse rate, respiratory rate, systolic blood pressure, pulse oximetry reading and presence of new onset confusion. Hospital clinicians are familiar with the NEWS2 scoring system, which has become a common language of sickness with positive implications for patient safety (especially in relation to sepsis). NEWS2 is recommended by NICE guidelines both in general and as a component of the critical care of COVID-19 patients, though it is not without its critics. Recently, there has been interest in using NEWS2 in a primary care setting for two linked purposes: earlier and more efficient detection of patients who require urgent transfer to hospital, and to aid communication with secondary care colleagues about such patients. A region-wide quality improvement initiative in the West of England produced high compliance with NEWS2 by general practitioners, and a statistically significant region-wide reduction in mortality from sepsis. However, whilst the NEWS2 score undoubtedly correlates with serious illness, there are theoretical arguments against its use in primary care. Notwithstanding some evidence of its validity in an pre-hospital setting when used by ambulance crews, it has not been formally validated in a general practice setting, so its sensitivity and specificity in that context are unknown. Its positive predictive value is low even in hospital and ambulance settings, and is likely to be even lower in primary care due to low prevalence of serious illness, though it may have some value in care homes. NEWS2 was designed to be used with longitudinal data (so-called “track and trigger”), not as a one-off assessment. A rise in NEWS2 appears to be a relatively late indicator of deterioration, typically triggering only in the last 12 hours before transfer to critical care. Whereas the NEWS2 score fits well with the work practices and routines of paramedics, general practitioners found it time-consuming and awkward to use. For all these reasons, NEWS2 might conceivably cause harm from both under- and over-referral.
All these problems may be compounded when assessing a patient with suspected COVID-19 in primary care, since it is a new disease whose clinical course does not mirror other pneumonias and most patients will be assessed remotely (i.e. by phone or video), meaning that the score will be incomplete. The UK Royal College of General Practitioners has, perhaps prematurely, cautiously endorsed NEWS2 alongside clinical judgement in the context of COVID-19. The recent NICE rapid guideline on management of COVID-19 pneumonia in the community makes the guarded statement that NEWS2 “may be useful” in assessing deterioration (on the basis that sepsis may arise as a complication of COVID-19) but that the patient should not be brought in for a face-to-face assessment solely to calculate a NEWS2 score (paragraph 3.7).

The nature of infection with SARS-CoV-2 is that significant numbers of patients present with silent hypoxia, running oxygen saturations in the 86-90% range or below, without significant breathlessness or respiratory distress. This is because COVID-19 is thought to cause dysregulation of pulmonary blood flow and shunting of deoxygenated blood. Signs of hypoxia may present subtly and late with extreme tiredness, headache and confusion. For this reason, careful and proactive monitoring (ideally with a peripheral pulse oximeter) is likely indicated in many patients. However, there is a crucial knowledge gap: we do not yet know enough about the illness trajectory and risk factors at community level to be able to anticipate which patients are more likely to run into difficulty beyond the known risks of male sex, older age, BAME groups, obesity, hypertension and diabetes. There is an urgent need to start monitoring these patients right now with the best available professional consensus and to rapidly gather data to establish and validate a data-driven risk score.

It is therefore urgent to develop and validate a primary care early warning score that is specific to COVID-19 and based on data that can be reliably collected during a remote consultation.

SUMMARY OF DEVELOPMENT WORK ON THE RECAP SCORE
The project follows the approach of a Learning Health System (LHS), where an infrastructure with common standards for data capture, analysis and knowledge utilisation is used to manage the cyclical validation of risk scores based on data collected in the routine healthcare system under study. The critical point is that this infrastructural approach to link data collection, analysis, validation and deployment as an LHS deals with the Achilles heel of routine data analysis: missing data not at random, difficulty defining the cohort, and biased and incomplete outcome ascertainment. We will use the capability of standardised templates and newly developed health system-wide data integration (such as in NW London) to develop a system for running a live prospective cohort study embedded in the health system. Faced with a new disease on which there is virtually no data outside the hospital setting, the starting point for such a system is a combination of rapid review and professional consensus. This allows a clinically useful service, providing suggestions based on professional
consensus, to be established whilst simultaneously collecting the rich standardised data required for subsequent refinements of the score.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement\textsuperscript{26} states that development of a prognostic model (of which an early warning score such as RECAP is one example) requires two phases: instrument development and instrument validation. We were advised that our methodology developing the initial instrument (termed from here on RECAP v0) (desk research and peer review) did not need NHS REC approval but that validating the instrument did. In this section, we describe the development work of v0.

As part of the Oxford COVID-19 rapid reviews service, Greenhalgh and Nunan have been tracking systematic reviews and large-scale observational studies describing the signs and symptoms of COVID-19 in both mild and severe disease since mid-March 2020.\textsuperscript{20} The review has been done according to Cochrane Collaboration standards for rapid reviews,\textsuperscript{27} and the included evidence has been assessed as robust (though necessarily in a largely Chinese population).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{symptoms.png}
\caption{Summary of predictive value of signs and symptom data in COVID-19}
\end{figure}

\textbf{Figure 1} illustrates the kind of data we’ll be using. Some symptoms (such as cough) don’t appear to discriminate well between mild and severe cases but are advised for collection in national guidance. Other symptoms (such as shortness of breath and chills) are commoner in severe cases so could contribute to a risk score. There are also, of course, some symptoms (such as severe chest pain, or signs of sepsis) for which a GP would likely send someone to hospital. Not all patients have COVID-19.
Using both the COVID-19-specific data above and more general ‘red flag’ indicators of deterioration or acute illness, we constructed the draft risk score shown below.

The RECAP score is currently being refined through a consensus method called Delphi. In this, a sample of 50 front-line clinicians (recruited through our own networks – almost all GPs but some nurse practitioners and paramedics) are being invited to comment on the choice of items, the wording of items, and the proposed scoring system. This is done using Survey Monkey to collect qualitative comments and quantitative rankings. A medically qualified qualitative researcher (TG) and a statistician (PT) are analysing these data and refining the instrument. We anticipate that by the mid May 2020 we will have a refined version of the RECAP score and will be ready to proceed to validation.

**RED ALERT CRITERIA: If patients have any of the following, consider 999**

These are adapted from draft criteria developed by the NHS England & Improvement Urgent and Emergency Care group (and also used in the primary care guidance).

**Severe breathlessness**
- Rapid, significant deterioration in breathing in the last hour
- New breathlessness at rest
- Newly unable to complete sentences
- Sudden onset of breathlessness

**Shock or peripheral shutdown**
- New confusion or reduced level of consciousness
- Extremities – cold and clammy to touch
- Pallor – skin is mottled, ashen, blue or very pale
- Reduced urine output – little or no urine in last 24 hours

**Other red flags which may be non-COVID-19 related e.g.**
- Severe central chest pain
- Collapse
<table>
<thead>
<tr>
<th></th>
<th>Heart rate (per minute)</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Refer urgently</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Use medically approved device if available, or patient's own. Lower threshold for tachycardia by 10 bpm if beta-blocker or other heart-slowing drug taken in past 24h. Adjust score if known to have physiological bradycardia (e.g. athlete).</td>
<td>51-90</td>
<td>41-50 or 91-110</td>
<td>111-130</td>
<td>≤ 40 OR &gt; 130, IF UNEXPLAINED</td>
</tr>
<tr>
<td>2</td>
<td>Respiratory symptoms and signs (use higher score from 2a and 2b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>Shortness of breath</td>
<td>Not significantly breathless</td>
<td>Breathless on moderate exertion</td>
<td>Breathless on mild exertion</td>
<td>SEVERE DIFFICULTY IN BREATHING; CAN’T COMPLETE SENTENCES AT REST</td>
</tr>
<tr>
<td>2b</td>
<td>Respiratory rate (per minute)</td>
<td>12-20</td>
<td>21-24</td>
<td>9-11 or 25-29</td>
<td>&lt;9 or ≥ 30</td>
</tr>
<tr>
<td>3</td>
<td>Hypoxia (use highest score from 3a, 3b and 3c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Oxygen saturation at rest</td>
<td>96% or above</td>
<td>95%</td>
<td>94%</td>
<td>≤ 93%</td>
</tr>
<tr>
<td>3b</td>
<td>Oxygen saturation after 40 steps on the flat</td>
<td>Fall of 0-1%</td>
<td>-</td>
<td>Fall of 2%</td>
<td>≥ 3%</td>
</tr>
<tr>
<td>3c</td>
<td>Profound tiredness or fatigue</td>
<td>None or mild</td>
<td>Noticeably more tired doing usual activities</td>
<td>Struggling to get out of bed</td>
<td>UNABLE TO SPEAK BECAUSE OF TIREDNESS</td>
</tr>
<tr>
<td>4</td>
<td>Fever (use worst score from 4a and 4b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>Measured temperature</td>
<td>≤ 38 °C</td>
<td>&gt; 38 °C</td>
<td>&gt; 39 °C or &lt; 35 °C</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>Feverish with shivers or chills</td>
<td>None</td>
<td>-</td>
<td>Shivers or chills</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Muscle pains</td>
<td>None or mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RISK FACTORS (use both 6a and 6b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>Is patient on the COVID-19 shielded list (or in your opinion, should they be)? Includes: organ transplant • current chemotherapy or immunotherapy • severe lung condition such as cystic fibrosis • sickle cell anaemia • high dose steroids or other immunosuppressants • blood or bone marrow cancer • lung cancer on radiotherapy</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6b</td>
<td>Do they have other risk factors for poor outcome? e.g.</td>
<td>No</td>
<td>1-2</td>
<td>3 or more</td>
<td></td>
</tr>
</tbody>
</table>

Clinical concern component (be guided by clinical concern whatever the RECAP score)
After assessing the patient, what is your level of clinical concern (regardless of RECAP score)?

<table>
<thead>
<tr>
<th>SCORE</th>
<th>MEANING</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 or more total or 3 on any item or extremely concerned</td>
<td>HIGH RISK</td>
<td>Consider urgent referral</td>
</tr>
<tr>
<td>4-6 or more total or high level of clinical concern</td>
<td>MODERATE RISK</td>
<td>See in hot hub or for remote monitoring</td>
</tr>
<tr>
<td>0-3 total</td>
<td>LOW RISK</td>
<td>Advice and monitor at home</td>
</tr>
</tbody>
</table>

The provisional scoring is as follows:

This is version 2 of the score out for comments on the Delphi. The refined score, version 3, will be called RECAP v0.

1.2 RATIONALE FOR CURRENT STUDY

Early warning scores (EWSs) are used quite a bit in medicine these days. For example, the National Early Warning Score (NEWS2) is used in hospital to alert nurses and doctors to someone who is deteriorating and may need urgent assessment and treatment. It consists of things like pulse, blood pressure, respiratory rate, oxygen saturation level and conscious level. The more abnormal these features are, the sicker the patient is likely to be. NEWS2 isn't used much outside hospital, and it isn't COVID-19-specific. We'd like to develop an EWS that is both COVID-19-specific (RECAP) and that can be used by GPs when having phone conversations or video consultations with patients worried about their symptoms.

2. STUDY OBJECTIVES

OBJECTIVES
With a view to supporting multiple validation studies undertaken in parallel and contributing to an open data repository, the objectives of this project are:

1. To define the parameters for a minimum study protocol (consisting of cohort eligibility, consent for data linkage, data elements collected, data linkage for outcome ascertainment).
2. To develop data definitions and standards for the RECAP score and any additional required elements using SNOMED codes, in order to enable a set of data definitions to be built into current healthcare data collection systems.
3. To collect data via groups of GPs, both locality-based e.g. a CCG, and cohort-based e.g. part of Royal College of GPs Research Surveillance Centre sentinel network.
4. Using data linkage, to follow cohorts of patients to three predefined outcomes: hospital admission, ICU admission, and death.
5. To collect qualitative data on clinicians’ experiences using the RECAP score.

RESEARCH QUESTIONS

1. What is the sensitivity, specificity, and positive and negative predictive value of the RECAP v0 score as used in the primary care assessment of COVID-19 patients?
2. How feasible and safe is the use of this score in this context?
3. Does the RECAP score add value over clinical judgement, and is it more accurate than other early warning scores e.g. NEWS2?
4. What is the performance and validation of a revised RECAP score?
5. How was GP experience using of the revised RECAP score?
3. STUDY DESIGN

Type of study: Cohort observation, database analysis, and qualitative research

Duration: 26 months

Number and type of subjects: Planned Size of Sample will be up to 10,000 for all cycles (two planned subsequent cycles will be based on data from the initial cycle) of patients being managed as clinical COVID-19 in primary care. A sample of 30 GPs will be involved in the qualitative study.

Purpose: Quantitative study – to derive and validate a risk score for patients presenting and being monitored in primary care with symptoms of COVID-19. Qualitative – to explore the utility of the RECAP score amongst GP users.

Recruitment and consent process

Quantitative study: We will be using templates embedded in health record systems and used in routine contacts for patients with suspected COVID-19. We will be linking records between primary and secondary care, but using sites where such governance procedures are already in place to allow this. For patients accessed via CCAS and Doctaly, we have been granted REC approval of COPI Notice for data sharing and data linkage in Oxford secured environment (see section 8.2: Consent for more information). As an additional safeguard, we will be collecting a code for consent to record linkage, supported by an on-line information sheet. We do not require explicit consent from patients for the record linkage study.

Qualitative study: GPs using the RECAP templates will be approached via the research team in Oxford University and explicit consent to attend a focus group will be obtained.

3.1 STUDY OUTCOME MEASURES

Primary outcome measure: Admission to hospital.
Secondary outcome measures: Admission to ICU and Death

4. PARTICIPANT ENTRY

The study will take place using routine care for patients with suspected COVID-19 being seen and managed in primary care. We are not undertaking any interventions or additional study procedures, simply ensuring that routine data is collected in health record systems in a reliable and consistent way. Analysis will take place on already agreed record linkage in existing secure environments. We will record consent to record linkage as part of the template as an additional safeguard. The consent to linkage question is supported by a link to an on-line information sheet for patients.

GPs and Practices will take part in the quantitative study by virtue of their membership of a Primary Care Organisation (PCO) (CCG, PCN) that is using the RECAP templates as part of their locality COVID-19 management plan OR because they are part of a research network (RCGP Research and Surveillance Centre).

For the qualitative study GPs will be invited to take part as being in a PCO using the RECAP templates. The qualitative study is supported by a specific GP Invitation letter, GP Information sheet and GP consent form.

4.1 PRE-REGISTRATION EVALUATIONS
No pre-evaluation tests will be administered.

The study will take place in a defined group of patients with clinical diagnosis of COVID-19 who have a series of remote contacts as part of remote monitoring for the management of deterioration in primary care.

Note: We will not be collecting any more data than would reasonably be collected by any clinician making any COVID-19 assessment, however, we WILL be coding these items according to an agreed code-set of SNOMED terms. The RECAP score consists of items such as temperature, pulse, and shortness of breath.

4.2 INCLUSION CRITERIA

SETTING: Being seen in a primary care setting where COVID-19 cases are occurring and either a practice-based triage system or a COVID-19 remote monitoring service, or local equivalent, is running.

CONSENT TO DATA LINKAGE: Patients locally recorded as being willing and able to give informed consent for data linkage either at a GP contact (entered on a template) or as part of a ‘platform service’ (checked by the patient on a template or via chatbot).

ABLE TO CAPTURE THE DATA: We are using templates containing a subset of SNOMED codes that have been selected by us and reviewed by NHSX, NHSE and the UK Faculty of Clinical Informatics. Templates will be deployed via participating localities (CCGs) for COVID-19 management, nationally via Ardens, EMIS, TPP, Adastra (used by CCAS) and the RCGP Research and Surveillance Centre, or via patient-facing platforms such as Doctaly (being used by SE London)

IDENTIFYING PATIENT RECORDS

Patient records to identify the cohort will have the following SNOMED code SNOMED - 873771000000107 | Consent given to participate in research study (finding) | inserted via the templates. These NIHR Research codes are implemented as <Code><CPMS><Number> where <number> is the CPMS study number after portfolio adoption. This provides a specific tag that can be used for record retrieval from whatever source.

ABLE TO LINK DATA WITH OUTCOMES:
Able to provide a linked data set for analysis relating defined cut points on the RECAP scores to the following outcomes; hospital admission, confirmed SARS-CoV-2 test result, ICU admission, and hospital outcome (discharge date and/or cause of death). We will work with localities that have the necessary data linkage and governance in place.

We will pilot the process in North West London’s Whole Systems Integrated Care CCG Collaborative (WSIC) and extend to South East London CCGs (Doctaly) and then nationally via RCGP RSC. We will also include the COVID Clinical Assessment Service (CCAS) (set up to support NHS 111 during the pandemic) and the patient facing platform Doctaly to pilot the process.
4.3 **EXCLUSION CRITERIA**

EXCLUSION CRITERIA: Not using a compatible electronic record system or using a remote monitoring system that cannot provide an output that is at least mapped to the appropriate SNOMED concepts.

4.4 **WITHDRAWAL CRITERIA**

All participants will be reassured they are free to withdraw from the study at any point. We will inquire whether data obtained up until the point of the withdrawal can be retained for analysis. If not, data will be destroyed.

5. **ADVERSE EVENTS**

5.1 **DEFINITIONS**

*Adverse Event (AE)*: any untoward medical occurrence in a patient or clinical study subject.

*Serious Adverse Event (SAE)*: any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients’ hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

5.3 **REPORTING PROCEDURES**

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, will be recorded as part of routine practice.

5.3.2 Serious AEs

The first part of the study is an observational cohort study embedded in routine (but rapidly evolving) clinical practice. Our only study activity is to provide for standardised collection of high granularity data for subsequent linkage and analysis. During the second part we will be providing a validated RECAP score v1 to practices. As this is embedded in a template in the EHR system it is not a medical device, but we do need to capture any serious AEs (SAEs) that might occur on its use.

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to COVID-19 and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the sponsor where in the opinion of the Chief Investigator, the event was:
• ‘related’, i.e., resulted from the administration of any of the research procedures; and
• ‘unexpected’, i.e., an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

6. ASSESSMENT AND FOLLOW-UP

GPs will be contacted once analyses have been carried out to report on study findings.

Definition of end of study: the end of the study is the point at which all study data has been collected by the University researchers.

7. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

Quantitative component of RECAP study

COVID-19 data from GPs electronic health record (EHR) will be transferred through computer networks to the RECAP template for analysis. Data analysis will be undertaken as set out below. Participating patients records will be coded with a SNOMED research code as having consented to record linkage for the purposes of RECAP.28

Sample size calculation
The study has two components.

• Component one (risk model development): we will develop a model to predict which patients will be admitted to hospital. (RECAP v1)
• Component two (validation - estimate model specificity): we will estimate the precision of the specificity of the model to predict which patients will be admitted to hospital. There will be differences in the following domains amongst these datasets, particularly in what concerns 1) cohort definition (first contact primary care v medium at risk group in follow-up) and 2) data elements collected during care, granularity and validity of linked outcome data (live sector wide data linkage (WSIC) v Hospital Episode Statistics
and ONS deaths). We will control for the latter by using agreed code sets and will explore sensitivity to cohort definition and outcome ascertainment. In particular, reliable data on SARS-CoV-2 test status are only available at present via WSIC.

Sample size for component one: Assuming that 10% of patients will be admitted to hospital, 0.05 acceptable difference in apparent and adjusted Cox-Snell R-squared, 0.05 margin of error in estimation of intercept, and a binary outcome based on admission to hospital and a maximum of 24 predictor parameters, we estimate that the minimum sample size required for new model development is 1317 participants enrolled for the development set (with at least 132 events expected for a 0.1 outcome prevalence and 5.49 events per predictor parameter).

Sample size for component two: The sample size calculation is based on the following assumptions:

1. 85% specificity would be the lowest level worth carrying forward because lower values would be considered too low clinically for such model to be used to make clinical decisions.
2. We aim to demonstrate a specificity of 90% such that the lowest model specificity is 85%.
3. Based on a 95% confidence interval and a precision of 0.05, an assumed specificity of 87% requires a sample size of 140 participants.
4. Assuming a prevalence of 10%, the required total sample size is 1400.

Total study sample size is 1317 + 1400 = 2717.

Assuming a loss to follow up of 6%, due to possible linkage failure or not recording admission, the necessary sample size is 2880 participants.

Analysis

- Component one analysis: model development
  We will take into consideration variables from three phases of the care pathway, namely admission to hospital, admission to ICU and mortality. The primary outcome is hospital admission following a diagnosis of COVID19.

  Using a logistic regression model, we will investigate the relationship between hospital admission and predetermined predictive factors. This will inform whether risk factors and comorbidities are significant to predict hospital admission. Similarly, we will run an analysis for secondary outcomes (admission to ICU and mortality).

- Component two analysis: model validation and specificity estimate.
  We will calculate the specificity of the model to predict hospital admission, together with other diagnostic factors such as sensitivity, positive predictive value and negative predictive value.

Qualitative component of RECAP study

We will collect qualitative data on clinicians’ experiences using the RECAP score, using two methods:

- Email discussion. We will use the existing secure, password-protected closed NHS discussion forum ‘Future NHS collaboration’ and specifically the ‘National deterioration forum’ (UK GPs and urgent care clinicians interested in assessing deterioration in
COVID-19). GPs and nurse practitioners in that forum who are using the RECAP score as part of the research study will be invited to join a closed discussion group ‘RECAP qualitative evaluation’. Admission to the forum will be subject to consenting to the entire discussion being analysed as part of the evaluation. Participants will be encouraged to discuss any aspect of the use of the RECAP score. We anticipate that up to 30 clinicians will participate in this discussion.

Focus groups. Clinicians participating in the RECAP study will be invited by random sampling to attend focus groups. Each focus group will have between four and eight other GPs carried out over a group video call, up to 30 clinicians will be invited. Focus groups will last up to one hour. GPs will be asked open-ended questions about their experience, based on issues raised in the RECAP email discussion forum described above.

Analysis
Focus groups will be transcribed, entered onto a qualitative database (NVIVO) and analysed thematically by clinically qualified researchers. Analysis will be oriented towards improving the design, layout and clinical accuracy of the score, and will be informed by theoretical models of clinical care and shared decision-making (e.g. assessment and explanation of risk, and socio-material aspects of technology-mediated decision support).

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL
The Study Coordination Centre has obtained approval from the North West - Greater Manchester East Research Ethics Committee Reference (REC) 20/NW/0266 and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT
If practices are using a clinical template, patients will be asked by their GP or Nurse Practitioner if they are happy for their pseudo-anonymised data to be used in a data linkage study. Because general practice is under extreme pressure, we don’t think it would be either feasible or ethical to require GPs to go through a full explanation of what the study entails and seek written consent. We did contemplate not asking patients at all, but we know this would require a lengthier ethics approval process and lives may depend on us validating the score as quickly as possible. Hence, we suggest a middle ground: the GP obtains verbal consent by asking the question “we are contributing data to a research study to look at the outcomes of COVID-19; would you be willing for your own pseudo-anonymised data to be part of that dataset?”. The template would include a check box to confirm verbal consent. We will also put information on a website to which the GP will provide a url if requested. No pressure will be put on patients to consent to this, and the website will make it clear that they may withdraw consent at any time. Localities using mobile health services with chatbots and or mobile templates for patient completion will provide the checkbox marked and link url as follows:

We are contributing data to a research study to look at the outcomes of Coronavirus. All personal details are removed, and the data is not directly linked to your records. The assessment information you just completed will be temporarily linked to your GP records and only medical staff will see it.
For a detailed explanation about the research and how we look after your data, visit https://imperialbrc.nihr.ac.uk/wp-content/uploads/2021/03/RECAP_Patient_information_Sheet.pdf.

Please reply YES to indicate your agreement for your data to be shared, or NO if you do NOT want your data to help research into Coronavirus.

If you answer NO to this question, you can still use this service. Your data will simply not be shared for research purposes.

For patients recruited through the Covid Clinical Assessment Service (CCAS), set up to support NHS111, GPs will ask for verbal consent to data linkage to support the use of prospective data collected during the consultation when using the RECAP template. Consent for data linkage for retrospective/ text data will be an automated process which has been granted REC approval under the COPI Notice. Patient data will be captured by Adastra (CCAS electronic health record) for analysis. A transparency notice will be stated on the NHS 111 website to state data may be used for a study at Imperial College London. Patients will also be sent an SMS message before their appointment with links to the study information sheet and research team contact details to let them know they will have opportunity to provide consent at the end of the consultation. Patients will receive the following SMS message:

Thank you for using NHS 111 service. We would like to inform you that, should you agree, your data may be used in the RECAP study. RECAP seeks to improve the management of patients with COVID-19 symptoms. You will have the opportunity to provide your consent at the end of your GP consultation. The study Participant’s Information Sheet can be accessed via this link (link provided).

Similarly, for patients recruited through Doctaly, consent to data linkage will also be an automated process subject to REC approval under the COPI Notice. A privacy notice will be also included in the Doctaly platform allowing patients the option to opt-out. Doctaly users will be able to withdraw their data at any time by updating their preferences on research participation in the platform. This will support the use of data to measure the study’s outcome measures as previously mentioned.

Please note: COPI notice is due to expire on 31.3.22 and provisions are currently in progress to transition to Regulation 5 to allow continued access to patient free-text data (CCAS) and Doctaly data previously under COPI notice.

8.3 CONFIDENTIALITY

Imperial College London as the study sponsor will preserve the confidentiality of participants taking part in the study and is registered with the ICO (Information Commissioner Office) as a data controller.

NHS numbers are the only identifiable data transferred from RCGP RSC practices, CCAS and Doctaly research sites to Oxford University secure environment (ORCHID). Before downloading the data to ORCHID, the NHS numbers are de-identified using a hashing algorithm and participants are assigned a unique ID in ORCHID (see section 9 Study Management). Specific age will also be replaced by an age-band. Please note, whilst text data from CCAS cannot be completely de-identified no identifiable information is used in the analyses.
8.4 INDEMNITY
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

8.5 SPONSOR
Imperial College London

8.6 FUNDING
Funders: Community Jameel Imperial College COVID-19 Excellence Fund, NIHR Oxford Biomedical Research Centre, NIHR Imperial Biomedical Research Centre, NIHR Imperial Patient Safety Translational Research Centre, Economic and Social Research Council, UKRI

No participants will receive payment in this study.

Research institutions agreed to cover research costs (training and template installation time) for RCGP Research and Surveillance Centre (RSC) practices participating in the study (whose amount will be determined by local clinical research networks (CRNs) but that has been calculated to be £98.70 by North West London CRN). This is to comply with the RCGP RSC conventions and avoid any potential disadvantages in practice recruitment.

For CCAS, the research team agree to cover research costs to the following;

- Study set up (one-off cost): £7373.48 (no VAT).
- Site initiation (one-off cost): £500 (no VAT).
- Business analyst (one-off cost): £626.52 (no VAT).
- Archiving (one-off cost): £500 (no VAT). Total: £9000

8.7 AUDITS
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT
The day-to-day management of the study will be co-ordinated through Brendan Delaney (chief investigator and study co-ordinator) and Erik Mayer (study co-ordinator).

Data management

No patient records or identifying information will be collected for this study. Digital data (e.g. de-identified data) will be managed within a Trusted research environment that has full access and security policies as approved by the Imperial Data Protection Office. Fully anonymised aggregated data can only be extracted once approved by the DPO.

In NWL, we have an established integrated care system ‘Whole Systems Integrated Care (WSIC)’ available to clinicians and other health professionals who are providing direct care to over 2.4 million patients in north-west London (roughly 95% of NWL patient population). This has been set-up by getting all the data controllers (primary care, acute trusts, mental health trusts, community trusts, and social care organisations) to sign up to an integrated care information sharing agreement. The linked integrated care data is available in a de-identified format for research purposes and we have the process in place to get approval for research
projects through the NWL Information Governance board. We have developed a consent to contact register by gaining explicit consent from patients to be contacted for research purposes and this register has now got roughly 20,000 patients and continuing to grow as we are exploring different ways to gain consent. WSIC is crucial to ensuring we have a dataset that can deal with potential issues of defining outcomes adequately. These will be dealt with by a series of sensitivity analyses on SARS-CoV-2 test status: definition of hospital admission, treatment in hospital.

In RCGP RSC network, practice data are encrypted and downloaded to Oxford University secure environment (ORCHID) using a secure FTP server. The ORCHID database at the University of Oxford only collects pseudonymised data associated with hashed NHS numbers. The encryption process uses a hashing algorithm (SHA2=512) as close to the source as possible. An encryption salt is held by a designated staff member of the University of Oxford. When a data linkage is required, the encryption salt holder sends the encryption salt to the data provider (NHS D). An encryption salt is then added at the end of the NHS number following the hashing algorithm. Data decrypted within the ORCHID secure environment are stored in a database, which is only accessed by the database administrator. Once within the ORCHID environment, data will be linked to outcomes (i.e., hospital admission, ICU admission and death as provided by HES and ONS databases) using an encrypted NHS number.

In South East London, patients will be recruited via Doctaly platform. GPs assessing patients that accessed via Doctaly, will complete clinical templates for managing patients with probable COVID-19 infection. A privacy notice will be included in the Doctaly platform where patients are able to opt-out. Doctaly users will be able to withdraw their data at any time by updating their preferences on research participation in the platform. The data collected via Doctaly platform will be securely exported to Oxford secure environment and processed as explained above. Data will be linked to hospital outcomes data (hospital admission date, ICU admission data, date of discharge/death and clinical values for COVID-19 tests).

For data obtained via COVID Clinical Assessment Service (CCAS), different procedures will apply to retrospective and prospective data. For prospective data, we will collect SNOMED clinical concepts as per the GP systems via a template integrated within their electronic health record system- Adastra. CCAS patients will receive an SMS via NHS Digital while waiting in the clinical queue that will provide information about the study prior to the GP consultation. GPs will then ask for verbal consent to data linkage (see section 8.2 consent). Only data from patients with a checked consent to record linkage will have their data extracted by CCAS Business Intelligence. For retrospective data, which consists of text entries in the record, we will access and link this data to HES and ONS outcomes the COPI (Control of patient information) notice. The use of data for research will be mentioned on the CCAS privacy notice with an email to opt out. Patients who choose to opt-out will be identified by CCAS data team and removed from RECAP dataset. Following the process explained above in this section, CCAS Business Intelligence team will transfer previously encrypted data to Oxford secure environment using Oxfile (https://help.web.ox.ac.uk/oxfile-large-file-exchange-service) and linked to hospital outcomes. Please note, whilst text data from CCAS cannot be completely de-identified no identifiable information is used in the analyses.
Please note: COPI notice is due to expire on 31.3.22 and provisions are currently in progress to transition to Regulation 5 to allow continued access to patient free-text data (CCAS) and Doctaly data previously under COPI notice.

10. PUBLICATION POLICY
Final report synthesising the findings which will also be presented via academic peer-reviewed publications and appropriate conferences, regular lay summaries to participating practices and relevant national groups such as RCGP.

11. REFERENCES


