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

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Name & Role	Date	Signature
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Clinical Queries

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder MRC application in progress to support this collaborative project.

The Delphi process has begun using 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

API	Application Programming Interface
BRC	Biomedical Research Centre
CCG	Clinical Commissioning Group
COVID-19	Coronavirus disease 2019
CPR	Clinical Prediction Rule
CTRG	Clinical Trials and Research Governance
EHR	Electronic Health Record
EMIS	Egton Medical Information Systems
GDPR	General Data Protection Regulation
GP	General Practitioner
GSTT	Guy's and St Thomas' NHS Trust
HL7 FHIR	Health Level 7 Fast Healthcare Interoperability Resources
HRA	Health Research Authority
IRAS	Integrated Research Application System
LHS	Learning Health System
NHS	National Health Service
NEWS2	National Early Warning Score 2
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
PPI	Patient and Public Involvement
REC	Research Ethics Committee
RECAP	Remote COVID-19 Assessment in Primary Care
RSC	Research and Surveillance Centre
RCGP	Royal College of General Practitioners
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SNOMED	Systematized Nomenclature of Medicine
TPP	The Phoenix Partnership
UK	United Kingdom
WSIC	Whole Systems Integrated Care

KEYWORDS

RECAP, primary care, COVID-19, SARS-CoV-2, General Practitioner, Patient, risk score

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 LINAKGE: 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: 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.

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.

We will pilot the process, in Oxfordshire and Southwark CCGs and in North West London's Whole Systems Integrated Care CCG Collaborative (WSIC).

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.

DURATION

12 months

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.[1] This guidance formed the basis of key sections of the NICE Rapid Guideline on management of COVID-19 pneumonia in the community.[2] 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).[3] 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.[4] 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.[5] 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).[6] NEWS2 is recommended by NICE guidelines both in general[7] and as a component of the critical care of COVID-19 patients,[8] though it is not without its critics.[4 9-11]

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.[12] A region-wide quality improvement initiative in the West of England produced high compliance with NEWS2 by general practitioners,[13] and a statistically significant region-wide reduction in mortality from sepsis.[14]

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,[12] it has not been formally validated in a general practice setting,[15] so its sensitivity and specificity in that context are unknown. Its positive predictive value is low even in hospital and ambulance settings,[4 12] and is likely to be even lower in primary care due to low prevalence of serious illness,[16] though it may have some value in care homes.[17] NEWS2 was designed to be used with longitudinal data (so-called "track and trigger"), not as a one-off assessment.[4] 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.[4] Whereas the NEWS2 score fits well with the work practices and routines of paramedics, general practitioners found it time-consuming and awkward to use.[18] For all these reasons, NEWS2 might conceivably cause harm from both under- and over-referral.[19]

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[20] and most patients will be assessed remotely (i.e. by phone or video), meaning that the score will be incomplete.[1] The UK Royal College of General Practitioners has, perhaps prematurely, cautiously endorsed NEWS2 alongside clinical judgement in the context of COVID-19.[21] 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).[2]

NHS England are developing guidance on remote monitoring of patients at risk of deterioration from COVID-19 in the community, including the use of pulse oximetry to guide management. This is intended to handle potential COVID-19 patients who require medical monitoring but are not deemed in need of emergency admission at point of initial contact. Some of these patients will be at risk of deterioration and require hospital treatment, therefore it is important for those responsible for their care to be able to identify these patients quickly and easily. While at home, these patients will need periodic objective monitoring to identify if they are at risk of deterioration, and prompt urgent clinical assessment and appropriate management.

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.[22] 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.[23] 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.[24]

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.[25] 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[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.[20] The review has been done according to Cochrane Collaboration standards for rapid reviews,[27] and the included evidence has been assessed as robust (though necessarily in a largely Chinese population).

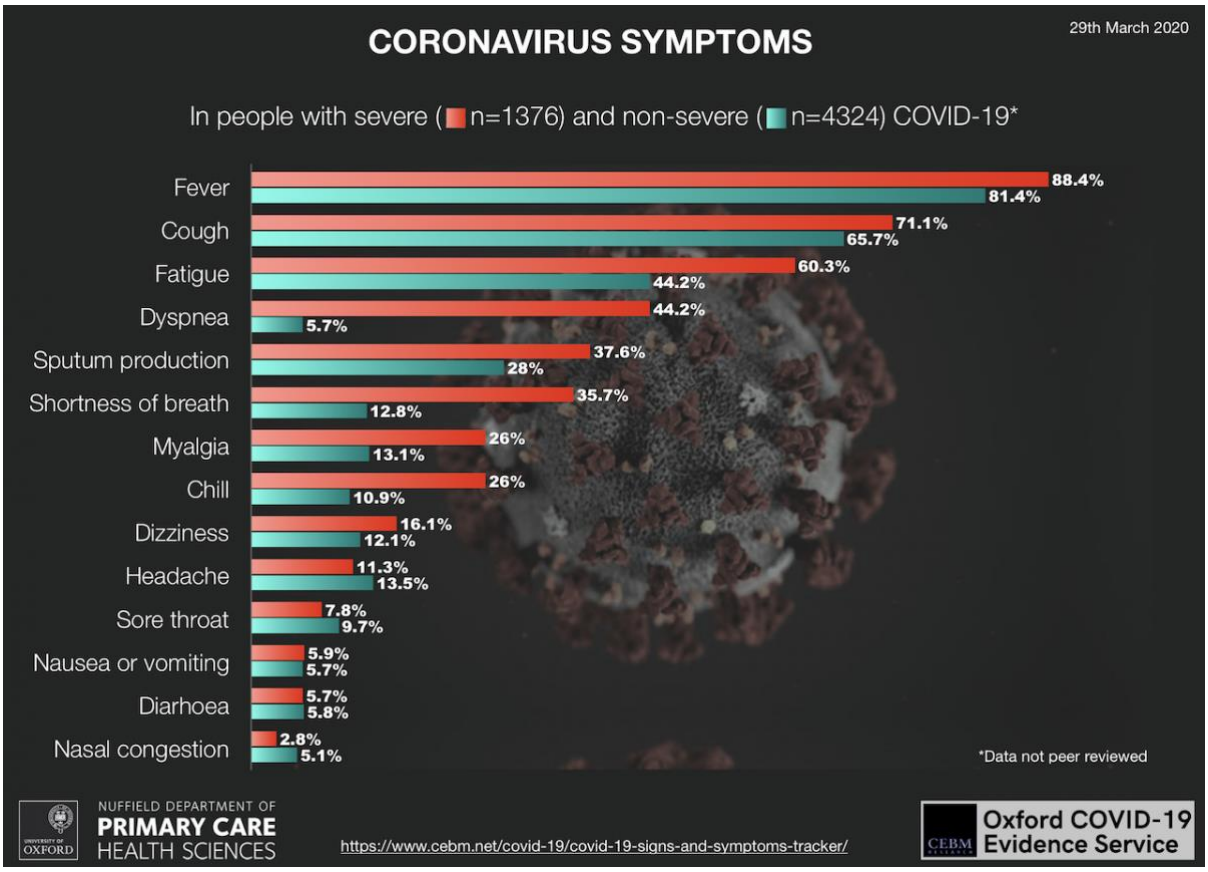

FIGURE 1: Summary of predictive value of signs and symptom data in COVID-19

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

		Score 0	Score 1	Score 2		Refer urgently
1	Heart rate (per minute) *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).*	51-90	41-50 or 91-110	111-130		≤ 40 OR > 130, IF UNEXPLAINED
2	Respiratory symptoms and signs (use higher score from 2a and 2b)					
2a	Shortness of breath *New breathlessness that patient or carer is concerned about. Take account of pre-existing conditions such as COPD.*	Not significantly breathless	Breathless on moderate exertion	Breathless on mild exertion		SEVERE DIFFICULTY IN BREATHING; CAN'T COMPLETE SENTENCES AT REST
2b	or Respiratory rate (per minute) *Assess by video, ask to place hand on chest. An anxious patient may be hyperventilating.*	12-20	21-24	9-11 or 25-29		<9 or ≥ 30
3	Hypoxia (use highest score from 3a, 3b and 3c)					
3a	Oxygen saturation at rest *Make sure patient's hands are warm and device is on correctly. Lower thresholds (typically by 6% but will vary) if patient has chronic lung disease with known hypoxia.*	96% or above ↓	95%	94%		≤ 93%
3b	Oxygen saturation after 40 steps on the flat *Do exertion test only if clinician in attendance or if saturation ≥ 96% at rest. Saturation levels may fall for 1 minute after stopping exercise.*	Fall of 0-1%	-	Fall of 2%		≥ 3%
3c	or Profound tiredness or fatigue *Most patients with COVID-19 feel some fatigue, but profound fatigue may be a feature of 'silent hypoxia'. Take account of patient's baseline level of fatigue.*	None or mild	Noticeably more tired doing usual activities	Struggling to get out of bed		UNABLE TO SPEAK BECAUSE OF TIREDNESS
4	Fever (use worst score from 4a and 4b)					
4a	Measured temperature *Tympanic thermometer preferred. Use peak temperature before paracetamol. A low reading may reflect user error.*	≤ 38 °C	> 38 °C	> 39 °C or < 35 °C		
4b	or Feverish with shivers or chills *A description by patient or carer consistent with rigors*	None	-	Shivers or chills		
5	Muscle pains	None or mild	Moderate	Severe		
6	RISK FACTORS (use both 6a and 6b)					
6a	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*	No	-	Yes		
6b	Do they have other risk factors for poor outcome? e.g. *• Age > 65 • BMI > 35 • male • non-White ethnicity • diabetes • hypertension • coronary heart disease • chronic kidney disease • adverse social circumstances*	No	1-2	3 or more		

Clinical concern component (be guided by clinical concern whatever the RECAP score)

7	After assessing the patient, what is your level of clinical concern (regardless of RECAP score)?	Low	Moderate	High		EXTREMELY HIGH

The provisional scoring is as follows:

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

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, ITU 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: 12 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. 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 teams in Oxford and KCL and explicit consent for interview will be obtained.

3.1 STUDY OUTCOME MEASURES

Primary outcome measure: Admission to hospital.
Secondary outcome measures: Admission to ITU 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 things like temperature, pulse, shortness of breath etc.

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 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 Oxfordshire and South East London CCGs and then nationally via RCGP RSC.

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 and serious 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.

Contact details for reporting SAEs
jrco@imperial.ac.uk
CI email (and contact details below)
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

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 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 18 predictor parameters, we estimate that the minimum sample size required for new model development is **988 participants** enrolled for the development set (with at least 99 events expected for a 0.1 outcome prevalence and 5.49 events per predictor parameter) and **424 enrolled for the test set**. (This is assuming we split the sample 70:30 and do the development calculation on the 70% and the validation calculation on the remaining 30%). Hence a total of 1412. Assuming a loss to follow up of 2%, due to possible linkage failure or not recording admission, the necessary sample size for the prediction model component is 1440 participants.

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.
5. Assuming a loss to follow up of 2%, due to possible linkage failure or not recording admission, the necessary sample size is 1430 participants.

Total study sample size is 1440+1430= 2870.

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: 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.

- Semi-structured interviews. Up to 30 clinicians participating in the RECAP study will be invited by random sampling to do a semi-structured interview by phone or video. They will be asked open-ended questions about their experience, based on issues raised in the RECAP email discussion forum described above.

Analysis
Interviews 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 xxx Research Ethics Committee (REC) 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 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 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 <INSERT LINK>.

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.

8.3 CONFIDENTIALITY
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

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
MRC (application in progress) are funding this study. The Delphi process has begun using existing internal funding from NIHR Oxford BRC.

No participants will receive payment in this study.

7.7 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 South East London, participating practices will complete clinical templates for managing patients with probable COVID-19 infection. Each template contains a clause covering, 'consent to use data for NHS research purposes', also including linkage of the patient's primary care data to secondary care COVID-19 data. Secondary care data will be provided by 'King's Health Partners', an NIHR Academic Health Sciences Centre (AHSC) alliance between Guy's and St Thomas Hospitals, King's College Hospital and King's College London. Secondary care NHS data will be confined to COVID-19 related healthcare episodes and will be extracted from both hospital Foundation Trusts. Both hospital Trusts will conduct data linkage between primary care data and their COVID-19 secondary care data, based on pseudonymised NHS numbers. Primary care data will be specified by the Doctaly template; secondary data will consist of hospital admission date, ICU admission date, date of discharge/death, clinical values for COVID-19 tests. Once linked, the data will be analysed in Rosalind, a research data warehouse environment for conducting analytics.

In Oxfordshire, participating practices will sign a data sharing agreement with Oxfordshire CCG – (all local practices are already part of an 'enterprise search and report' scheme which allows centralised searching and reports, but in other practices, data will have to be extracted manually). This data sharing agreement will be drawn up by Oxfordshire CCG and approved by the Chair of the CCG and also by Prof Greenhalgh from the University of Oxford, and will comply with both CCG and University policies

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.

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