

e-Appendix 1.

Hospitalization or **O**utpatient **M**anag**E**ment of patients
with a confirmed or likely SARS-**C**o**V**-2 infection.

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	Protocol	Version No: 2 Date: 04/14/2020



Hospitalization or Outpatient Management of patients with a confirmed or likely SARS-CoV-2 infection

Hospitalization or outpatient management of patients with a confirmed or likely SARS-COV-2 infection: Quasi-experimental interventional before-and-after study on professional practices after obtaining an expert consensus using the Delphi method.

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(According to version 3 dated 12/16/2019 of the framework protocol of Angers University Hospital)

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Hospitalization or outpatient management of patients with a confirmed or likely SARS-CoV-2 infection: Quasi-experimental interventional before-and-after study on professional practices after obtaining an expert consensus using the Delphi method.

SUMMARY

Study classification

Interventional study with minimal risks and restrictions

Context and grounds for the study

With around 700,000 confirmed cases and 30,000 deaths worldwide at the time of writing, SARS-CoV-2 infections are a global public health issue (1). Clinical presentations differ greatly, ranging from mere rhinitis to serious lung diseases that may lead to death (2). In the PRINCEPS study describing the characteristics of COVID-19 patients in China, 41% of patients required oxygen therapy, among which 2% required invasive ventilation (2). This suggests that more than half of the patients did not require hospital care and could potentially have been treated at home. At times of exceptional health situations, the choice between hospitalization and outpatient care is crucial as it affects hospital capacity.

In cases of lung infections, using a risk score for unfavorable outcome could help identify low-risk patients and limit the need for hospitalization (3). Many models for this already exist: PSI, CRB-65, CURB-65, qSOFA and SOFA (4-9). Some have been assessed in seasonal influenza virus infections (PSI, CURB-65 and qSOFA) (10) and/or in confirmed cases of COVID-19 (SOFA, CURB-65) (11). The clinical items of these scores differ, however, and many are difficult to use in emergency medicine because they are based on biological parameters (PSI, CURB-65, SOFA). Moreover, they do not include all the pragmatic elements that are considered in a referral decision, such as comorbidity decompensation or the impossibility to provide specific care or to follow up at home, etc.

As such, defining reliable and consensual criteria is a public health issue against a background of substantial strain on the healthcare system. The HOME-CoV study will first obtain a consensus among a wide panel of experts using the Delphi method in order to create a simple rule applicable in the Emergency Department: the HOME-CoV rule.

Our study hypothesis is that introducing consensual non-hospitalization criteria in emergency facilities for patients with a confirmed or likely COVID-19 infection will help reduce the hospitalization rate without increasing the risk of unfavorable progression.

Primary objective and endpoints:

The primary objective is to show using hierarchical analysis that, compared to normal past practices, introducing consensual non-hospitalization criteria in emergency facilities for patients with a confirmed or likely COVID-19 infection:

- 1) does not increase the unfavorable progression rate at D7 (safety endpoint),
- 2) reduces the hospitalization rate (efficacy endpoint).

The primary endpoints are:

- 1) The unfavorable progression rate, defined as the need for intubation or death (Stage ≥ 6 on the *Ordinal Scale for Clinical Improvement* developed by the World Health

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Organization) in the 7 days following admission to the Emergency Department, between the period before introducing the HOME-CoV rule and the period after introducing it.

- 2) The hospitalization rate (> 24 hours) after admission to the Emergency Department between the period before introducing the HOME-CoV rule and the period after introducing it.

Analysis based on the efficacy endpoint is only performed if non-inferiority is shown based on the safety endpoint.

Study design and conduct

Quasi-experimental interventional before-and-after study on professional practices combined with obtaining an expert consensus using the Delphi method.

Obtaining an expert consensus using the Delphi method:

Based on a first list of criteria that includes all the criteria taken into account as part of the various scores found in literature as well as pragmatic items that can affect the possibility of treating a patient at home in practice, experts (emergency physicians, infectious disease specialists, geriatricians, ethicists) anonymously express their opinion on a maximum of 10 items during 3 to 4 successive rounds until a consensus of at least 75% is obtained (12). The criteria approved make up the HOME-CoV rule. This step is completed immediately, at the same time as the first observation phase of assessing professional practices.

Assessment of the intervention:

Before phase:

During the first observational phase before introducing the HOME-CoV rule, patients reporting to participating emergency facilities with a confirmed or strongly suspected SARS-CoV-2 infection are assessed for potential inclusion. After explaining the protocol to them clearly and collecting their express consent to take part, the investigator collects the patient's clinical and paraclinical data, including all the criteria on the list that was used to obtain the expert consensus. The physician makes known their decision regarding outpatient treatment or hospitalization and specifies the criteria, among those listed, based on which the decision was made.

Rule implementation:

At the end of the observational period, the HOME-CoV rule resulting from the expert consensus is shared with all the emergency physicians and teams who are sure or likely to admit COVID-19 patients. The rule is shared through various channels (email, wall notices, pocket cards, etc.) and implementing it is made easier thanks to a digital tool for supporting decision-making, available on smartphones and computers.

After phase:

During this phase, physicians are explicitly encouraged to follow the HOME-CoV rule when making patient referral decisions.

Similarly to the before phase, patients reporting to participating emergency facilities with a confirmed or strongly suspected SARS-CoV-2 infection are assessed for potential inclusion. After explaining the protocol to them clearly and collecting their express consent to take part, the investigator collects the clinical and paraclinical data of patients included, including all the criteria on the list that was used to obtain the expert

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consensus. The physician makes known their decision regarding outpatient treatment or hospitalization and specifies the criteria, among those listed, based on which the decision was made. The 3 phases (observational, implementation and after phase) will last a maximum of two months from the first inclusion date.

Patient follow-up:

Data regarding clinical status progression according to the *Ordinal Scale for Clinical Improvement* developed by the World Health Organization for COVID-19 are collected through hospitalization records and/or during a telephone follow-up at D7 and D28 with patients, their loved ones, their attending physician or their carers.

The registry of deaths is also checked if a patient is lost to follow-up.

Inclusion criteria

- Adult patient (≥ 18 years old);
- Admitted for a COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR test or considered likely by the physician in charge of the patient;
- Not requiring treatment in the Continuing Care or Resuscitation Units or not subject to a decision to limit active treatment;
- Having given their express consent to take part in the study;
- Patient registered with or covered by a social security system.

Exclusion criteria

- Patient for whom the main diagnostic hypothesis at the Emergency Department is not a SARS-CoV-2 infection but a different differential diagnosis;
- Patient admitted to the Emergency Department 18 or more hours ago;
- Patient who cannot be followed-up at D28 for any reason;
- Patient with a poor understanding of French;
- Patient already included in the study;
- Individual in detention by judicial or administrative decision;
- Individual under compulsory psychiatric treatment;
- Individual placed under a legal protection measure;
- Individual unable to give their consent.

Data circulation and collection

The data will be collected in a case report form, either digital (Ennov Clinical) or paper depending on each center's choice. Patients are identified by the sequence number of their inclusion in the study.

The database conforms to the recommendations laid down by the French Data Protection Authority (CNIL) (MR01) as regards identifiable data (no last name or first name, date of birth collected in the format month/year, only the first letter of first and last names collected), data management and data security.

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In centers that do not have sufficient staff to carry out the telephone follow-up at D7 and D28, centralized telephone follow-up will be carried out subject to the CNIL's authorization.

Number of study participants

4,000 patients, i.e. 2,000 per period

Study duration

Inclusion duration: 2 months

Participation duration: 28 days

Study duration: 3 months

Expected outcomes and perspectives

The HOME-CoV study examines a key but seldom assessed aspect of patient management: hospitalization criteria for patients admitted to the Emergency Department for confirmed or strongly suspected COVID-19.

Obtaining a national multidisciplinary expert consensus using the Delphi method is an approved approach used increasingly often when data in literature is limited. Moreover, given the urgency of the situation, the study will help obtain a consensus quickly. Using before-and-after analysis, the HOME-CoV study will help assess, in a scientific quasi-experimental manner, how implementing this consensual rule regarding hospitalization criteria affects patient outcomes.

The expected benefits are substantial. For patients identified as low-risk, the possibility to stay at home rather than be hospitalized should improve their quality of life and prevent unnecessary exposure in the context of the pandemic. For others, recognizing that their health condition justifies hospitalization means that they will receive appropriate monitoring and care, and will probably reduce the risk of their condition deteriorating.

For physicians, having access to support with decision-making through criteria recognized and approved by experts and their peers will help them feel confident about their decisions in uncertain times. For society as a whole, defining and applying consensual hospitalization criteria helps organize care and resources effectively, particularly hospital beds.

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1. Context and scientific grounds for the study

1.1. Current state of the art

With close to 700,000 confirmed cases and 30,000 deaths worldwide, SARS-CoV-2 infections are a global public health issue (1). On January 30, 2020, WHO declared that the COVID-19 epidemic was a public health emergency of international concern (PHEIC) (13). Clinical presentations of SARS-CoV-2 infections differ greatly, ranging from mere rhinitis to serious lung diseases to death (2). In the main study describing the characteristics of COVID-19 patients in China, 41% of patients required oxygen therapy. Among them, 5% required non-invasive ventilation and 2% required invasive ventilation (2). This suggests that more than half of the patients did not require hospital care.

At times of exceptional health situations, the choice between hospitalization and outpatient care is crucial because the hospitalization rate affects hospital capacity within the Emergency Department and the institution as a whole. In cases of lung infections, using a risk score for unfavorable outcome or death could help identify low-risk patients and limit the need for hospitalization (3).

There are many risk prediction models for acute bacterial pneumonias and, more broadly, for sepsis (PSI, CRB-65, CURB-65, qSOFA and SOFA (4-9)). Some scores have been assessed in seasonal influenza virus infections (PSI, CURB-65 and qSOFA) (10). In a retrospective study involving 191 confirmed cases of COVID-19, age, SOFA and D-dimer concentration were independent risk factors for death (11). The clinical items of these scores greatly differ, however, and many are difficult to use in emergency medicine because they are based on biological parameters (PSI, CURB-65, SOFA, D-dimers) (Table 1). Moreover, they do not include all the elements that are considered in a referral decision, such as the need for care that can be provided in hospital only (oxygen therapy), comorbidity decompensation (heart failure, diabetes, etc.), the impossibility to provide specific care at home, and other factors.

As such, defining reliable and consensual criteria is a public health issue against a background of substantial strain on the healthcare system. The HOME-CoV study will start with obtaining a national consensus among a wide panel of experts using the Delphi method in order to create a simple rule applicable in the Emergency Department: the HOME-CoV rule.

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The purpose of HOME-CoV is to assess, through a quasi-experimental interventional before-and-after study, how implementing consensual hospitalization criteria (the HOME-CoV rule) affects professional practices as regards safety and efficacy.

Table 1. Comparison of items across scores.						
Scores	PSI Fine	CUR B-65	CRB- 65	SMART- COP	qSOFA	SOFA
Age > 65 years	Weight	✓	✓			
Neoplasia	✓					
Liver disease	✓					
Heart failure	✓					
Cerebrovascular disease	✓					
Kidney disease	✓					
Impaired consciousness	✓					
Confusion		✓	✓	✓	✓	
RR > 30/min	✓	✓	✓	✓		
RR < 22/min					✓	
Oxygen saturation < 90%				✓		
Systolic blood pressure > 90 mmHg	✓	✓	✓	✓		✓
Systolic blood pressure > 100 mmHg					✓	
Diastolic blood pressure < 60 mmHg		✓	✓			
Temperature < 35°C or > 40°C	✓					
HR > 125 bpm	✓			✓		
Arterial pH < 7.35	✓			✓		
Urea > 11 mmol/L	✓					
Urea > 7 mmol/L		✓				
Albumin < 35 mmol/L				✓		
Sodium < 130 mmol/L	✓					
Glucose > 14 mmol/L	✓					
Hematocrit < 30%	✓					
Thrombocytopenia < 150 x10 ⁹ /L						✓
Bilirubinemia						✓
Kidney failure						✓
Partial pressure of oxygen < 60 mmHg	✓			✓		
PaO ₂ /FiO ₂ ratio < 250				✓		✓
Pleural effusion	✓					
Multilobar pneumonia on x-ray				✓		

1.2.Study hypotheses

Our study hypothesis is that introducing consensual non-hospitalization criteria in emergency facilities for patients with a confirmed or likely COVID-19 infection will help reduce the hospitalization rate without increasing the risk of unfavorable progression.

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1.3. Justification of methodology choices

The choice of a quasi-experimental before-and-after study was made by taking into account resource constraints (the Emergency Department faced with this health crisis) and time constraints (the need to provide answers as soon as possible to help guide practices in light of data unavailability).

The study includes a Delphi method that helps obtain an expert consensus regarding a daily challenge in emergency facilities (12). It seemed important to share widely the consensus in France once it had been obtained. As such, a cluster-randomized trial by center or a stepped wedge cluster randomized trial could not be considered. The methodology chosen is therefore the simplest and the most appropriately adapted to our question and to the exceptional health situation we face.

The choice to perform hierarchical analysis based on two endpoints as the main analysis is justified by the fact that too high an increase in the number of patients discharged home and required to isolate could limit their access to healthcare and negatively affect disease progression. It therefore seemed necessary to show that there would be no increase in the unfavorable progression rate (non-inferiority analysis) before demonstrating the rule's efficacy as regards discharging patients home.

The urgency of the exceptional health situation linked to COVID-19 infections justifies setting up the study within a very short period of time and conducting it quickly thanks to the participation of many centers and a relatively short follow-up time (28 days).

2. Study objectives and endpoints

2.1. Primary objective and endpoint

The primary objective is to show using hierarchical analysis that, compared to normal past practices, introducing consensual non-hospitalization criteria in emergency facilities for patients with a confirmed or likely COVID-19 infection:

- 1) does not increase the serious unfavorable progression rate at D7 (safety endpoint),
- 2) reduces the hospitalization rate (efficacy endpoint).

The primary endpoints are:

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1) The serious unfavorable progression rate, defined as the need for intubation or death (Stage ≥ 6 on the *Ordinal Scale for Clinical Improvement* developed by the World Health Organization) in the 7 days following admission to the Emergency Department, between the period before introducing the HOME-CoV rule and the period after introducing it.

The *Ordinal Scale for Clinical Improvement* is a scale specific to COVID-19 put forward by WHO in February 2020. It has 9 scores (14).

0: Patient at home with no clinical or virological evidence of infection

1: Ambulatory patient at home with no limitation of activities

2: Ambulatory patient at home with limitation of activities (or oxygen)

3: Hospitalized patient with mild disease, no oxygen therapy

4: Hospitalized patient with mild disease, oxygen therapy (prongs, mask)

5: Hospitalized patient with severe disease, under non-invasive ventilation or high-flow nasal oxygen therapy

6: Hospitalized patient with severe disease, under intubation and invasive ventilation

7: Hospitalized patient with severe disease, under intubation and with an additional organ failure justifying invasive therapy (renal replacement therapy, amine vasopressors, extra-corporeal membrane oxygenation)

8: Death for any reason.

2) The hospitalization rate after admission to the Emergency Department between the period before introducing the HOME-CoV rule and the period after introducing it. A visit to the Emergency Department lasting > 24 hours will be considered a hospitalization.

2.2.Secondary objective(s) and endpoint(s)

The secondary objectives are:

i. Assess how implementing consensual criteria regarding non-hospitalization (the HOME-CoV rule) in emergency facilities affects the outcome of patients with a confirmed or strongly suspected SARS-CoV-2 infection, based on time until D28.

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- ii. Assess the rate of actual compliance with the HOME-CoV rule in practice after it has been implemented.
- iii. Assess the predictive capabilities of the HOME-CoV rule performed at inclusion based on time.
- iv. Assess and compare the predictive capabilities of the HOME-CoV rule and the CRB-65, CURB-65, PSI, qSOFA and SOFA scores based on time.
- v. Analyze the intervention's impact in the sub-group of patients with a confirmed SARS-CoV-2 infection.
- vi. Analyze the outcome of patients not hospitalized after their admission to the Emergency Department.

The secondary endpoints are:

- 1) The serious unfavorable progression rate, defined as the need for tracheal intubation with mechanical ventilation or death (Stage ≥ 6 on the *Ordinal Scale for Clinical Improvement* developed by the World Health Organization) in the 28 days following inclusion.
- 2) The rate of compliance with the HOME-CoV rule criteria specified in the expert consensus after the rule has been implemented.
- 3) The area under the ROC curve of the HOME-CoV rule based on inclusion time at D28, to predict:
 - mortality for any reason;
 - serious unfavorable progression, defined as the need for tracheal intubation with mechanical ventilation or death (Stage ≥ 6 on the *Ordinal Scale for Clinical Improvement* developed by the World Health Organization) measured from inclusion to D28.
- 4) The area under the ROC curve time-dependent on the HOME-CoV rule compared to that of the CRB-65, CURB-65, PSI, SOFA and qSOFA scores to predict, for patients in the interventional phase:
 - mortality for any reason within 28 days following inclusion;
 - serious unfavorable progression, defined as the need for tracheal intubation with mechanical ventilation or death (Stage ≥ 6 on the *Ordinal Scale for Clinical*

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Improvement developed by the World Health Organization) measured from inclusion to D28.

5) The endpoints will be the same as those specified above, measured in the sub-group of interest, i.e. patients with a SARS-CoV-2 infection diagnosis confirmed either by RT-PCR testing or a chest CT scan.

6) The status of patients not hospitalized according to the *Ordinal Scale for Clinical Improvement* developed by WHO at D7 and D28.

3. Study design

3.1. Study type

HOME-CoV is a quasi-experimental interventional before-and-after study on professional practices combined with obtaining an expert consensus using the Delphi method.

Obtaining an expert consensus using the Delphi method:

Based on a first list of criteria defined by the scientific committee, experts (emergency physicians, infectious disease specialists, geriatricians, ethicists) anonymously express their opinion on a maximum of 10 items during 3 to 4 successive rounds until a consensus of at least 75% is obtained (12). The criteria approved make up the HOME-CoV rule. This step is completed immediately, at the same time as the first observation phase of assessing professional practices.

Assessment of the intervention through a before-and-after study:

The study is divided into two phases or periods: an initial phase before the HOME-CoV rule is introduced and an interventional phase after the rule is introduced.

During both phases, and in a strictly identical manner before and after introducing the rule, the investigators assess patients for potential inclusion, collect patient clinical and paraclinical data (including all the criteria on the list that was used to obtain the consensus of experts) and indicate their referral decisions (hospitalization or not).

Patients are followed up at D7 and D28 (consultation of hospital records and/or telephone call) to determine the clinical status progression according to the *Ordinal Scale for Clinical Improvement* developed by the World Health Organization for COVID-19.

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3.2. Justification of the number of people to be included in the study

Considering that the unfavorable progression rate defined by the need for tracheal intubation for artificial ventilation or death would be 5% at D7 from admission to the Emergency Department, without a significant difference between the two periods, 1,469 patients should be included and analyzable in each period in order to show, with a power of 80%, that the upper limit of the 95% confidence interval of the difference between the two periods does not exceed 2% (non-inferiority margin as an absolute value) in favor of the period before the intervention (unilateral analysis).

Considering that 34 centers (in France and Belgium) took part in each period (i.e. 50 clusters) and that the intra-class correlation amounted to 0.02, an inflation factor of 1.3 must be applied, i.e. a total number of 4,000 patients (2,000 in each period), allowing for the possibility of up to 5% of patients lost to follow-up.

This number will be sufficient to show, as part of hierarchical analysis, a 6% difference in the hospitalization rate (60% during the period before and 54% during the period after) with a power of 80%, an alpha risk of 5% and an intra-class correlation of 0.02.

4. Screening of study participants

4.1. Inclusion criteria for study participants

- Adult patient (≥ 18 years old);
- Admitted for a COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR test or considered likely by the physician in charge of the patient;
- Not requiring treatment in the Continuing Care or Resuscitation Units or not subject to a decision to limit active treatment;
- Patient registered with or covered by a social security system;
- Patient who has given their express consent.

4.2. Exclusion criteria for study participants

- Patient for whom the main diagnostic hypothesis at the Emergency Department is not a SARS-CoV-2 infection but a different differential diagnosis;
- Patient admitted to the Emergency Department 18 or more hours ago;
- Patient who cannot be followed-up at D28 for any reason;
- Patient with a poor understanding of French;
- Patient already included in the study;
- Individual in detention by judicial or administrative decision*;

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- Individual under compulsory psychiatric treatment*;
- Individual placed under a legal protection measure*;
- Individual unable to give their consent*.

Given the low risks linked to the study and the expected potential benefits, pregnant, parturient and breastfeeding women who are able to give their own consent may be included.

**Such individuals cannot be included because they are unable to give their own consent and, in light of the exceptional epidemic circumstances linked to this study, the inclusion procedures would be too complex to put in place.*

5. Care and treatments administered to study participants

5.1.Consensual criteria for non-hospitalization: the HOME-CoV rule

Non-hospitalization criteria are defined by an expert consensus according to the Delphi method. The method is recommended when scientific evidence is scant. The process involves giving anonymous iterative questionnaire surveys to a panel of professional experts, specializing in different areas if possible, until a consensus is obtained.

To develop the HOME-CoV rule, the consulted experts who accepted to take part are emergency physicians, infectious disease specialists, geriatricians and ethicists.

The study scientific committee created a first list of criteria including all the criteria taken into account as part of the various scores found in literature to stratify the risk of infectious lung diseases as well as pragmatic items that can affect the possibility of treating a patient at home in practice and taken into account in hospitalization rules for other disorders (such as the HESTIA rule for patients with a pulmonary embolism)(15-17).

During the first round of the Delphi approach, experts anonymously express their opinion on a maximum of 10 items using an online questionnaire. They can also add any criteria they deem important that are not mentioned on the initial list. The answers are given within 48 hours. The organizer, i.e. the principal investigator, analyzes the results. Criteria approved by 90 or more percent of experts are kept, and those rejected by 90 or more percent are removed. During the second round, the remaining criteria and those added during the first round are assessed. Experts once again express their opinions, within 48 hours after the questionnaire is sent, on a number of items equal to 10 minus the number of items approved during the first round. The principal investigator analyzes the results of the second round. Criteria approved by 75 or more percent of experts are kept, and those

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rejected by 75 or more percent are removed. The remaining criteria are put forward during a third round, and so forth until a consensus of at least 75% is obtained (12). The criteria approved make up the HOME-CoV rule.

This step is completed immediately, at the same time as the first observation phase of assessing professional practices.

5.2. Definition of assessment and intervention periods

The study is divided into two phases or periods: an initial phase before the HOME-CoV rule is introduced and an interventional phase after the rule is introduced.

Before phase:

During the first observational phase before introducing the HOME-CoV rule, patients reporting to participating emergency facilities with a confirmed or strongly suspected SARS-CoV-2 infection are assessed for potential inclusion. After explaining the protocol to them clearly and collecting their express consent to take part, the investigator collects the patient's clinical and paraclinical data, including all the criteria on the list that was used to obtain the expert consensus. The physician makes known their decision regarding outpatient treatment or hospitalization and specifies the criteria, among those listed, based on which the decision was made.

Rule implementation:

At the end of the observational period, the HOME-CoV rule resulting from the expert consensus is shared with all the emergency physicians and teams who are sure or likely to admit COVID-19 patients. The rule is shared through various channels (email, wall notices, pocket cards, etc.) and implementing it is made easier thanks to a digital tool for supporting decision-making, available on smartphones and computers.

After phase:

During this phase, physicians are explicitly encouraged to follow the HOME-CoV rule when making patient referral decisions.

Similarly, to the before phase, patients reporting to participating emergency facilities with a confirmed or probable SARS-CoV-2 infection are assessed for potential inclusion. After explaining the protocol to them clearly and collecting their express consent to take part, the investigator collects the clinical and paraclinical data of patients included, including

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all the criteria on the list that was used to obtain the expert consensus. The physician makes known their decision regarding outpatient treatment or hospitalization.

The 3 phases (observational, implementation and after phase) will last a maximum of two months from the first inclusion date.

Patient follow-up:

Data regarding clinical status progression according to the *Ordinal Scale for Clinical Improvement* developed by the World Health Organization for COVID-19 are collected through hospitalization records and/or during a telephone follow-up at D7 and D28 with patients, their loved ones, their attending physician or their carers.

Individuals in charge of patient follow-up check the public registry of deaths if a patient is lost to follow-up (<https://www.data.gouv.fr/fr/datasets/fichier-des-personnes-decede/>).

5.3.Associated care and treatment

Apart from the follow-up specific to the study and to the HOME-CoV rules used in period 2, such as support with decision-making (hospitalization or not), care and follow-up are carried out as normal in accordance with clinical recommendations and standard procedures.

6. Study conduct

6.1.Pre-screening/Recruitment

Individuals eligible to take part in the study are patients admitted to emergency facilities in participating centers for a confirmed or strongly suspected SARS-CoV-2 infection.

The investigator may pre-screen patients using their medical records according to the various inclusion criteria that could be assessed at the time without informing the patient.

6.2.Inclusion procedure

During their visit to the Emergency Department (inclusion visit), if the patient meets the screening criteria for the study, the investigator provides them with oral and written (a letter written in a language that the patient understands) information and answers any of their questions. If a patient accepts to take part, the investigator collects their consent.

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The information date, the cooling-off period and the date that the express consent form is signed are recorded in the patient's source folder.

6.3. Study participant follow-up

6.3.1. Inclusion visit

After the patient is included, the investigator collects the clinical and paraclinical data of included patients, including all the criteria on the list that was used to obtain the expert consensus. The physician makes known their decision regarding outpatient treatment or hospitalization and specifies the criteria, among those listed, based on which the decision was made.

The patient's final referral is collected:

- Discharge home, including family home and nursing home (EHPAD);
- Hospitalization. Patients whose visit to the Emergency Department exceeds 24 hours are considered hospitalized.

For hospitalized patients, the need for oxygen therapy or lack thereof is indicated (level 3 or 4 on the OSCI developed by WHO).

6.3.2. Assessment at D7

The clinical status progression of patients at the seventh day (D7) after admission to the Emergency Department (D0) is collected according to the OSCI developed by WHO. To this end, the records of hospitalized patients are analyzed and/or the patients, their loved ones, their attending physicians or their carers are contacted by phone at D7 or in the following days.

6.3.3. Assessment at D28

The clinical status progression of patients at the 28th day (D28) after admission to the Emergency Department (D0) is collected according to the OSCI developed by WHO. To this end, the records of hospitalized patients are analyzed and the patients, their loved ones, their attending physicians or their careers are contacted by phone at D28 or in the following days.

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6.4. Withdrawal of a study participant

Study participants can request to withdraw from the study at any time and for any reason.

The investigator may either temporarily pause or permanently end a person's participation for any reason that would best serve the interests of that particular person in case of a serious undesirable effect or a new factor arising in the study.

If a patient is lost to follow-up, the investigator makes every effort to regain contact with the person and to provide the follow-up foreseen by the study. In case of early withdrawal, the investigator records the reasons in as much detail as possible.

Participants lost to follow-up or who withdraw early from the study are not replaced.

The data collected for patients lost to follow-up or who withdraw early from the study will be used at the analysis stage, including in cases where consent is withdrawn (unless the patient requests to exercise their right to have their data erased). If the patient requests to have their data erased, the data required to assess data relating to safety will be stored.

6.5. Study duration

Study duration

Inclusion duration: 2 months

Participation duration: 28 days

Study duration: 3 months

7. Risk/benefit ratio

The foreseeable risks and constraints for participants, as described in the paragraphs below, are acceptable in light of the expected benefits.

7.1. Benefits

7.1.1. Individual benefits

The expected benefits are substantial. For patients identified as low-risk, the possibility to stay at home rather than be hospitalized should improve their quality of life and prevent unnecessary exposure in the context of the pandemic. For others, recognizing that their health condition justifies hospitalization means that they will receive appropriate care and will reduce the risk of their condition deteriorating. Strict, consensual criteria also help

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reassure patients that the decision to hospitalize them or not is not affected by a hospital's bed capacity.

7.1.2. Collective benefits

For physicians, having access to support with decision-making through criteria recognized and approved by peers and experts will help them feel confident about their decisions in uncertain times. For society as a whole, defining and applying consensual hospitalization criteria helps organize care and resources effectively, particularly hospital beds.

7.2.Risks

Theoretical risks to patients are linked to home-based care with mandatory isolation that could limit their access to care if their clinical condition deteriorates and result in delayed treatment. Applying the HOME-CoV rule is likely to increase the rate of home-based care. However, criteria are approved in a consensual way by many experts. Moreover, physicians responsible for patients can choose not to follow the HOME-CoV rule. In such cases, they must specify their reasons for doing so.

8. Safety assessment

As the study involves human participants and presents minimal risks and constraints, adverse events/adverse effects/incidents must be declared to different health watchdogs as applicable to each product or practice in question (scrutiny of care, pharmacovigilance, materials vigilance, hemovigilance, etc.), in accordance with current regulations.

It is recommended that declaring physicians specify that the patient is included in a clinical study and indicate the exact clinical trial in question.

9. Statistics

Descriptive analysis. Quantitative variables will be described using mean +/- standard deviation when their distributions can be considered normal. Otherwise, they will be described using median and interquartile range. Qualitative variables will be described using numbers and frequencies. A comparison of patient characteristics between the two

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referral strategies will be assessed using Student's t-test, the Mann-Whitney U test or Fisher's exact test depending on the context.

Primary objective. First, to balance the two patient groups between the two referral strategies, propensity score analysis with multilevel data will be performed by center (18). The analysis will be performed using Inverse Probability of Treatment Weighting (IPTW) (19), using the WeightIt R package.

To meet the primary objective, the question about the safety rule will first be answered. This will involve calculating the 95% confidence interval of the difference of the rate of intubation or death (composite safety endpoint) at D7 between the intervention period and current practice. This confidence interval will be calculated within a mixed logistic model including a random effect on the center. The calculation will be performed using the lmerTest R package. If the upper limit of this interval does not exceed the non-inferiority margin, defined in the protocol at 2%, the non-inferiority of the intervention period will be confirmed.

The efficacy endpoint can then be analyzed, if and only if the non-inferiority is shown. The purpose of this hierarchical strategy is to manage the multiple testing, i.e. to not increase the alpha risk.

This efficacy endpoint will also be assessed within a mixed logistic model including a random effect on the center. The HOME-CoV rule will be deemed effective only if the hospitalization rate is significantly lower in the intervention group.

Secondary objectives. The first secondary objective will be assessed in the same way as the primary safety objective. The only difference concerns assessing the endpoint, which will be done at D28.

Dynamic assessment of the prognostic accuracy of the various scores at inclusion will be assessed using time-dependent AUC as well as their confidence intervals.

The prognostic accuracy at different times of the HOME-CoV rule will be deemed adequate if the lower limit of the 95% confidence interval of the AUC is higher than 0.7.

Time-dependent AUCs will be assessed and compared using the timeROC R package (20). Optimum adjustment of multiple testing will be carried out to allow for a stringent control of the FWER at 5% (Blanche, P., Dartigues, J. F., & Riou, J. 2020. *Biometrics*, [IN PRESS]).

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All analyses will be performed using R software (R Foundation for Statistical Computing; 2008/. <http://www.R-project.org>). All statistical tests will be performed with p-values of 5%.

Missing data. There are no plans to perform imputation of missing data. Missing data will, however, be analyzed in order to determine whether they are informative and whether they are likely to cause a potential screening or information bias.

Multiple testing. Objectives will be managed in a hierarchical manner, allowing for fewer multiplicity concerns. Moreover, when necessary, adjustment will be performed to allow for control of the FWER at a risk of 5%.

10. Data management

10.1. Data collection methods

All the data relating to this study are collected using a standard electronic case report form (eCRF) or a paper case report form (CRF) depending on each center's choice and based on valid documents (patient's medical records). In the CRF, telephone follow-up questionnaires and patients are identified by a unique number made up of the center number and the patient's number in the center. The initials of the first and last name are also collected.

In light of the exceptional epidemic circumstances, it is expected that some centers may be unable to carry out the telephone follow-up at D7 and D28. For centers unable to follow up on included patients by phone at D7 and D28, Angers University Hospital will carry out the telephone follow-up, provided that it obtains authorization to do so from the French Data Protection Authority (CNIL). The data required to perform this centralized follow-up will not be shared until the authorization has been obtained.

For centers unable to follow-up, identity data necessary to perform the centralized follow-up will be collected using a paper form. The data will then be faxed to the team responsible for centralized follow-up only after authorization has been obtained. Data collected during the centralized follow-up will be included on the eCRF. The original copies of the centralized follow-up questionnaires will be sent by the coordination center to the investigation centers regularly throughout the study so that patient medical records can be archived.

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Patient identities and their personal health information will be kept confidential by restricting access to their records and to CRFs at all times. Patient-identifying data can be viewed only by study investigators and qualified staff responsible for conducting the study as well as assessors appointed by the sponsor to ensure that data is accurate, and by other members of regulatory bodies legally authorized to access the data. Lastly, confidential data will be shared if required by applicable laws and regulations.

The eCRF (Ennov Clinical) is managed by the Delegation for Clinical Research and Innovation (DRCI) of Angers University Hospital. It can be accessed using an Internet browser.

10.2. Data circuit and confidentiality

Individuals who have direct access to the data take all the necessary precautions to ensure the confidentiality of information relating to study participants, and particularly their identity and the results obtained. These individuals are bound by professional secrecy (according to the terms defined by Articles 226-13 and 226-14 of the French Penal Code).

Data are collected in coded form. Study participants are identified by a number made up of the center number and their inclusion order number used at the center. Only the first letters of the study participant's name and last name are collected, along with the month and year of their birth.

Each center keeps a mailing list, for which the center's principal investigator is responsible. This list is kept for the prescribed duration for this type of study.

10.3. Right to access data and source documents

In accordance with Good Clinical Practice:

- the sponsor ensures that each study participant gives their written consent to access to their personal data, which is strictly necessary for quality control purposes.
- investigators ensures that the documents and individual data strictly necessary for this control are available to the individuals responsible for follow-up, quality control, study auditing and, where necessary, inspections by relevant authorities.

10.4. Quality control and assurance

A monitoring plan is arranged according to the study risks, as defined by the sponsor's procedures.

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10.5. Archiving

The investigator and the sponsor ensure that study documents and data are stored in accordance with current regulations. The methods used to store these essential documents must ensure that the documents remain complete and legible for the entire period for which their storage is required.

The investigator is responsible for the storage of key study documents at the study site. If the investigator leaves the institution, they must inform the sponsor and delegate responsibility for the continuity of written records.

11. Ethical considerations and regulations

11.1. Study classification

For France, this study involving human participants is classed as an interventional study with minimal risks and constraints in accordance with French Decree of April 12, 2018 establishing the list of types of study mentioned in part 2 of Article L.1121-1 of the French Public Health Code given that the HOME-CoV rule spread across and implemented at participating centers is likely to influence the decision whether to hospitalize or not patients included in the study.

For Monaco, this study is considered an interventional study.

11.2. Institutional Review Board and competent authority

The study file (including the protocol, the summary, and the patient information sheet) has been submitted to the Institutional Review Board (Comité de Protection des Personnes, CPP) Ouest IV, which delivered a favorable opinion with regard to conducting this study for France.

The study file was also submitted to the Consultative Institutional Review Board of the Principality of Monaco, which delivered a favorable opinion with regard to conducting this study for Monaco, as well as to the Institutional Review Board of Saint-Luc University Clinic and Liège University Hospital, which delivered a favorable opinion with regard to conducting this study for Belgium.

If the investigator makes substantive changes to the study file, they must be approved by the sponsor, who must request the opinion of the Institutional Review Board (CPP) before the study can be conducted.

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The sponsor will inform the Institutional Review Board (CPP) of the study end date within 90 days. The study end date will be the day that the last participant stops taking part in the trial or, if applicable, the theoretical study end date specified in the protocol (if the inclusion objective is not achieved and an extension is not requested).

11.3. Processing of personal data

Data processing for this study falls within the framework of the "Reference Methodology" (MR-001) in accordance with the provisions of the French Data Protection Act (Law No. 78-17) as amended of January 6, 1978. Angers University Hospital, the study sponsor, has signed an agreement to comply with this "Reference Methodology" (declaration number: 1174822).

The data relating to this study is processed in accordance with the EU General Data Protection Regulation, which entered into force on May 25, 2018 and with the French Data Protection Act.

An authorization request will be submitted to CNIL to ensure centralized follow-up of patients in centers that are unable to follow-up themselves. The data required to perform this centralized follow-up will not be shared with the coordination center until authorization has been obtained from CNIL.

11.4. Protocol specificities

11.4.1. *Concomitant participation in another study and definition of the exclusion period*

This protocol does not forbid participating in another study at the same time, nor does it set an exclusion period during which the study participants cannot take part in another interventional study.

11.4.2. *Indemnity of study participants*

No indemnity or compensation for any constraints incurred is foreseen for study participants.

11.4.3. *Insurance*

The Sponsor has taken out an insurance policy for the entire duration of the trial, guaranteeing its own civil liability and that of all physicians and employees involved in the study (insurance provided by SHAM, Société Hospitalière d'Assurances Mutuelles: policy

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number 147412). The Sponsor will also provide full compensation for any harmful consequences of the study to participants and their beneficiaries, unless it is able to prove that the damage is not attributable to its fault or to that of any person involved in the study, without it being possible to hold them responsible or liable for a third party's actions or the voluntary withdrawal from the study by a person who had initially consented to take part in the study.

12. Regulations relating to publication

The papers and scientific reports corresponding to this study will be drafted under the responsibility of the study's coordinating investigator, together with the chief co-investigators and associated scientists. The co-authors of the report and publications are the investigators and clinicians involved, on a pro-rata basis according to their contribution to the study, as well as the methodologist and/or biostatistician and associated researchers.

The study's main findings must be the subject of a final report and a specific publication and/or scientific presentation. Unless specifically authorized, no study phases may be the subject of an oral presentation or poster before the corresponding manuscript is accepted by a referenced journal.

Angers University Hospital is mentioned in all publications regarding this study.

The study will be registered on an open-access website (ClinicalTrials.gov) before the first participant is included in this study.

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e-Appendix 2. Multimodal intervention.

1. Four video conference slots with the investigators comprising:
 - the presentation of the background and the aims of HOME-CoV rule,
 - the presentation of the way to assess each item of the HOME-CoV rule,
 - inclusion and follow-up of enrolled patients,
 - a question-and-answer session.
2. *Poster and pocket cards presenting:*
 - inclusion and non-inclusion criteria in the study,
 - the HOME-CoV rule.
3. Promotion of the implementation of the HOME-CoV rule in local electronic Health Record.
4. Forum
 - Instant messaging between all the investigators.

e-Appendix 3. The Ordinal Scale for Clinical Improvement is a scale specific to COVID-19 put forward by WHO in February 2020.

0: Patient at home with no clinical or virological evidence of infection

1: Ambulatory patient at home with no limitation of activities

2: Ambulatory patient at home with limitation of activities (or oxygen)

3: Hospitalized patient with mild disease, no oxygen therapy

4: Hospitalized patient with mild disease, oxygen therapy (prongs, mask)

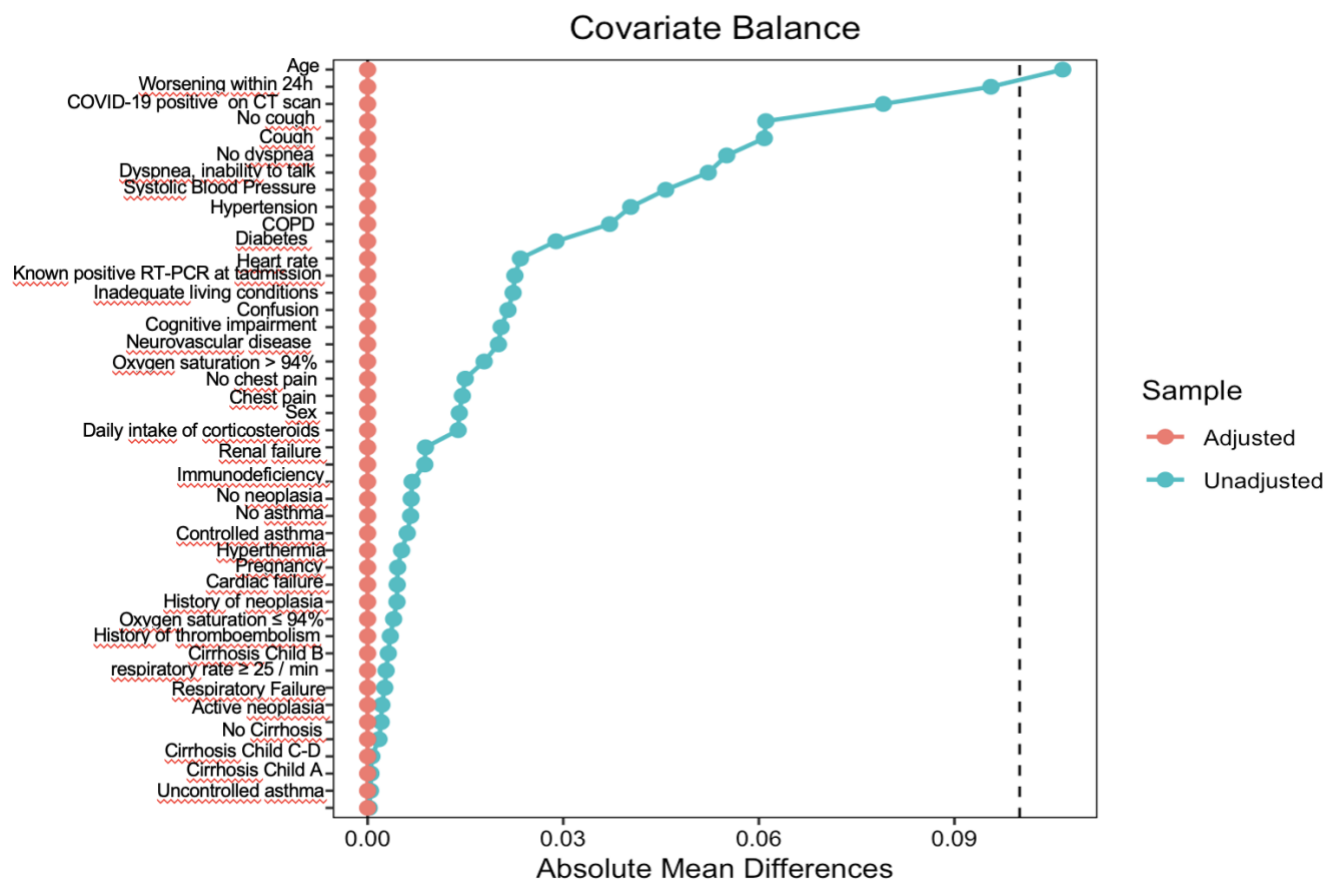
5: Hospitalized patient with severe disease, under non-invasive ventilation or high-flow nasal oxygen therapy

6: Hospitalized patient with severe disease, under intubation and invasive ventilation

7: Hospitalized patient with severe disease, under intubation and with an additional organ failure justifying invasive therapy (renal replacement therapy, amine vasopressors, extra-corporeal membrane oxygenation)

8: Death for any reason.

e-Figure 1. Love Plot for Balance in Baseline Characteristics.



COVID-19: CoronaVirus Disease-19; CT scan: Computerized Tomography; COPD: Chronic Obstructive Pulmonary Disease;; RT-PCR: Reverse Transcriptase – Polymerase Chain Reaction for SARS-CoV-2

e-Table 1. Characteristic of patients with positive RT-PCR SARS-CoV-2.

Characteristics	Total n=529 (%)
Age – mean \pm SD – yr	55.9 (\pm 20.2)
Female sex – no. (%)	290 (54.8)
<i>Medical history – no. (%)</i>	
Severe cognitive impairment	9 (1.7)
COPD state III/IV	5 (0.9)
Chronic respiratory failure	6 (1.1)
Controlled asthma or unstable asthma	45 (8.5)
Severe or End-stage renal disease (GFR < 30ml/min)	15 (2.8)
Hepatic cirrhosis child B or C	4 (0.8)
Chronic cardiac failure NYHA III/IV	4 (0.8)
Hypertension	188 (35.5)
Diabetes	92 (17.4)
History of thromboembolism	7 (1.3)
Cancer history or active cancer	14 (2.6)
Immune deficiency and HIV	5 (0.9)
<i>Signs and symptoms – no. (%)</i>	
Anosmia, ageusia, dysgeusia	149 (28.2)
Cough	378 (71.5)
Dyspnea	341 (64.5)
Diarrhea	119 (22.5)
Chest pain	139 (26.3)
Confusion, impaired alertness	43 (8.1)
Worsening in the last 24 hours	282 (53.3)
Heart rate \geq 120 beats/min	32 (6.1)
Systolic blood pressure < 90 mmHg	6 (1.1)
Body Mass index \geq 30 kg/m ²	89 (16.9)
Pulse oxygen saturation \leq 94% in ambient air or necessity of oxygen therapy	172 (32.6)
Respiratory rate \geq 25/min	28 (5.3)
Ability to speak or count without resuming breathing < 8 seconds	64 (12.4)

e-Table 2. Characteristics of patients with an adverse evolution at 7 days.

<i>Patient characteristics</i>	Adverse evolution n=57 (%)	No adverse evolution n=2943 (%)
<i>Demographic characteristics</i>		
Age – mean ± SD – yr	80 ± 14	51 ± 20
Female sex – no. (%)	29 (50.9)	1616 (54.9)
<i>Medical history – no. (%)</i>		
Severe cognitive impairment	3 (5.3)	21 (0.7)
COPD stage III/IV	7 (12.3)	50 (1.7)
Chronic respiratory failure	4 (7.0)	40 (1.4)
Controlled or unstable asthma	6 (10.5)	315 (10.7)
Severe or end-stage renal disease (GFR < 30ml/min)	2 (3.5)	51 (1.7)
Hepatic cirrhosis child B or child C	0 (0)	17 (0.6)
Chronic cardiac failure NYHA III/IV	2 (3.5)	35 (1.2)
Hypertension	36 (63.2)	834 (28.3)
Diabetes	15 (26.3)	347 (11.8)
History of thromboembolism	4 (7.0)	158 (5.4)
Cancer history or active cancer	8 (14.0)	266 (9.0)
Immune deficiency and HIV	4 (7.0)	84 (2.9)
Inadequate living conditions	23 (40.4)	376 (12.8)
<i>Signs and symptoms – no. (%)</i>		
Anosmia, ageusia, dysgeusia	12 (21.1)	786 (26.7)
Cough	36 (63.2)	1956 (66.5)
Dyspnea	49 (86.0)	1893 (64.3)
Diarrhea	10 (17.5)	846 (28.7)
Chest pain	9 (15.8)	1137 (38.6)
Confusion, impaired alertness	19 (33.3)	116 (3.9)
Worsening in the last 24 hours	27 (47.4)	1379 (46.9)
Heart rate ≥ 120 beats/min	4 (7.0)	181 (6.2)
Systolic blood pressure < 90mmHg	2 (3.5)	17 (0.6)
Temperature, mean ± SD, °C	37.2 ± 1.5	36.8 ± 1.4
Body mass index ≥30kg/m ²	8 (14.0)	417 (14.2)
Pulse oxygen saturation ≤94% in ambient air or necessity of oxygen therapy	32 (56.1)	620 (21.1)
Respiratory rate ≥25/min	30 (52.6)	457 (15.5)
Ability to speak or count without resuming breathing < 8 seconds	13 (22.8)	282 (9.6)

e-Table 3. Comparison of the rate of the evolution of symptoms with the need to be hospitalized and the need for oxygen therapy at least, according to the HOME-CoV rule and according to the place of treatment (adjusted population).

		Observational period		Interventional period		Comparison
Proportions						
HOME-CoV Rule	Management	N patients	%	N patients	%	Absolute difference (95%CI)
Positive	Home treatment	374/1243	30.1	296/1235	24.0	- 6.1 (-9.4; -2.8)
	Hospitalization	320/1243	25.8	312/1235	25.3	- 0.5 (-1.3; -0.3)
Negative	Home treatment	464/1243	37.3	560/1235	45.3	+ 8 (6.4; 9.4)
	Hospitalization	75/1243	6.0	67/1235	5.4	- 0.6 (-1.3; -0.3)
Evolution toward a moderate or severe form of COVID-19						
HOME-CoV Rule	Management	N patients	%	N patients	%	Absolute difference (95%CI)
Positive	Home treatment	2/374	0.5	2/296	0	0
	Hospitalization	41/320	12.8	26/312	8.3	- 4.5 (-5.2; -0.7)
Negative	Home treatment	0/464	0	0/560	0	0
	Hospitalization	4/75	5.3	2/67	3.0	- 2.3 (-3.4; -0.5)
*Moderate COVID-19 was defined as cases in which patients require at least oxygen therapy (WHO-OSCI ≥ 4). 95%CI: 95% confidence interval						