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ORIGINAL ARTICLE

# The methodology of a "living" COVID-19 registry development in a clinical context

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## Abstract

**Objective:** The aim of this study was to describe an innovative methodology of a registry development, constantly updated for the scientific assessment and analysis of the health status of the population with COVID-19.

**Study Design and Setting:** A methodological study design to develop a multi-site, Living COVID-19 Registry of COVID-19 patients admitted in Fondazione Don Gnocchi centres started in March 2020.

**Results:** The integration of the living systematic reviews and focus group methodologies led to a development of a registry which includes 520 fields filled in for 748 COVID-19 patients recruited from 17 Fondazione Don Gnocchi centres. The result is an evidence and experience-based registry, according to the evolution of a new pathology which was not known before outbreak of March 2020 and with the aim of building knowledge to provide a better quality of care for COVID-19 patients.

**Conclusion:** A Living COVID-19 Registry is an open, living and up to date access to large-scale patient-level data sets that could help identifying important factors and modulating variable for recognising risk profiles and predicting treatment success in COVID-19 patients hospitalized. This innovative methodology might be used for other registries, to be sure which the data collected is an appropriate means of accomplishing the scientific objectives planned.

**Clinical trial registration number:** not applicable 

*Keywords:* COVID-19; Registry; Living systematic review; Real World Data; methodological study; rehabilitation

## 1. Introduction

On 30 January 2020, the World Health Organization (WHO) declared a state of emergency over the coronavirus disease 2019 (COVID-19) outbreak and, on 12 March 2020, declared it a pandemic [1]. Since then, we are in state of emergency and researchers all over the world were engaged in research aimed at monitoring, developing and evaluating preventive and therapeutic strategies against COVID-19 [2,3]. A constant monitoring of COVID-19 pandemic evolution requires the collection of RWD in a systematic registry while the information on COVID-19 characteristics is accumulating rapidly. In the literature, there are different registries of clinical trials on COVID-19 with the aim to study specific treatments for

### What is new?

- The integration between evidence synthesis and expert opinion is the core of Evidence-Based Clinical Practice, but it could be considered as a novelty for the development of a registry, in which the main aim is to collect appropriate date to achieve scientific purposes. The living systematic review integrated with the focus group discussion allowed us to keep constantly updated whether prospective data collection through the registry was an appropriate means of accomplishing the scientific assessment and analysis of the health status of the population with COVID-19, improving the data quality in terms of accuracy, consistency, completeness and correctness and consequently, the quality of the registry itself.

Competing interests: The authors declare that they have no competing interests and they have not received any funding for the study.

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the management of the disease [4,5], but as far as we know, they do not seem to report a clear explanation of the methodology used for their development. Usually, planning a registry follows a specific methodology [6] and this paper is presenting the methodology of a COVID-19 Registry development criteria used to define a standardised registry to monitor the COVID-19 outbreak and its diffusion in different clinical settings. Our methodology integrated two specific methodologies to the standard methodology of registry development, which are evidence synthesis and focus group discussion within a multidisciplinary experts team. Our effort was to develop a registry to be widely adopted in order to provide both clinical and epidemiological descriptions of COVID-19. Therefore, the aim of this study was to describe an innovative methodology of the development of a registry constantly updated for the scientific assessment and analysis of the health status of the population with COVID-19 in different clinical settings.

## 2. Methods

### 2.1. Design

A methodological study design was used to develop the Fondazione Don Carlo Gnocchi (FDG) Living COVID-19 Registry, a multi-site registry of COVID-19 patients admitted in FDG centres during the pandemic period, which started in March 2020. It was approved by the Institutional Ethics Committee before the commencement of the study and a written informed consent was obtained from all participants before enrolment into the registry.

### 2.2. Sampling and participating centres

FDG is a non-profit foundation dedicated to rehabilitation of all people with different health conditions and disabilities, as well as the personal assistance of elderly people. FDG includes 28 centres allocated in different Italian regions for a total of 3700 beds. The geographical distribution of all FDG centres in Italy is presented in Figure 1.

FDG centred, which had admitted patients with COVID-19, were included in the registry for a total inclusion of 17 centres (57%): 5 rehabilitation centres, nine nursing homes and 2 IRCCS research hospitals with rehabilitation perspectives. All these FDG centres were asked to register all COVID-19 and post COVID-19 patients admitted.

The inclusion criteria for COVID-19 registry enrolment were: 1. COVID-19 symptomatic patients (age$\geq$18 years) after a positive nasopharyngeal and oropharyngeal swab result and/or a clinical presentation suggestive for COVID-19, with the presence of signs and symptoms, such as cough, fever ($\geq$37.5 °C) and shortness of breath and 2. post COVID-19 asymptomatic patients after two negative swabs results admitted to a FDG centres for rehabilitation interventions.

### 2.3. Procedure

The research questions of the registry were: 1. to describe the epidemiology of FDG in patients with COVID-19, 2. to compare epidemiological characteristics between rehabilitation and geriatric clinical settings available in FDG and 3. to describe the effects of COVID-19 sequelae which may be addressed with a rehabilitation intervention. The procedure for the definition of the architecture of the registry and data elements to be included in the registry was based on 2 approaches: a living literature review [7] of current evidence constantly published on COVID-19 and a Focus Group Discussion with the involvement of clinical experts who were facing the COVID-19 emergency in FDG. The development process was composed of 3 steps: 1. structure of registry proposal, 2. development of a registry prototype and 3. definition of the final version of the registry (*Development*). The prototype of the registry was developed by biomedical engineers (A.M. and S.C.) and tested involving a pilot sample of a few patients (*Testing*). After feedback with clinicians, the final version of FDG Living COVID-19 Registry was produced (P*roduction*). Before starting with data entry, we planned a specific training on the use of the registry for all healthcare professionals delegated in rehabilitation and geriatric clinical settings for the data entry. The timeline and the flow-chart of registry development plan is reported in Figure 2.

#### 2.3.1. Living literature review

The aim was to identify the epidemiological and clinical characteristics of patients with COVID-19 disease. A search strategy on COVID-19 was performed during three different periods. The first period was on 21 March 2020, the second period was between 22 March and 6 April 2020 and the third period was between 7 April and 20 April 2020. PubMed, Cochrane Library and National Institute Health and Care Excellence (NICE) Guidelines databases were investigated using the keywords “COVID-19″ and “SARS-CoV-2″ as free terms. Considering the low level of evidence produced on COVID-19 [8,9] and the missing of systematic reviews in that period, the search strategy was filtered for the main biomedical journals, including Annals of Internal Medicine, British Medical Journal (BMJ), Journal of the American Medical Association (JAMA), Lancet, Nature Medicine, New England Journal of Medicine (NEJM) and Cochrane, and only observational and epidemiological studies addressing prevalence, incidence, severity of the disease, and sequelae and mortality of COVID-19 published in English language were included and used for the identification of registry data elements. One reviewer (M.P.) selected the related evidence with the supervision of a second reviewer (C.A.). We collected data on patients characteristics (age, sex, exposure history, chronic medical histories), signs and symptoms

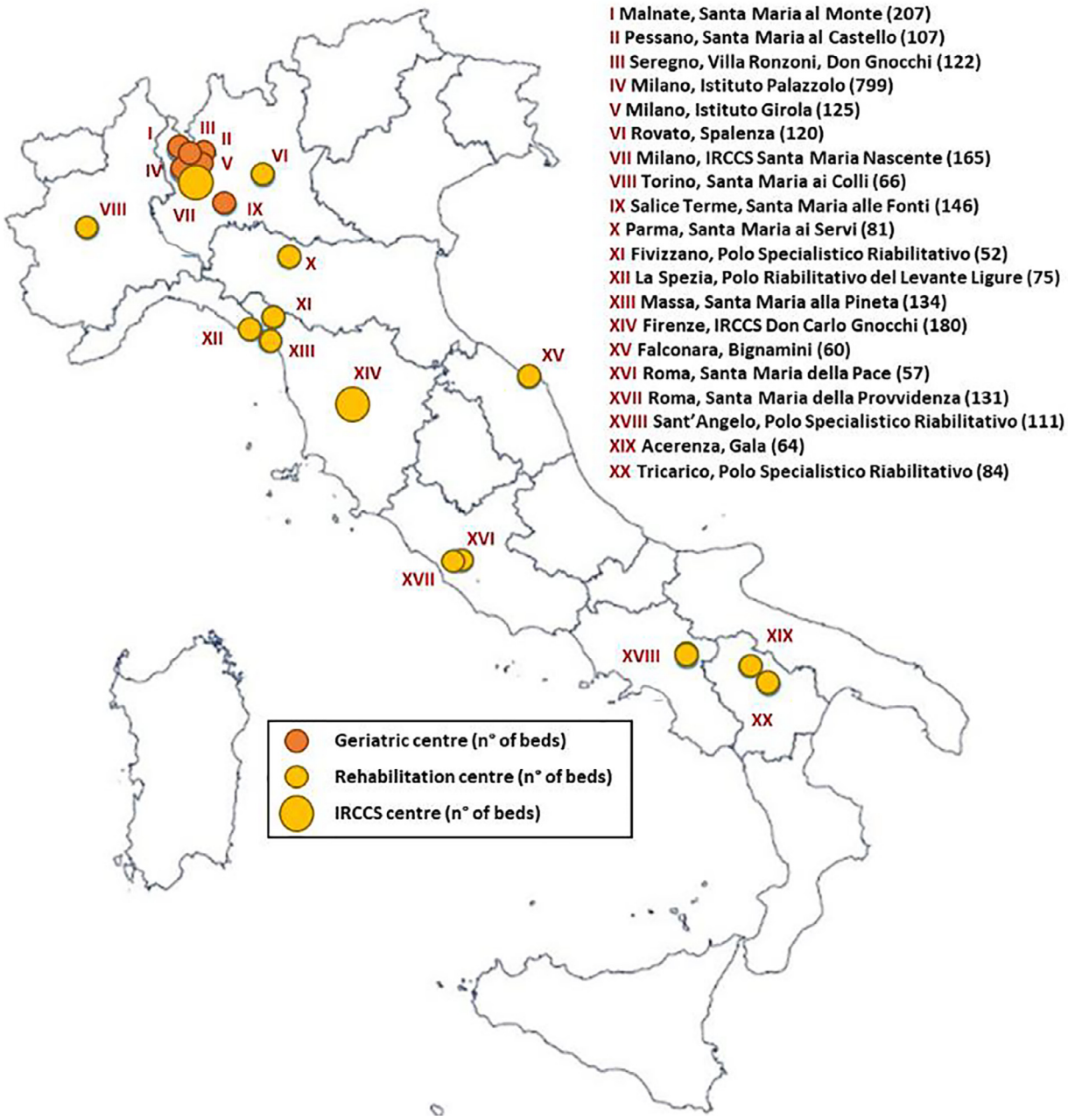


**Fig. 1.** Geographical distribution of all FDG centres in Italy. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

on admission, comorbidity, laboratory results, co-infection with other respiratory pathogens, radiological examinations for all patients with laboratory confirmed SARS-CoV-2 infection, treatment received for 2019-nCoV and clinical outcomes.

*2.3.2. Focus group discussion*

The aim of the focus group was to discuss which data, suggested by the living literature review, were more appropriate in defining the final registry data elements. The participants were a multidisciplinary team, involving clinicians, methodologists and biomedical engineers members of FDG clinical and scientific teams. They were recruited on the basis of their experience in the following disciplines: clinical epidemiology, virology, cardiology, pneumology, geriatric, physical and rehabilitation medicine, psychology, biomedical engineering and methodology of research.

Evidence synthesis was performed by a methodologist and it was presented to experts for the discussion. The process involved the formulation of specific research questions founded on the results of the living literature review proposed at each focus group meeting. The following discussion was guided by a methodologist who acted as a mod-

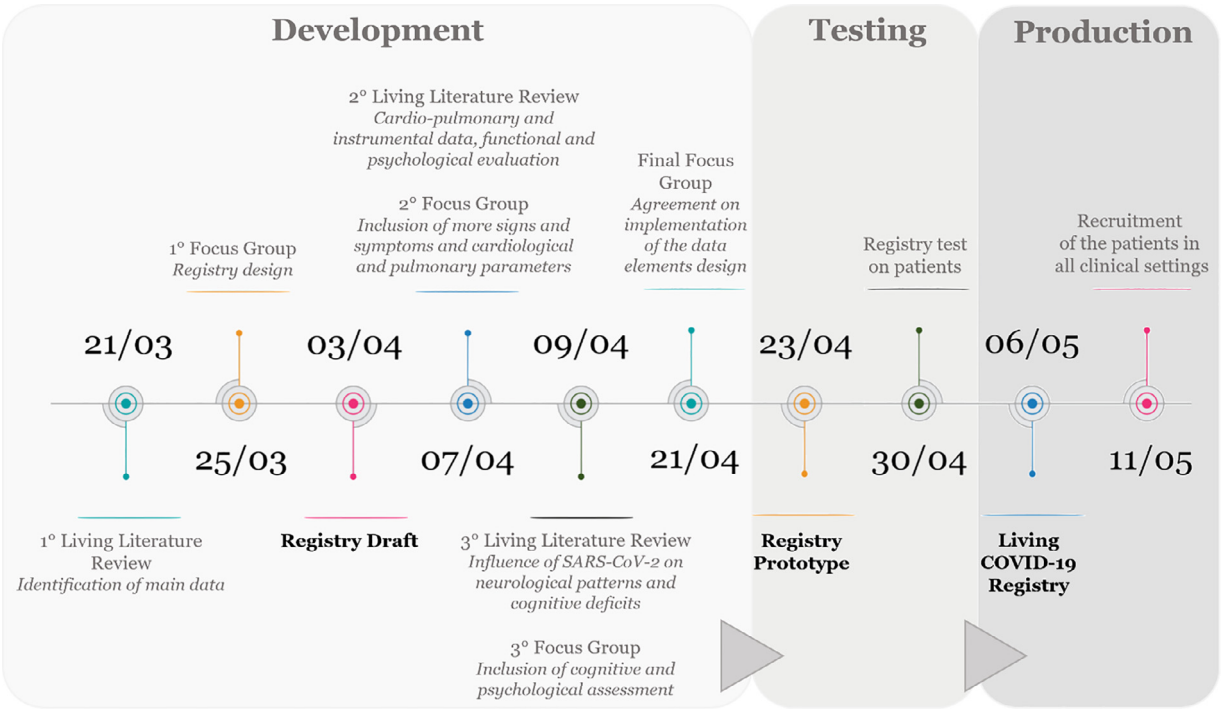


**Fig. 2.** Timeline and flow-chart of the registry development. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

erator to obtain agreement between the experts for each research question proposed. Considering the fast evolution of the pandemic's spread, we planned 3 focus groups meetings, where the biomedical engineers kept the data set constantly updated at each agreement reached. A final focus group meeting, including all clinical experts, was organised to reach the final agreement on the architecture and content of the registry. In each focus group, different experts were involved on the basis of the research question proposed for that meeting.

Usually, the analysis of focus group data is performed using the terminological analysis of the discussion transcription [10], but due to the time limit related to the pandemic's spread, the final agreement was analysed only describing the different opinions coming from the discussion and no assumption was made. This allowed us to achieve a more rapid agreement on the final version of the registry.

### 2.4. Development instrument of registry

When the final data elements were defined, the registry was developed using Research Electronic Data Capture (REDCap) software, a secure web-based metadata-driven electronic data capture software for designing and managing databases and surveys [11].

## 3. Results

### 3.1. Living literature review

From 7471 retrieved records from PubMed and the NICE database in all three periods, after removing duplicates and filtering for journals, 424 studies were selected. Of these, 396 records were excluded because they were expert opinions, letters to editors, case reports and case series, obtaining a total of 28 observational studies included for the identification of the main data elements of the registry. The selection method is illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart (**Fig. 3**). The data elements extracted from the living literature review were recorded and used to build the first draft of the core data set that has been discussed by experts in each focus group to define the final data elements.

### 3.2. Registry development

After the selection of the articles of the first living literature review, the first focus group was conducted with the aim of identifying the main data elements of the registry draft. The evidence synthesis showed that demographic data, symptoms, laboratory values, comorbidities, treatments and clinical outcomes were the most important data collected in the studies [12–15]. After discussion, an agreement for the first structure was reached. All details are reported in **Table 1**.

When the registry draft was finalised, the second focus group was conducted and a second literature review update was performed. Seven studies were selected and discussed with the experts. These studies highlighted more specific signs and symptoms, chronic hypertension and other cardiovascular comorbidities as related to COVID-

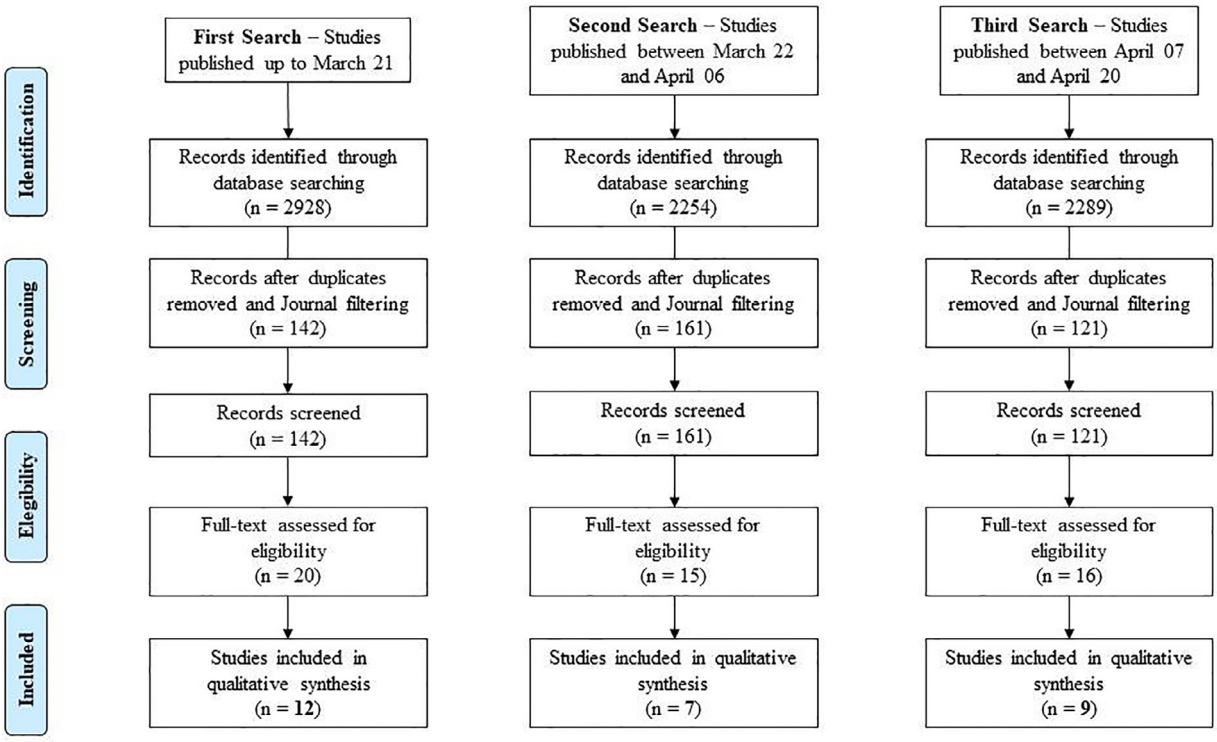


**Fig. 3.** Flow-chart of the living systematic review.

**Table 1.** Draft structure of the registry

| Modules | No Fields | Admission | During Recovery | Discharge | References |
|---|---|---|---|---|---|
| Demographic and clinical characteristics at admission | 53 | | | | Huang 2020 |
| Signs, symptoms and vital functions devices in admission | 40 | | | | Huang 2020, Chen 2020 |
| Daily clinical diary | 47 | | | | Huang 2020 |
| Diagnostic tests for Sars-CoV-2 infection | 7 | | R[a] | | Huang 2020; Fuk-Woo Chan 2020 |
| Instrumental data | 10 | | R[a] | | Shi 2020 |
| Haematochemical and blood gas tests | 24 | | R[a] | | Huang 2020 |
| Quality of life evaluation | 19 | | | | |
| Clinical evaluation at discharge | 33 | | | | Zhou 2020 |

**Legenda**:.
[a] repeating modules.

19 [16,17]. At the end of the discussion, an agreement was achieved on the inclusion of new signs and symptoms, cardio-vascular comorbidities, International Classification of Disease (ICD)−10 for the clinical diagnosis and the evaluation of dyspnoea with the Modified Borg Scale. The "diagnostic tests for SARS-CoV-2 infection" and "instrumental data" modules were also filled in including data referring to the acute phase, even if it happened earlier than the admission to a FDG centre. This allowed us to obtain more information about the infection during the acute and post-acute phase.

After the third living literature review update was performed, nine studies were selected and their results presented to the experts at the third focus group. The literature highlighted the influence of SARS-CoV-2 on neurological patterns and various cognitive deficit as consequence of COVID-19, such as prominent agitation and confusion [18–20]. After the discussion, agreement was achieved on the inclusion of cognitive and psychological assessment in the data set.

The final focus groups involved all experts and the aim was to discuss the final draft of the registry after the last updates. Final agreement was achieved regarding the implementation of the data elements proposed during the previous focus group meetings.

**Table 2.** Registry prototype structure

| Modules | No | Admission | During the recovery | Discharge | References |
|---|---|---|---|---|---|
| Demographic and clinical characteristics at admission | 75 | | | | Huang 2020 |
| Signs, symptoms and vital functions devices in admission[b] | 52 | | | | Hjelmesæth 2020; Fotuhi 2020; Hong 2020 |
| Pre-admission acute phase of post-infection patients[b] | 27 | | | | |
| Diagnostic tests for Sars-CoV-2 infection | 8 | | R[a] | | Huang 2020; Fuk-Woo Chan 2020 |
| Instrumental data | 26 | | R | | Shi 2020 |
| Laboratory tests | 38 | R[a] | R[a] | R[a] | Huang 2020 |
| Functional evaluation[b] | 30 | | R[a] | | Liu 2020 |
| Nutritional evaluation[b] | 30 | | R[a] | | Laviano 2020 |
| Cognitive evaluation[a] | 11 | | R[a] | | Zarrabian 2020 |
| Psychological[b] and quality of life evaluation | 77 | | R[a] | | Mahase 2020 |
| Clinical evaluation at discharge | 78 | | | | Zhou 2020 |

**Legenda**:.
[a] repeating modules;.
[b] new modules.

### 3.3. Registry testing

After the final agreement of experts, a registry prototype was developed by biomedical engineers. All evaluation scales were selected also taking into account those already in use inside the FDG clinical settings. This allowed for a better applicability of the evaluations, avoiding a time-consuming process of protocol adaptations for healthcare workers. The prototype structure is reported in Table 2.

On 30 April 2020, the prototype was tested by bioengineers using laboratory data and successively by healthcare professionals on twelve patients to evaluate its applicability in inpatients clinical settings (rehabilitation and geriatric). The test highlighted the following elements: the mean compiling time was 60 min and the data were successfully collected. This test helped improving the applicability of the registry and a guide was introduced to explain how data had to be collected and entered into the registry.

During the test phase in the geriatric clinical setting, a "cognitive deficit evaluation" in elderly patients was added to the registry as a new module [21]. The final structure is reported in Table 3.

### 3.4. Living COVID-19 registry production

The final FDG living COVID-19 Registry includes 12 modules with 520 fields in total. The recruitment of the patients started on 11 May 2020 and currently, the data of 847 patients was entered into the registry up to date. The distribution of the patients' data collected in each clinical setting is the following: 655 in a rehabilitation setting and 192 in a geriatric setting (nursing homes); the population was composed of 543 patients with COVID-19 and 205 post COVID-19 patients admitted for rehabilitation services. The compiling percentage of the identifying variables was 98% for signs and symptoms module, 82% for frailty scale, 96% for mechanical ventilation type, 84% for ICD-10 diagnostic codes, 100% for Cumulative Illness Rating Scale (CIRS), 82% and 63% for Barthel index in admission and discharge respectively and 87% and 82% for COVID-19 pharmacological therapy in admission and discharge respectively. This means a good reliability of the data collected and it highlights the importance of the registry for standardising the data collection in order to compare the clinical evolutions of COVID-19 in each clinical setting.

The data entry is still ongoing and the Living COVID-19 Registry will remain operative and constantly updated as long as there are COVID-19 patients as a management tool for supporting clinical decision-making processes. All data included in the registry are reported in supplementary material.

## 4. Discussion

The originality of this study was the innovative methodology used for developing a Living COVID-19 Registry, which was periodically updated by living systematic review of the scientific literature and by focus group with an interdisciplinary experts team moderated by a methodologist to obtain consensus on the architecture and fields to be included. The final version of the registry includes 520 fields filled in for 847 patients recruited from 17 FDG centres, that admitted COVID-19 patients disseminated throughout

**Table 3.** Final registry structure

| Modules | No. of fields | Before admission | Admission | During the recovery | Discharge | References |
|---|---|---|---|---|---|---|
| Demographic and clinical characteristics at admission | 73 | | | | | Huang 2020 |
| Signs, symptoms and vital functions devices in admission[b] | 58 | | | | | WHO/2019-nCoV/Clinical_CRF/2020.3 |
| Retrospective evaluation of the acute phase of post-infection patients[b] | 19 | | | | | Huang 2020; Hjelmesæth 2020; Fotuhi 2020; Hong 2020 |
| Diagnostic tests for Sars-CoV-2 infection | 7 | R[a] | | R[a] | | Huang 2020; Fuk-Woo Chan 2020 |
| Instrumental data | 25 | R[a] | | R[a] | | Shi 2020 |
| Laboratory tests | 39 | | R[a] | | R[a] | Huang 2020 |
| Functional evaluation | 21 | | | | | Liu 2020 |
| Nutritional evaluation | 5 | | | | | Laviano 2020 |
| Cognitive evaluation | 10 | | | | | Zarrabian 2020 |
| Psychological and quality of life evaluation | 77 | | | | | Mahase 2020 |
| Cognitive deficit evaluation[b] | 102 | | | | | Berger 2020 |
| Clinical evaluation at discharge | 93 | | | | | Zhou 2020 |

**Legenda**:.
[a] repeating modules;.
[b] new modules.

Italy. The acceptance rate was estimated around 58% and the data collected has been useful for a better control and knowledge of COVID-19 consequences [22,23]. The result is a registry that is evidence and experience-based, according to the evolution of a new pathology that was not known before the outbreak of March 2020 and with the aim of building knowledge to provide better quality of care to COVID-19 patients.

Up to 3 May 2021, there were 4053 registries on COVID-19 (https://covid-evidence.org/database), which are studying the effects of drugs in morbidity outcomes as primary outcomes. Most of them are still ongoing and no studies describing the methodology of development of these registries have been published, which is an essential element to ensure the transparency and replicability of the methods [24]. The standard methodology of registry development requests different steps [6] including the definition of the core data set, patient outcomes, and target population. These data elements must have potential value in the context of the current scientific and clinical climate, must be chosen by a team of experts and should relate to the purpose and specific objectives of the registry. But this standard methodology does not describe which criteria the experts have to be used to chose these data elements. Therefore, the main strengths of our registry were 2-fold. Firstly, the use of two strong methodologies, such as "living" literature review and focus group discussion. This was an important and innovative element of development, because we used the strength of evidence, constantly updated, to guide the choice of data elements performed by the experts after a consensus agreement and the observation of the clinical consequences of COVID-19 on the patients who recovered in rehabilitation and geriatric clinical settings. We are aware that the integration of evidence synthesis with expert opinion is the core of Evidence-Based Clinical Practice is a long standing feature of guideline development, but it could be considered as a novelty for the development of a registry, because it has never been used before. The main elements of registry development are: articulate the purpose of the registry; determine if a registry is an appropriate means to achieve the purpose; identify key stakeholders; and assess the feasibility of a registry. The living systematic review integrated with the focus group discussion allowed us to keep constantly updated whether prospective data collection through the registry was an appropriate means of accomplishing the scientific assessment and analysis of the health status of the population with COVID-19 improving the data quality in terms of accuracy, consistency, completeness and correctness and consequently, the quality of the registry itself.. Secondly, this methodology allowed big data collection of clinical manifestations of COVID-19, offering complementary evidence about RWD that may be used to lead observational studies whose results could then be pursued in randomized clinical trials.

Consequently, the result is the building of a living registry that contains RWD. In the current pandemic, intense research efforts are underway to identify effective interventions as soon as possible [24–26]. The time, clinical pressures and the difficult circumstances in conducting clinical

trials increase the chances of spurious results, which may be not applicable to clinical practice because they often do not reflect the heterogeneous patient population encountered in clinical settings [27,28]. In particular, the clinical trials on COVID-19 are not only already very wide but also fragmented and currently exceeding a thousand registered trials that were developed with no control and without any description of the development methodology [24]. In this context, an evidence and clinical-based registry, gathering RWD, can be used to generate complementary evidence for a better understanding of the natural history and on the demographic profile of COVID-19 deaths and comorbidities coming from the reports of different countries and settings [29,30].

### *4.1. Limitations*

The emergency status highlighted some limitations. Firstly, a structured questionnaire for the focus group was not possible to use due to the time limit related to the pandemic containment. Consequently, the final agreements were analyzed only describing the different opinions coming from the discussion. Secondly, the pandemic restrictions do not allow us to involve patients and citizen as focus group participants.

## 5. Conclusion

Our registry is proposed as an answer to the need of having real-time studies of the occurrence of COVID-19. Its innovative methodology of development might reduce the limitations of the real word studies, improving the consistency and statistical validity of data collection and ensuring the transparency and replicability of the methods, increasing our ability to answer research questions.

In this context, a Living COVID-19 Registry may provide open, living and up to date access to large-scale dataset that could help identifying important factors and modulate variables for recognising risk profiles and predicting treatment success in COVID-19 patients. This innovative methodology might be used for other registries, to be sure which the data collected through a registry is of good quality in terms of accuracy, consistency, completeness and correctness and it is an appropriate means of accomplishing the scientific objectives planned.

## Contributors

Maria Chiara Carrozza (M.C.C.) study idea, paper review and acceptance. Chiara Arienti (C.A.) study design, paper writing and acceptance. Andrea Mannini (A.M.), Silvia Campagnini (S.C.), Michele Patrini (M.P.) and Chiara Fanciullacci (C.F.) data analysis, support to data collection, text editing, paper review and acceptance. Stefano Giuseppe Lazzarini (S.G.L.) and Lorenzo Brambilla (L.B.) text editing, paper review and acceptance.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.11.022.

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