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Title	Development of the Canadian COVID-19 Emergency Department Rapid Response Network population-based registry: a methodology study
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Reviewer 1	Dr. Stephen DiTommaso
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General comments (author response in bold)	Well, this is a very complex study. As a practicing clinician, I will comment mainly on the practical applications of the study. The objectives of the study appear to be very ambitious, but are stated very generally. There are no examples of any specific research questions. The authors will perform correlations on as many variables as possible, looking for trends and associations. They intend to elaborate clinical decision rules: will these clinical decision rules be evaluated and reported separately? Will the clinical decision rules be utilised evenly across all sites, or if not, how will uptake be managed and reported? This study is so vast and so comprehensive that I think each component should be published separately. **The clinical decision rules will be derived and evaluated separately. Decision rules will be utilized evenly across all sites. Each decision rule will be published separately. This protocol describes the creation of a population-based registry of consecutive cases suspect and confirmed COVID-19 cases. Changes to Manuscript: The manuscript text was clarified throughout to address this reviewer's concern.** I suspect that statistical analysis will be very difficult, for the following reasons: 1) There were different phases of data collection, because the study admits to being "reiterative" (ie adapting quickly to changing needs and trends), and because of significant differences between data collection between sites (some prospective, all retrospective, etc). This challenge will likely complexify as new diagnostic and treatment modalities evolve very rapidly in the coming months. **The text was confusing. Thanks for identifying. We only used prospective data collection to verify the accuracy and completeness of 32 critical data points, which we feared would not be well captured through retrospective chart review. Kappa agreement was good and prospective data collection was terminated. The majority of data used for clinical decision rule development are retrospective variables. We are integrating new data elements as new diagnostic modalities and vaccines have been licensed for use.** **Changes to Manuscript: The section on data sources was adjusted to provide clarity.**

	2) The researchers admit that they will collect vast amounts of data, which they consider to be an advantage (for example, less chance of omitting small subgroups of patients). However, it will be a challenge to judge the significance of their post-hoc analyses of so many clinical and demographic subgroups. Any sub-group correlations will likely require confirmation in further studies, but by that time, the pandemic will almost certainly have changed in many ways, so subsequent validation of the authors' findings may well become impossible. **We agree that the COVID-19 pandemic is dynamic and we cannot predict the changes that will occur. We have assembled a strong team of clinicians and scientists who will be able to judge the clinical usefulness of the results generated from the registry. An advantage of our data collection is that we will be able to develop clinical decision rules with data collected earlier in the pandemic and conduct validation studies with data collected later in the pandemic. Additional validation studies in other countries will depend on the robustness of our findings.** **Changes to Manuscript: None.** 3) I am concerned about the reliability of telephone follow-up, to which the authors give mention. How feasible will this telephone follow-up be? I spend a part of every day fruitlessly trying to get through to my patients in order to answer their messages, to discuss lab results, etc. Also, what biases will occur: will patients without telephones, or who don't agree to be followed-up, or who don't answer their telephones be different in some way from the patients who are eventually contacted? **We have similar concerns. We have piloted the data collection in three provinces using three different study teams and identified tricks to optimize success and are confident based on this pilot that this is feasible. We are only collecting data points that we can otherwise not obtain using chart review. Thus, while our follow-up data will have some limitations, we believe it will nonetheless be highly valuable (e.g., racial data, socioeconomic data, patient-reported outcomes).** **Changes to Manuscript: Data sources section on follow up data was clarified to include the pilot.** When will the authors publish their findings? Are there any fixed time intervals, or will publication occur after recruitment of a predetermined number of subjects? It would be helpful to know at which points in time the authors plan to analyse their data. **The data is cut when the sample size for any proposed study has accrued. For the first clinical decision rules the data was cut on Nov 11 2020. We have just cut the data for the second clinical decision rules on January 4th, 2021. We hope these will be published shortly.** **Changes to Manuscript: None.** Reinfection rates are unknown, as are the clinical manifestations of second Covid-19 infections. This was not a concern during the first wave. However, from now on, I wonder how researchers will distinguish between primo infections and Covid-19 reinfections? **This is an excellent point. We are unable to collect viral genomic data (it is not available to us). So, we will only be able to ascertain reinfections in**

	patients with temporally discreet infections. If we do observe reinfections we will be able to characterize them, as we will capture full chart abstraction on all subsequent episodes. **Changes to Manuscript: None.** The Covid-19 pandemic is a very labile phenomenon, as governments and individual citizens and organisations all attempt to modulate transmission in so many different and concurrent ways, not to mention the impact of imminent vaccination programmes. Agile surveillance is necessary to rapidly identify useful information on epidemiological trends and treatment effects. However, interpretation of data and therefore generalization of results will be very challenging, and statisticians will have their hands full trying to evaluate the statistical validity and clinical usefulness of the observations which will be generated by this study. **We agree that the COVID-19 pandemic is dynamic and we cannot anticipate every** **change that occurs. We have assembled a strong team of clinicians and scientists who will be able to** **judge the statistical validity and clinical usefulness of the results generated from the registry. We note** **that the Protocol Review and Publication Committee will ascertain the potential usefulness of each** **proposed study before commencing.** **Changes to Manuscript: None.**
Reviewer 2	Dr. Balthasar Hug
Institution	Luzerner Kantonsspital, Luzern, Switzerland
General comments (author response in bold)	General comments The authors submit a protocol for data gathering in COVID-19 affected patients throughout Canada. They plan to collaborate on the basis of 50 ED departments in eight Canadian provinces. With this data, the authors plan to create clinical decision support algorithms, devaluate treatments and set up clinical studies. This is all very timely and the amount of collaboration with all these protocol participants is impressive. There are a few aspects that I would advise to discuss beforehand as outlined below. Title On p. 1 we learn about the competing interests and funding of this project. In fact, this is public-private collaboration and should be called that way in the title. I would leave the title as it is now and add “Protocol for a…(CCEDRRN) – a Public-Private Collaboration” or the like. With this it is clear that private companies are part of the project. These companies are interested in these data, which should be acknowledged for in this transparent way. **This network is not a public-private collaboration. The network is funded through public funds only and four out of five funding sources were peer reviewed. Competing interests were declared by two of the authors, which was reported in compliance with the network’s conflict of interest policy. Both declarations are managed within the network.** **Changes to Manuscript: None.** Methodology The one inherent problem this protocol has, is that it will be out of time once it’s

	published because of the vaccinations coming up in the next few months. These vaccinations show very good results and will change the momentum of the actual Covid-19 pandemic. It is puzzling to read that the very companies that produce these vaccinations are paying some of the collaborators of this manuscript. The word “immunization” or “vaccination” does not appear in any part of this protocol. Maybe it was devised before publication of the vaccination results? Once the vaccination is here, this whole project will be endangered because of lack of interest and timeliness. **The lack of any influence by industry was clarified above. This was a misinterpretation of a COI declaration that is managed by the network using our COI policy. Vaccination was anticipated and there are variables attributed to vaccination already in the database.** **Changes to Manuscript: Treatment and prevention strategies were expanded to include vaccination throughout the manuscript to address this reviewer’s concern.** In this light I would recommend the authors to devise this protocol as general basis in a more generic way so it can be adapted to any other emerging infectious disease. The latter will come for sure the only question is when. Interestingly, the authors mention this but only in one sentence on p. 10, lines 19-23: "By introducing a novel ED-based framework to rapidly collect national population-level data, we have developed a model that may be applied in other countries and to other emerging infectious diseases." In my view the protocol should be crafted this way and then secondarily adapted to the Covid-19 pandemic. This way, the authors will be able to have all their valuable work endure longer in the shape of a national database for emerging ID diseases. **Agreed.** **Changes to Manuscript: In the impact section of the interpretation we have expanded on this and suggested scalability and preparation for the next pandemic.** Tables Should be adapted in a generic way as discussed above in the methodology section e.g. tables 1 and 2. **We are unclear what is meant above.** **Changes to Manuscript: None.** Table 3: It is unclear where these kappa coefficients derive from. This is usually computed from the study data itself. Are these limits the authors have agreed upon or is this from some published work? The authors reference this with ref#20, a publication from 1960. How can you publish a kappa (observed relative agreement between observers) if you don't have the data yet? **Agreed this section on prospective data collection and kappa statistic was confusing. Changes to Manuscript: The text was adjusted in data sources and data quality sections and the associated Table was adjusted to be consistent with the text. We have used a more recent reference.**