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COMMENTARY

Supporting frontline clinicians in the time of the pandemic: Rapid response pharmacology team

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1 | INTRODUCTION

Since the early days of the COVID-19 pandemic, a long range of medications have been tried in the fight against the novel coronavirus: antivirals, antimalarial drugs, antibiotics, steroids, and numerous biologicals. None of them were licensed against COVID-19 either in the United Kingdom, the United States, or EU, or Russia. In addition to all the known challenges with the off-label use, many of those medications have significant safety issues, such as potentially dangerous drug interactions, pro-arrhythmic effects, teratogenicity, or organ toxicity. At the same time, both media and politicians have spread news about efficacy of certain medications. Such claims were not based on proper evidence and sometimes were simply factually incorrect. Navigating through this complexity, which in the setting of severe COVID-19 turned to be a true pharmacological minefield, demands high competence and broad knowledge.

Russia, as well as over 10 other countries in Eastern Europe and Central Asia, historically lacks clinical pharmacists as a profession, in contrast to the United Kingdom, the United States, Canada, Australia, and majority of the European countries. Hence, the clinical pharmacologists are necessitated to deal with every aspect of rational, safe, and effective medication use alone.[1] In Russia, for over 500 000 medical doctors, there are about 800 clinical pharmacologists, who are often overloaded with clinical consultations, assessing and reporting adverse drug events, and advising the hospital medication committees. Due to this high daily workload, clinical pharmacologists have to focus on controlling and adjusting the use of specific drug groups and ensuring adherence to local and national guidelines. With the off-label use of medications becoming the only option, this situation poses extra challenges to clinical pharmacologists in the frontline. It is also important to take into account that in Russia, a country spread across 11 time zones, there are many rural areas, which are remote but not isolated from the pandemic's threat, and which often have limited health care provision and do not have clinical pharmacologists present.

2 | ESTABLISHMENT OF PharmaCOVID

In early March 2020, there were just about 15 000 cases of COVID-19 in Russia, yet this number was growing exponentially, and global challenges with obtaining high-quality scientific advice became apparent. A group of clinical pharmacologists based in Moscow and several other cities started a project aimed to support clinical pharmacologists and medical doctors of other specialties working across the country by establishing an online competence centre for complex pharmacological problems in patients with COVID-19 (PharmaCOVID).

The concept and methodology of the centre was mainly based on our knowledge of Drug Information Centers (DIC) in Scandinavia and the United States. We performed analysis of the existing publications describing the DIC structure and methodology and adapted them to establish a makeshift specialized rapid response DIC. The main purpose of the centre was to provide evidence-based information about drugs used against COVID-19, especially in patients with multiple pre-existing conditions, polypharmacy issues, kidney or liver failure, and elderly patients. Additionally, we aimed to use clinical requests and our answers for research and teaching purposes, as well as to contribute to medication safety monitoring.

Karin B. Mirzaev, MD, PhD, and Yury Kiselev, MD, PhD, contributed equally to this work.

PharmaCOVID was established with its core at the Russian Medical Academy of Continuous Professional Education (Academy), state-owned largest national CME institution for Russian medical doctors of all specialties. Nine clinical pharmacologists, further referred to as experts, volunteered to work at the centre *pro bono*, utilizing their spare time and time which had become available under the lockdown in their permanent jobs. Four experts were based in Moscow, while others worked remotely from their locations in the regions. All meetings were held online due to the geographical constraints and the social distancing imposed by the authorities. One expert was chosen as the permanent scientific leader based on work experience and academic achievements, and another member of the team had the role of the daily operational manager. Scientific leader maintained an overall advisory role, the right to approve recommendations, and a mediatory function in case of disagreements. Operational manager was responsible for the initial screening of the incoming questions, assigning urgency level and delegating the questions to the experts, as well as follow-up of the further work and timely dispatch of the recommendations to the addressees. An overview of the centre's structure and function is presented as a flow chart in Figure 1.

Clinicians used online request forms at the academy web site to send their questions. During the early phase, access to the request

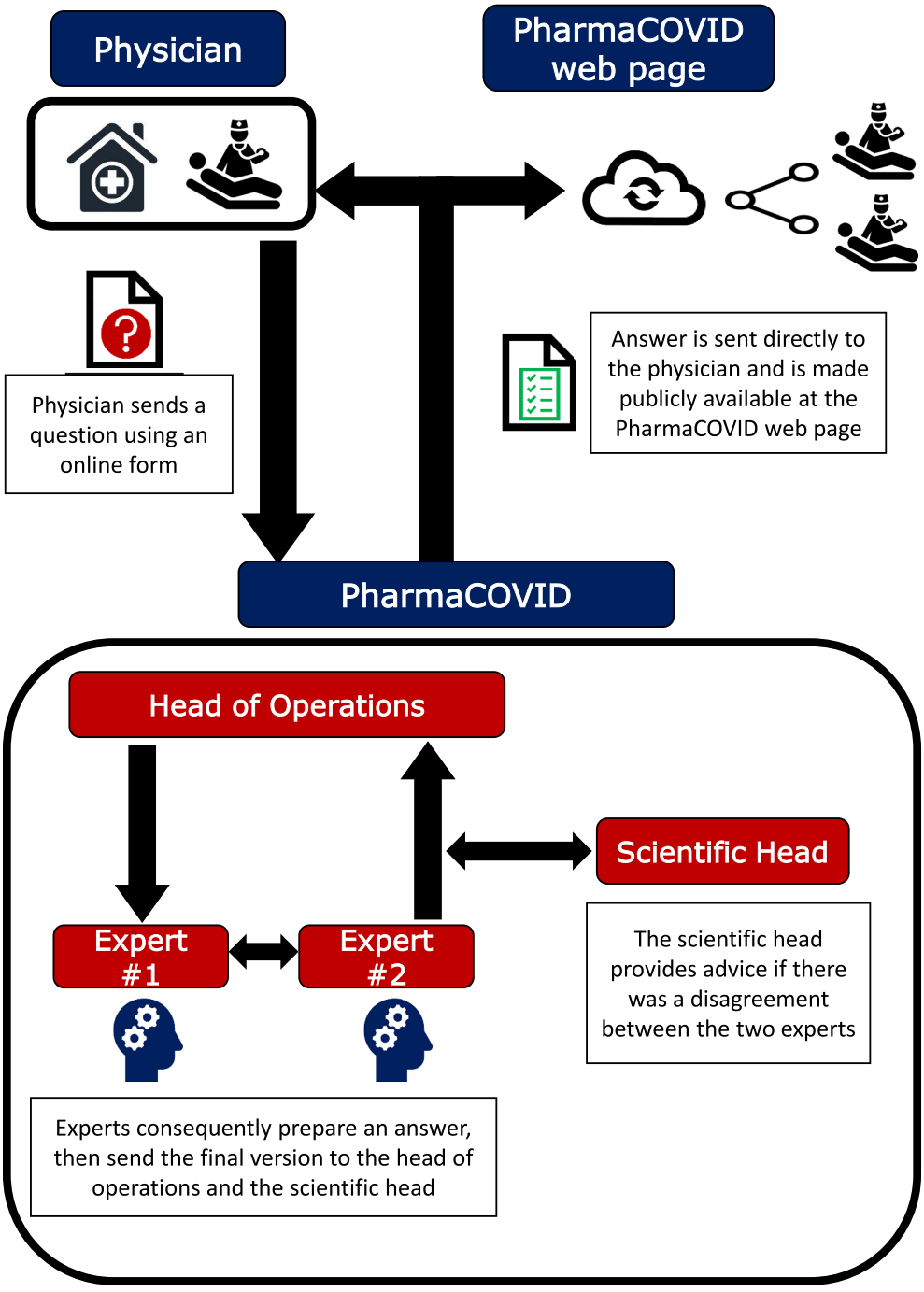

FIGURE 1 PharmaCOVID workflow and operational structure

form was provided to doctors from several major hospitals in Moscow, which were designated by health care authorities as COVID-19 specialized clinics. It has also been decided to answer selected questions from a nationwide online platform used by almost half of Russian clinical pharmacologists—mainly when it was suspected that leaving a particular pharmacological issue unresolved may have put patients at risk.

The request forms included a checklist designed to make sure that we would receive only COVID-related questions, a free-text field for the doctor to provide a short summary of the problem, and a number of fields for filling in clinical details, brief case history, laboratory data, and other relevant information. Every effort has been made to de-identify health information in order to preserve patients' privacy. After initial screening and sorting, two experts were assigned to each question to assess it independently, using available clinical evidence via PubMed, Google Scholar, clinicaltrials.gov, national and foreign guidelines, drug–drug interaction databases, and information digests published by academic centres elsewhere—a standard layout of our answers is presented in Table 1. All references were included in the recommendation texts. In order to comply with the national regulations and to respect individual clinician's right to independent decision making, the answers were shaped as recommendations based on assessment of given clinical situations, rather than direct advice on how to treat a given patient. These recommendations were sent directly to the authors of the questions and published at the centre's web site fully available to the public. Importantly, the experts always had special focus on the language used in the recommendations, in order to make it as simple and concise as possible, as this has been shown as a major factor limiting the practical usefulness of DIC answers elsewhere.[2]

TABLE 1 Standard answer layout

- Title, date, names of the experts
- Question
- Brief summary of the answer
- Introduction
  - General information about the medicine (name, ATC code, regulatory status, mechanism of action, main therapeutic indications and contraindications, specific restrictions) – if any of the above are significantly different in Russia and abroad[a], then a brief summary is provided
  - Preclinical and clinical rationales for potential use in patients with COVID-19
- Evidence base and expert recommendations
  - Results of relevant *in silico*, *in vitro*, *in vivo* and clinical studies, including (if relevant) design and dosages used in planned or ongoing clinical trials
  - Russian and foreign guidelines and recommendations, including statements and positions of professional societies
  - Relevant official documents from Russian and foreign authorities
  - PharmaCOVID recommendations on the clinical use of the medicine in question
- Safety aspects, including contraindications, known and predicted adverse effects and drug interactions, recommendations for safety monitoring
- Conclusions
- References

[a]The United States, the United Kingdom, the EU, Canada, and Australia are typically used as reference countries in our answers.

3 | PRELIMINARY EVALUATION

During the first 3 months of its work PharmaCOVID has received a broad variety of questions—see Table 2 for the brief overview of examples. On average, our answers had 20 references and consisted of 1300 words. We have covered specific topics such as dosing regimen and choice of administration route for an interleukin-6 inhibitor, and broad ones—safety measures in patients receiving antimalarial medications. Some doctors wondered about the off-label use of globally approved medications, while others had specific inquiries about medications licensed and available only in Russia. Some physicians wanted our opinion about clinical usefulness of unlicensed supplements and unorthodox treatments. The centre has become widely known among clinical pharmacologists and other physicians in Russia and several neighbouring countries, and publicly praised for objectiveness, impartiality, and strict adherence to the principles of evidence-based medicine. By mid-July 2020 our answers have been downloaded more than 21 000 times, and the website has had over 33 000 unique visitors. We have been recognised by the Ministry of Health of Russia, which has sent a formal letter to all regional health authorities, health care institutions, and universities, advising to use the answers published by PharmaCOVID. The ministry is also using our scientific advice in revising national COVID-19 guidelines.

Our centre is not entirely unique; similar initiatives have been launched in the United Kingdom, the United States, France, Australia, Canada, and elsewhere. Teams of experts performing rapid analyses of evidence and/or producing answers to the clinicians' questions are usually based at universities,[3–5] or affiliated to professional societies,[6] or international initiatives,[7] HTA agencies,[8,9] and health care systems.[10–12] However, most of them have either somewhat different functions or a different focus. Distinct features of our centre are as follows: (a) we accept questions regarding pharmacological treatment of patients with COVID-19, (b) we provide rapid answers within three timeframes (6, 24, or 72 h), and (c) we aim specifically towards clinicians and researchers rather than general public. Publicly available and thoroughly implemented system for quality control is the major strength of our centre.

We believe that our model can be replicated and scaled up in practically any region or country, as it requires only a limited set of resources, is fully digitalised, and has successfully passed the test of a pandemic. Specifically, countries with limited or fragmented resources could benefit from implementation of our model. For smaller countries sharing similar challenges and health care systems, a transnational centre could be an effective resource-sparing solution. International bodies, and specifically the World Health Organisation, could consider using our model and provide the essential guidance and coordination for similar projects.

TABLE 2 Short summary of some questions received by PharmaCOVID and the answers generated

Question	Recommendation on use	Comments
"Could we administer subcutaneous solution of sarilumab intravenously, and in which dose?"	Not recommended for routine use, only in clinical trials	Dosage and safety monitoring suggestions provided
"Are inhibitors of interleukin-17 potentially useful in treating patients with acute respiratory distress syndrome in COVID-19?"	Not recommended for routine use, only in clinical trials or against CRS in selected severely ill patients	Safety monitoring suggestions provided
"Which measures are required to ensure safe use of hydroxychloroquine in patients with COVID-19?"	Perform risk assessment, focus on ECG, comorbidities, and drug interactions	Suggestions on hydroxychloroquine use depending on QTc provided
"Is bromhexine effective in preventing infection with SARS-CoV-2?"	Not recommended for routine use, only in clinical trials	
"Is it possible to use favipiravir in patients with COVID-19?"	May be considered in hospitalised patients, some evidence for antiviral activity exists	Poorly predictable pharmacokinetics is highlighted; safety measures advised
"Is methylprednisolone effective against acute respiratory distress syndrome in COVID-19, and how should it be dosed while combined with tocilizumab?"	No evidence is found for methylprednisolone efficiency in COVID-19 with or without tocilizumab	Critically ill patients can be treated with systemic steroids, should interleuikin-6 inhibitors be unavailable
"Shouldn't we consider using tofacitinib against acute respiratory distress syndrome in COVID-19?"	Not recommended for routine use, only restricted use in clinical trials	
"How should we dose anti-COVID-19 medicines in patients with chronic kidney disease, including those on dialysis?"	Dosage recommendations are provided	
"Are inhalations of hyaluronidase solution useful against acute respiratory distress syndrome in COVID-19?"	Not recommended for routine use, only in clinical trials	
"Can we use dipyridamole as thromboprophylaxis in patients with COVID-19?"	Not possible to recommend for routine clinical use, individualised approach is advised	
"What is the evidence behind using vitamin D3 as prevention and treatment for COVID-19?"	There is no evidence for efficiency of vitamin D3 supplementation in treatment or prevention of COVID-19	
"Can remdesivir be used to treat hospitalised patients with COVID-19?"	Could potentially be used to treat hospitalised patients who require respiratory support	Not available or licensed in Russia

Note: Answers are tailored for Russian clinical practice, are provided merely as examples, and may become outdated by the time of publication of this paper.

4 | CONCLUSION

While the COVID-19 outbreaks in most of Europe appear to have been stabilized, we are still seeing a significant growth in the number of cases in Russia, the United States, Central Asia, Latin America, and Africa. Many patients are still in hospitals, and more will inevitably be hospitalised, while the progress in finding effective and safe treatments has been limited, and challenges in obtaining and implementing evidence-based pharmacological advice are still acute.

Working on PharmaCOVID project, we created an infrastructure and gained unique experience that will be useful for rising on similar challenges. We hope that our example may serve as an inspiration for colleagues across the globe, as our model can potentially be used in other countries or regions where rapid access to a clinical pharmacologist or a pharmacist is not always possible.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

K.B.M., Y.K., and D.A.S. conceptualized the manuscript. K.B.M. and Y.K. also did the literature search, wrote the first draft, and edited every draft. D.V.I. and V.A.O. contributed to writing of the first draft. K.B.M., Y.K., D.V.I., V.A.O., and D.A.S. edited the manuscript.

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