



# Global research collaboration in a pandemic-challenges and opportunities: the COVID-19 Global Rheumatology Alliance

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## Purpose of review

This review discusses the coronavirus disease-2019 (COVID-19) Global Rheumatology Alliance (GRA), the reason for its formation, the challenges with running the registry, and future opportunities for global collaborative research in rheumatology.

## Recent findings

The GRA has been successful in collecting and publishing a large volume of case data on patients with rheumatic disease with COVID-19. In addition, the GRA has published reviews, opinion pieces, and patient-directed summaries of research to further assist in disseminating timely and accurate information about COVID-19 in rheumatic diseases. There have been numerous challenges in the journey but they have been addressed through a collaborative problem-solving approach.

## Summary

The initial objectives of the GRA to describe the outcomes in patients with rheumatic disease who developed COVID-19 have been achieved. There has been extensive use of the data in the clinic and also to try and understand the mechanisms of disease and opportunities for drug repurposing. There remain numerous important areas for research which the GRA will continue to pursue as the pandemic evolves.

## Keywords

coronavirus, COVID-19, observational study, outcomes research, registry

## INTRODUCTION

The global coronavirus pandemic presented a huge challenge to the rheumatology community and patients with rheumatic disease. However, it also provided an impetus to create a wide-ranging global research collaboration to address urgent issues [1]. The COVID-19 Global Rheumatology Alliance (GRA) was formed in early March following a conversation on Twitter and had an ethics exempted RedCap registry open for submission 10 days after the project started [2,3]. The mission of the GRA is to collect, analyze, and disseminate information about coronavirus disease-2019 (COVID-19) and rheumatology to patients, physicians, and other relevant groups to improve the care of patients with rheumatic disease. The vision is to bring together the global rheumatology community to curate and disseminate accurate and comprehensive knowledge to advance rheumatology care during the COVID-19 pandemic.

## ACHIEVEMENTS

To date the GRA has published a descriptive piece on the first 110 contributed cases [4<sup>¶</sup>] as well as a study

examining the risk factors for hospitalization in a series of 600 patients with rheumatic disease [5<sup>¶¶</sup>,6]. The most recent work is an analysis of almost 4000 patients examining risk factors for COVID-19 death [7<sup>¶¶</sup>]. Early data on the lack of protective effect of hydroxychloroquine in COVID-19 was also produced to dispel misinformation about the drug [8<sup>¶</sup>]. Moreover, a study of the disproportionate impact of COVID-19 on racial/ethnic minorities

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## KEY POINTS

- The COVID-19 Global Rheumatology Alliance was able to rapidly institute an online case registry to quickly collect case data on rheumatic patients with COVID-19.
- Although there are limitations in the study design the GRA has been able to develop a good picture of how patients with rheumatic disease fare with COVID-19 and direct further work.
- There remain many unaddressed important questions for the field of rheumatology during this pandemic and it is likely the GRA will play a role in helping to address these questions.

who have rheumatic diseases has been published [9<sup>\*\*\*</sup>]. These outputs and their key findings are summarized in Table 1. In addition to these published reports from the physician registry, there have been teams of clinicians and scientists working on important questions, who have produced a systematic review and meta-analysis of the use of antirheumatic therapies for the treatment of COVID-19 and a scoping review on the acute respiratory virus adverse events from antirheumatic therapies [10,11]. A review on the treatment of hyperinflammation in COVID-19 was also published [12].

In addition to these important data articles and literature reviews, members of the GRA also advocated for a scientific approach to the assessment of potential COVID-19 therapies to both promote safe clinical practice in the treatment of COVID-19 and

also to ensure that medications like hydroxychloroquine were available for patients with rheumatic disease who needed them [13–16]. The survey for patients of their pandemic experiences was also disseminated and results are being analyzed for publication [17].

Wider contributions were also made by those contributing to the GRA with participants contributing to management guidelines including the European League Against Rheumatism (EULAR), Asia-Pacific League of Associations for Rheumatology, and US National Institutes of Health efforts, generating lay summaries for the public, disseminating information to the press and through social media, and completing other studies and reviews relevant to COVID-19 in the rheumatic diseases [18–23].

## CHALLENGES

Although the GRA has accomplished a remarkable amount, establishing a global collaboration of this scale over a short period has not been without its unique set of challenges. Here, we discuss some of the challenges encountered and reflect on the processes the collaborative instituted to solve them.

### Early challenges

Much of the first several weeks of establishing the GRA involved developing collaborations and infrastructure at record speed.

A key initial challenge was establishing the Institutional Review Board's (IRB) approvals for the

**Table 1.** Articles published by the COVID-19 Global Rheumatology Alliance (GRA), using data from the physician reported registry

Article	No. of patients	Outcome	Key findings
Gianfrancesco <i>et al.</i> [4 <sup>*</sup> ]	110	Descriptive	5% death rate, 35% hospitalization rate
Konig <i>et al.</i> [8 <sup>*</sup> ]	80	Descriptive	Hydroxychloroquine use does not prevent COVID-19, or reduce COVID-19 severity
Gianfrancesco <i>et al.</i> [5 <sup>***</sup> ,6]	600	Hospitalization	Age and moderate/high doses of glucocorticoids increased odds of hospitalization. No increased rate of hospitalization with DMARDs, biologics, or JAK inhibitors at group level
Gianfrancesco <i>et al.</i> [9 <sup>***</sup> ]	1324	Hospitalization, ventilatory support, and death	Racial/ethnic minorities with rheumatic disease and COVID-19 had increased odds of hospitalization and ventilatory support
Strangfeld <i>et al.</i> [7 <sup>***</sup> ]	3729	Death	Moderate/high disease activity, rituximab, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, mycophenolate, and tacrolimus associated with increased odds of COVID-19 death

DMARDs, disease modifying anti-rheumatic drugs; JAK, Janus kinase.

registry. It was important to develop a flexible data collection system that was easily accessible, secure, and did not require patient consent. During the pandemic, many institutions, including the University of California, San Francisco, committed to expediting IRB review for COVID-19 related projects. This was critical in allowing the GRA IRB to undergo timely review in less than 48 h. Once the initial IRB approval was obtained, a large network of collaborators around the United States and globally worked to adapt the IRB materials for their individual institutions. For example, investigators working in the US Veterans Affairs health systems sought individual institutional approvals and eventually applied for central approval. Globally, we learned that IRB procedures differ substantially from country to country. Some countries, such as Canada, required that individual institutions have separate IRB approvals before participating in the registry. Others, such as the Philippines or Argentina, could obtain central approvals that would apply to all institutions. It was also recognized that strategically and due to European Union General Data Protection Regulations, which have specific data protection, storage, and privacy requirements, a separate provider survey was required for Europe, and a partnership with EULAR was established. The final RedCap survey was provided to EULAR so an identical European registry could be established. The EULAR registry is stored at the University of Manchester (data processor), with EULAR being the data controller. Data from the two parallel registries is combined for analysis.

From the outset, the GRA sought to foster global collaboration. A key challenge was to develop networks where none had existed before. Overcoming this challenge involved using social media in a way that it had rarely been used in rheumatology [24]. Rheumatologists with large followings on platforms such as Twitter quickly disseminated information about the GRA and invited collaborators to communicate on the team platform called Slack. A website was also developed ([www.rheum-covid.org](http://www.rheum-covid.org)) that allowed people to both contribute cases to the registry and access clinical outcome data that had been collected. It also enabled access to proforma documents for IRB approvals and other logistical tasks. This allowed rapid crowdsourcing of work, including the IRB approvals mentioned above and facilitated the recruitment of a series of regional leads around the world. This digital infrastructure was central to the rapid growth and broad participation in the GRA. A similar endeavor was undertaken by EULAR, who developed their own website ([https://www.eular.org/eular\\_covid19\\_database.cfm](https://www.eular.org/eular_covid19_database.cfm)).

One important early difficulty was creating a case report form that requested enough information

to adequately assess COVID-19 outcomes and clinical and demographic factors, without overburdening busy clinicians. After several iterations, we arrived at a balanced form that could be completed relatively quickly (10–15 min) while providing enough information to allow us to answer the most pressing questions.

An additional early challenge was ensuring scientific rigor and validation despite the compressed project timelines. There were many initial concerns about the integrity of the data. Would rheumatologists complete the case report forms accurately? Would there be duplicate entries? Would someone try to hack the open web-based database platform? Key to overcoming these challenges was having experienced data teams in both Europe and the United States monitoring registry implementation, performing regular data validity checks, developing algorithms to remove duplicates, and instituting procedures to re-contact physicians when data were missing. National investments in scientific infrastructure were critical to this rapid mobilization. In the United States, work relied on the infrastructure already available through a National Institute of Arthritis, Musculoskeletal and Skin Diseases Clinical Research Core, while in Europe, research infrastructure supported by EULAR to support an epidemiology unit was key.

One key challenge was that many of those contributing to the GRA were practicing clinicians. Therefore, at a time when their contributions were often needed clinically, there were also the demands of contributing to the functioning of the GRA. These challenges were addressed with open and honest conversations about what people could and couldn't contribute at any given time. In addition, it was quickly realized that the strengths of the assembled group largely were in clinical and epidemiological research. This led to discussions with the American College of Rheumatology (ACR) and EULAR about both what funding might be available and how that might be best managed. The ACR and EULAR were both able to provide much appreciated logistical and administrative support to enable the members of the GRA to concentrate on the data collection and analysis efforts.

One aspect of the case collection that enabled rapid increases in case numbers was the integration of country-specific registry data. Cases from the French, German, Italian, Portuguese and Swedish registries were transferred and merged with data from the EULAR database, and registries from countries such as Brazil were merged, reducing duplication of effort. The umbrella of EULAR, a truly pan-European organization fostering a multitude of activities in areas of research, patient care, and

education, facilitated the interaction with national scientific societies of rheumatology (themselves members of EULAR), whereas legal and administrative support from EULAR facilitated practical aspects such as setting up data-sharing agreements with relevant institutions and/or societies. Similarly, research groups globally mobilized quickly to set up data use and transfer agreements to share data with the GRA. The technical aspects of data transfers can be challenging as the various registries use different data collection platforms and formats. This task required interaction of technical teams, mapping of the databases, harmonization efforts, and the creation of export/import tools.

### Later challenges

The limitations of a voluntary physician contributed registry are clear, but in the emerging environment of the early days of the pandemic it was very fit for purpose. As the pandemic further evolves it is clear that other study designs are required [25]. The initial data collected by the GRA was valuable in helping define risk profiles and provide comparative data on rheumatic disease patients; however, there remain significant limitations in the way the project is structured. These limitations include the convenience sampling aspect of the physician registry and the lack of comparator groups, both COVID-19 patients without rheumatic disease and/or understanding the denominator for the cases that have been reported. These issues can potentially be addressed by utilizing large health systems and systematically assessing all rheumatic disease patients for infection. This would enable comparisons to be made with both rheumatic disease patients who did not develop COVID-19 and also other patients in the health system who developed COVID-19 but do not have rheumatic disease. The nature of these types of projects is very resource intensive. Groups outside of the GRA are doing some of this type of work already. Moreover, the registry does not capture the patient journey, namely long-term COVID-19 outcomes, such as rehabilitation and recovery data, limiting the ability to view and assess longitudinal outcomes beyond hospitalization, ventilatory support, and mortality.

There is a clear need to improve representation of countries in Latin America, Africa, and Asia in the registry. This will enable region-specific trends to be observed. Often in low-resource settings the medications used and alternatives are very different to those commonly used in Europe and North America so there remains a need to have good knowledge about the patterns of disease and outcomes across all continents and resource settings. The GRA

instituted a grants scheme, administered through the International League of Associations for Rheumatology, to support investigators in countries that were underrepresented in the registry. The purpose of the grants scheme was to provide some support to enable the systematic collection of patients with rheumatic disease who developed COVID-19 to enable them to be entered into the database. The grant scheme can also help initiate and support regionally relevant COVID-19 clinical research in areas that lacked the resources to do this previously.

With the constantly growing database of reported cases, there is another growing problem. That of data management, there is a need for a data analytic infrastructure that can assist multiple investigators with different projects. To address region-specific issues, it is important to be able to deliver country-specific data to nations that are using the GRA to perform national studies. The two data hubs that make up the GRA at the University of California San Francisco and the University of Manchester both have excellent infrastructure and have been able to accommodate the growing requests for specific data analytic projects. The GRA has developed transparent, peer-reviewed policies to assist in assigning data analytic resources to the multiple investigators running studies with increasing amounts of information. Ensuring GRA data remains a global and heavily utilized resource needs careful management to ensure the integrity of the data is maintained and high-quality research can continue to be published.

The funding of the alliance is an issue which will likely shape the capacity to branch out into new projects or build on existing projects. Although the initial enthusiasm from industry to support this case was very encouraging and much appreciated, it is almost inevitable that the perceived importance of the alliance will track with the trajectory of the pandemic over time. To branch out into nonpandemic projects, alternate funding sources will need to be found, and the structure and function of the organization will likely have to change to fit both the new projects and new funding sources going forward.

## OPPORTUNITIES

### During the pandemic

There remain many unanswered questions for rheumatology and patients with rheumatic disease in this pandemic. The emerging questions encompass important areas like vaccines and vaccinations and post-COVID-19 syndromes. These are both important areas for future research effort but it remains to be seen if the GRA, as it is currently configured, is in



the best situation to lead efforts in these spaces. Both of these research areas will likely benefit from consented research studies with repeated clinical contacts and serial collection of data as well as biospecimens. Therefore it is likely that other study designs are going to be better suited to addressing these important areas. But with the structures and wide network currently in place and a large team with in-depth experience of the rheumatic diseases in the pandemic the GRA is well suited to support efforts in these spaces.

There is also the opportunity to combine data with different registries that are capturing COVID-19 data, particularly those with affinities to rheumatology given mechanistic links in disease pathogenesis or the use of similar drugs (e.g., inflammatory bowel disease: <https://covidibd.org/>, psoriasis: <https://psoprotect.org/>). Differences in format and data elements collected may make it challenging to combine data from multiple registries, but collaborating across projects represents an important opportunity to address specific research questions (e.g., specific treatments).

## After the pandemic

The opportunity to leverage the existing collaboration that now exists for further topics is exciting. There is likely to come a time when either the majority of the clinical problems presented by the COVID-19 pandemic will have an evidence base to guide them or the impact of the pandemic will be substantially reduced through the uptake of an effective vaccine(s). It will be interesting to see if there is interest in building on the success of the alliance in tackling research related to COVID-19 and turn our attention to tackling other global issues that confront our speciality. We see the strength of the alliance as being able to leverage a global group of clinicians to provide cases with wide geographical distribution. The advantages of this are that low-frequency events may be able to be collected and collated in a way that has never been done before. For example, cases of rare diseases, or rare manifestations of diseases, or low-frequency drug side-effects may be future research directions for the alliance.

## CONCLUSION

Although the GRA has achieved much, there is much further work to be done. A major success of the GRA has been the rapid collaborative mobilization of the rheumatology community worldwide. The informal feedback from colleagues that the work of the GRA is being used to help clinicians and patients guide their way through the pandemic

is reassuring that we are fulfilling our stated vision. However, there remain many further issues to address in the current pandemic. There might be an opportunity to leverage the existing collaboration to address some of these topics, whereas others can only be addressed by other organizations and more resource-intensive study designs.

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## Conflicts of interest

*J.Y. reports personal fees from AstraZeneca, personal fees from Eli Lilly, grants from Pfizer, outside the submitted work. P.R. reports personal fees from Abbvie, Atom Bioscience, Eli Lilly, Janssen, Novartis, Pfizer, Roche, and UCB, and nonfinancial support from BMS, all outside the submitted work. P.M.M. has received consulting and/or speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche, and UCB, all unrelated to this manuscript.*

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