



September 15, 2021

Elizabeth Barr, Ph.D.
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RE: Request for Comments on Chronic Debilitating Conditions in Women in Preparation for
“Advancing NIH Research on the Health of Women: A 2021 Conference”

Dear Dr. Barr:

On behalf of the Lupus Research Alliance, thank you for the opportunity to submit comments to the National Institutes of Health's (NIH) Office of Research on Women's Health (ORWH) and the Advisory Committee on Research on Women's Health (ACRWH) as the ORWH and ACRWH prepare for an October 2021 conference on advancing women's health research. We understand that this conference will focus on a number of topics, including chronic debilitating conditions in women, and respectfully submit the comments below to highlight the research needs related to lupus, a chronic condition that disproportionately impacts women and, in particular, women of color. We would urge, as part of the conference, an examination of the gaps in research in our understanding of lupus and potential solutions for bridging those gaps, including expanding public-private opportunities for research collaboration. We would also welcome the opportunity to provide a speaker, panel participant, or any other assistance you may need with regard to lupus or related topics at the October conference.

Systemic lupus erythematosus (SLE) or lupus is a complex, multisystem autoimmune disease predominantly affecting women and typically diagnosed during childbearing years (ages 15-44).¹² Ninety percent (90%) of people with lupus are female, and lupus is up to three times more prevalent in women of color than in Whites. In SLE, a breakdown in immune tolerance leads to the production of autoantibodies against a variety of nuclear antigens. Autoantibodies in turn form immune complexes which deposit in different organs such as kidneys, joints and skin leading to lupus nephritis, arthritis, and rashes to name just a few of the disease manifestations. Lupus is a leading cause of premature cardiovascular disease, heart attack, stroke, and kidney disease among young women. In fact, SLE is the fifth and sixth leading cause of death among young Black and Hispanic women ages 15–24 and 25–34, respectively.³

SLE is characterized by periods of flares and remissions leading to organ damage accrual over time and increased mortality and morbidity when compared to the general population. While

¹ Ward M, Access to Care and the Incidence of End Stage Renal Disease Due to Systemic Lupus Erythematosus. *J Rheumatol*. 2010 June; 37(6): 1158-63.

² Yazdany J, Feldman C, Liu, J, et. Al. Quality of Care for Incident Lupus Nephritis Among Medicaid Beneficiaries in the United States. *Arthritis Care Res*. 2014 April; 66(4) 617-624.

³ Yen, E. Y. and Singh, R. R. (2018), Brief Report: Lupus—An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000–2015. *Arthritis Rheumatol*, 70: 1251-1255. doi:10.1002/art.40512.

lupus can impact any organ, some of the most severe and debilitating forms of the disease include lupus nephritis, a kidney inflammation that can result in end-stage renal disease, and neuropsychiatric lupus (NPSLE) causing seizure, brainstem dysfunction, stroke, or psychosis.

Lupus affects an estimated 200,000 people in the United States.⁴ Other estimates range from 161,000 to 322,000 Americans with SLE.⁵ One of the difficulties of diagnosing and treating lupus is the heterogenous nature of the disease. In addition, there is no single test to diagnose SLE, and lupus patients report that it can take four to six years and an average of three doctors to get diagnosed. As the ten-year survival rate decreases from 80-90% to 60% with advanced stage disease⁶, early detection is critical.

Lack of Safe and Effective Therapies

Given the complex nature of lupus and the absence of a cure, treatment is focused on preventing flares, managing symptoms, and reducing organ damage. A variety of medications are used to treat lupus, many of which have major side effects including infection, osteoporosis, depression, hair loss and weight gain to name just a few. Importantly, to date, only three drugs have been approved specifically to treat lupus. The U.S. Food and Drug Administration's approval this year of anifrolumab-fnia, a first-in-class type I interferon receptor antagonist indicated for adults with moderate to severe SLE, represents the first new treatment for generalized SLE in more than a decade.

In addition to medications to treat lupus symptoms, patients may be on medications to treat conditions related to lupus such as high blood pressure, or blood clots. Medications used to treat the disease, such as corticosteroids or other immunosuppressants, can cause toxicity, increased susceptibility to infection or osteoporosis, and can lack efficacy in some patients.^{7,8,9,10} The unpredictable nature of the disease, the need for long term treatments, and the effects of disease activity and treatment can severely impact the quality of life for individuals with lupus.

Health Disparities in Lupus

Lupus is a leading cause of death in young women of color. An August 2018 population-based study¹¹ found that lupus, previously ranked among the top 20 causes of death in all women, rose to new levels of grave concern as the 5th and 6th leading cause of death among young Black and Hispanic women ages 15-34 -- just behind cancer, heart disease and HIV.

⁴ Izmirly, PM, Parton, H, Wang L, et. al. Prevalence of Systemic Lupus Erythematosus in the United States: Estimates from a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol* 2021 73(6):991-996

⁵ Helmick, C.G., Felson, D.T., Lawrence, R.C., Gabriel, S., Hirsch, R., Kwoh, C.K., et al, for the National Arthritis Data Workgroup. (2008). [Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I](#). *Arthritis Rheum*; 58(1):15–25

⁶ Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. *Arthritis Research and Therapy*. 2012;14(suppl4)s4:1-9.

⁷ Gladman DD, G. C. (2000;27(2)). The Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus international comparison. *J Rheumatol*, 373- 376.

⁸ Calvo- Alen J, McGwin G, Toloza S, et al. Systemic lupus erythematosus in a multiethnic US Cohort (LUMINA);XXIV. Cytotoxic treatment is an additional risk factor for the development of symptomatic osteonecrosis in lupus patients: results of a nested matched case control study. *Ann Rheum Dis*. 2006;65(6)785- 790).

⁹ Haque S, Gorden C, Isenberg D et. al. Risk factors for clinical coronary artery disease in systemic lupus erythematosus: there lupus atherosclerosis evaluation of risk (LASER) study. *J Rheumatol*. 2010, 37(2):322- 329.

¹⁰ Zonana-Nacach A, Yanez P, Jimenez-Bladeras FJ et al. Disease activity, damage and survival in Mexican patients with acute sever systemic lupus erythematosus. *Lupus*. 2007;16(12):997-1000.

¹¹ Yen, E. Y. and Singh, R. R. (2018), Brief Report: Lupus—An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000–2015. *Arthritis Rheumatol*, 70: 1251-1255. doi:10.1002/art.40512.

Five-year survival in people with lupus has improved from 50% in the 1950's to over 90% currently¹²¹³ but mortality remains high and is on the rise compared to the general population. Mortality rates among traditionally underserved populations with lupus are over three times as high as Caucasians, and they are more likely to experience multiple comorbidities such as cardiovascular disease and diabetes, and worse health outcomes and related quality of life.¹⁴¹⁵¹⁶¹⁷¹⁸ The reasons for these health disparities are complex, and include genetics, comorbidities and socioeconomic challenges. Access to healthcare and active engagement of the patient in their own care are particularly important factors. In 2050, it is estimated that half of the U.S. population will be people of color, further highlighting the need to advance lupus research given its disproportionate impact on women of color.¹⁹

Issues Associated with COVID-19

The coronavirus pandemic has exacerbated issues of structural racism in the ability to access health care services and the urgent need for people of color to participate in clinical trials. Disparities seen in COVID-19 infection rates have served as a stark reminder of the inequity that exists within the American health care system and the social determinants of health that contribute to these health disparities. The disparities that have become so evident in the COVID-19 pandemic mirror other health disparities impacting individuals with lupus. The current national focus on the impact of systemic racism inherent in the United States health care system is a catalyst for systemic change. Lupus research and participation in clinical trials by individuals of color can be part of this push for a more equitable health care system.

Need for Continued Federal Investment in Lupus Research and Lupus Drug Development

We are grateful for NIH's funding of a large number of critically important projects, which have led to the development of new experimental models, increased understanding of disease mechanisms, and identification of new targets to name just a few of the advances. Much remains to be done, and significant sustained funding will be required. According to NIH's Research, Condition, and Disease Categorization (RCDC) system, funding for lupus research in fiscal year 2020 reached \$134 million – the highest level since 2009. While the estimated funding for lupus research projects growth--\$136 million (FY2021) and \$139 million (FY2022) it still does not make up for the impact of stagnant biomedical research funding from the previous decade. But, much more remains to be done to advance research into lupus, including developing a clear understanding of cellular and molecular disease pathways, and the genetic basis underlying different clinical features and treatment responses in patients. Filling this fundamental gap in

¹² Urnamoto KM, Michet CJ Jr, Thumboo J, Sunku J, O'Fallon WM, et al. Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. *Arthritis Rheum.* 1999;42(1):46-50. 2009;61(10):1462-1466

¹³ Lim SS, Drenkard C, McCune WJ et al. Population-based lupus registries: advancing our epidemiologic understanding. *Arthritis Rheum.* 2009;61(10):1462-1466.

¹⁴ Alcaron GS, McGwin G, Rosman JM et al. Systemic lupus erythematosus in three ethnic groups. XIX. Natural history of the accrual of the American College of Rheumatology criteria prior to the occurrence of criteria diagnosis. *Arthritis Rheum.* 2004;51(4):609-15.

¹⁵ Alcaron GS, McGwin G, Uribe A, et al. Systemic lupus erythematosus in a multiethnic lupus cohort (LUMINA)xvii. Predictors of self-reported health-related quality of life early in the disease course. *Arthritis Rheum.* 2004;51(3):465-74.

¹⁶ Costenbader KH, Desai A, Alcaron GS et al. Trends in the incidence, demographics, and outcomes of end stage renal disease due to lupus nephritis in the US from 1995-2006. *Arthritis Rheum.* 2001;63(6):1681-88.

¹⁷ Hanley JG, Urowitz MB, Su L, et al. Seizure disorders in systemic lupus erythematosus results from an international, prospective, inception cohort study. *Ann Rheum Dis.* 2012.

¹⁸ Feldman C, Hiraki L, Liu J. et al. Epidemiology and Socio demographics of Systemic Lupus Erythematosus and Lupus Nephritis Among US Adults with Medicaid Coverage, 2000-2004. *Arthritis & Rheumatism.* 2013;65(3):753-763.

¹⁹ Artiga, Samantha, et al. "Disparities in Health and Health Care: Five Key Questions and Answers". Kaiser Family Foundation - Racial Equity and Health Policy, <https://www.kff.org/racial-equity-and-health-policy/issue-brief/disparities-in-health-andhealth-care-five-key-questions-and-answers/>, accessed November 13, 2020

knowledge is critical for the identification of potential new targets for intervention as well as for stratifying patients—based on active disease mechanisms—for both clinical trials and care.

We would also urge you to consider how greater engagement through partnerships between relevant federal agencies, patient and professional groups, and industry could assist in driving advancements in lupus research. A 2015 National Institutes of Health Action Plan for Lupus Research, prepared by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, recommended such collaboration as a mechanism for developing a precision medicine approach to disease treatment and prevention. In our view, this type of engagement will be critical to fill current gaps in lupus research and to improve lupus diagnosis and treatment.

Thank you again for the opportunity to submit comments and we look forward to further exploration of these issues at the October conference. If we can provide any additional information or can offer any assistance with providing lupus-related expertise for the conference, please contact me at 646-884-6090 or tstaeva@lupusresearch.org.

Sincerely,



Teodora P. Staeva, PhD
Chief Scientific Officer