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Concerning the
National Institutes of Health and Food and Drug Administration FY 2017 Appropriations

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We are pleased to offer testimony on the need for a public/private safety registry for pediatric patients with inflammatory bowel disease (IBD). **Specifically, we request on behalf of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the Pediatric IBD Foundation Subcommittee consideration of the following report language to the Fiscal Year 2017 Labor, Health and Human Services, Education and Related Agencies Appropriations bill**:

Pediatric IBD Safety Registry: The vast majority (an estimated 80 percent) of medications prescribed by physicians to treat children with inflammatory bowel disease (IBD) are prescribed "off-label" without any mechanism to monitor safety. The Committee recognizes the need for a national pediatric IBD population-based database to capture information on evidence-based health outcomes related to specific therapies and interventions, including concomitant medications and adverse events, and to make data accessible to physicians, patients, industry, researchers, and federal agencies. The Secretary, acting through the National Institutes of Health, in consultation with the Food and Drug Administration, is encouraged to enter into cooperative agreements with public or private entities for the collection, analysis and reporting of data on pediatric IBD.

Prevalence of Inflammatory Bowel Disease — An estimated 1.6 million Americans are living with IBD (Crohn's disease and ulcerative colitis), with nearly one in four patients diagnosed under 20 years of age. IBD is a chronic inflammatory disorder of the intestines that does not have an identifiable cause (such as infection). Pediatric IBD causes the immune system to become inappropriately active, causing injury to the intestines. IBD does not have a medical cure but can be managed effectively through medication or other treatments. When IBD is not effectively managed, children do not grow normally because of a lack of absorption of nutrients. Many suf-

fer constant intestinal pain causing them to miss school, have chronic diarrhea, multiple surgeries and, in some instances, wear colostomy bags.

Treating Inflammatory Bowel Disease — Treatment of a child with active Crohn's disease typically involves an induction regimen that includes a potent therapy with a rapid onset of action. If a remission is achieved, the patient can be transitioned to a maintenance regimen, typically involving medications with a slower onset of action and fewer side effects. The selection of drugs for induction and maintenance depend on age, disease severity, location, and clinical course. In general, very young children with IBD are more likely to have severe or refractory disease, and to have an identifiable genetic cause of the disease (monogenic IBD).

The ideal goal of treatment is clinical and laboratory remission with mucosal healing, not just symptomatic improvement. However, achieving this goal must be balanced against the risks of IBD therapies. Patients who achieve clinical, laboratory, and endoscopic remission may have better long-term outcomes. Optimal care therefore typically includes one of the following approaches:

- Accelerated *"step-up"* therapy for most patients – Initiate treatment with the least potent drug predicted to be effective, promptly step-up therapy to more potent drug if response is incomplete.
- *"Top-down"* therapy for selected high-risk patients and often minority children – Early treatment with a highly potent immunosuppressant (e.g., anti-tumor necrosis factor antibody) for patients with high risks of complicated disease.

With either approach, close monitoring of patients is important to assess for remission (including upper endoscopy and colonoscopy) and to monitor for drug toxicities.

Why a Pediatric IBD Registry is Needed — There are many pediatric diseases and conditions for which great benefit could be derived through coordinated data collection. However, the creation of a pediatric IBD registry, which could serve as a model for other condition-based registries, should be more immediately supported by Congress for the following reasons:

Monitoring the Safety of Off-Label Prescribing — When medications are prescribed for the treatment of IBD in children, the vast majority of these medications (an estimated 80 percent) are not approved by the Food and Drug Administration (FDA) for the indication at the time they are given — meaning, they are not approved by the FDA for use in children and are therefore used "off-label." Medications used to treat IBD are first approved in adults and approval for children may come many years later, if at all, for a variety of reasons which we believe must also be addressed by Congress and the FDA. When medications, often found to be highly effective, are prescribed off-label to children, there is no mechanism to monitor safety, including potential side-effects and contra-indications. For example, a medication approved for treatment of Crohn's disease in adults was recently found to cause a rare but fatal lymphoma in boys who received the medication in combination with another Crohn's treatment. A national registry might have identified this problem much earlier.

Expediting the Approval of Drugs for Pediatric Indications — When medications are prescribed off-label, such is the case with medications to treat pediatric IBD, families frequently incur significant out-of-pocket costs. This is because insurers will not cover medications for indications that are not FDA-approved, even though they are prescribed by physicians and are essential to properly and effectively treat these children, for whom there are few FDA-approved options. A pediatric IBD registry would help expedite drug approvals and encourage drug companies to pursue pediatric indications for FDA-approved drugs by allowing them to access a central data repository rather than establishing cost-prohibitive, proprietary, drug-specific registries for safety monitoring. Moreover, a registry would greatly enhance global pediatric drug development so medications that carry serious side-effects to treat IBD disease can be avoided and prescribed in more thoughtful evidence-based ways or replaced with better therapies.

Informing Physician Decision-Making — A public-private pediatric IBD registry would be accessible to physicians and patients to aid in treatment decision-making. The need for better data to inform treatment decision-making is of particular importance when caring for minority populations. Recent epidemiologic studies describe incidence rates of IBD among African American children have approached and even surpassed those in Caucasians. Furthermore, studies have shown that African American children are diagnosed later, when compared to Caucasian children. This could be for a variety of reasons, although it is speculated that the older age of IBD diagnosis among African American children may be due in part to a low index of suspicion for IBD in minority children among medical providers because IBD has traditionally been viewed as a disease of Caucasians and adults. Furthermore, under-represented minorities often have decreased access to medical care or different patterns of health care seeking behavior thereby leading to much longer delays in diagnosis of IBD in African American children than in Caucasian children and, more importantly, the initiation of critically needed IBD therapy.

Studies continue to show that the disease natural history in African American children is more aggressive, prone to more complications, and requires more interventions, including more powerful medications (i.e., biologics) at earlier stages of the disease after initial diagnosis (i.e., top-down therapy). *Top down* therapy (starting with an immune system suppressing biologic) has also been shown to be more commonly employed in African American pediatric populations with IBD, thus putting these children even more at risk for long-term use of these medications. Additionally, reporting adverse effects and safety monitoring is presently voluntary in the United States — a factor which further contributes to the difficulties facing underserved populations.

IBD in minority populations — African American, Hispanic, African Caribbean — is clearly and substantially increasing in its frequency, and, represents a more aggressive type of IBD. Therefore, it is paramount that a mechanism be in place to monitor safety of the medications used to treat children with IBD, including minority populations.

Maintaining a Central IBD Data Repository — The goal of the aforementioned report language is the creation of a central data repository, which would supplement proprietary, drug-specific registries. Children being treated with IBD medications benefit from FDA-mandated registries,

but these registries are often single product and proprietary. Since children are often on multiple products, these registries do not monitor the safety of drug interactions. In addition, most pediatric IBD therapies (approximately 80 percent) are off-label and manufacturers are not required to collect data on off-label use. Furthermore, significant safety data captured on a competitor's medication may not be made public, and these registries lack uniformity of data collection.

Building on Previous Federal Investments — We envision that existing IBD registries would share data points with the public IBD registry which would connect to an existing registry for pediatric rheumatology (CARRA — Childhood Arthritis and Rheumatoid Research Alliance). Connection to the CARRA registry would benefit both pediatric IBD and rheumatology patients because these auto-immune diseases are often treated with the same medications. CARRA was started with a $7.5 million grant to the National Institutes of Health (NIH) in 2009 as a result of funding through the American Recovery and Reinvestment Act. Building on this federally-funded registry would encourage data sharing, extend the government's return on investment, and allow federal regulators and researchers to access data without having to rely on proprietary registries. Presently CARRA is the only registry that meets federal data sharing requirements per 21CFR-11. We appreciate the interest by many in Congress of a post-marketing data sharing system that could facilitate drug approval for treating rare diseases like pediatric IBD, particularly in diseases where many products are used off-label, thus relieving manufacturers from the obligation of collecting data. Fulfilling the vision of such a post-marketing data sharing system would require each component (i.e., each registry) to meet compliance with 21CFR-11. Therefore the development of a pediatric IBD registry that meets 21CFR-11 requirements and its interconnectivity with the CARRA registry, which already meets these requirements, would offer an excellent demonstration of registry interconnectivity.

Conclusion — A number of organizations have previously joined NASPGHAN and the Pediatric IBD Foundation in calling for a pediatric IBD registry, including the American Medical Association, the American Academy of Pediatrics and the American Gastroenterological Association.[1] We believe report language specifying the need for a pediatric IBD registry is necessary for the initiation of a public-private partnership. Indeed, this language provides flexibility to the NIH and the FDA to initiate collaborative arrangements with other public and private entities as they did with the CARRA registry, which is an independent 501(c)(3). In this way, the registry is supported with a minimal outlay of federal resources.

On behalf of the thousands of children with IBD, their families, and pediatric gastroenterologists, we thank you for your consideration of our request.

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[1] Letter to Sen. Llamar Alexander and Sen. Patty Murray, September 9, 2015.