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The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR): An Emerging Knowledge Commons

Katherine J. Strandburg and Stefan Bechtold

INTRODUCTION

This chapter reports our study of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the NIH Rare Diseases Clinical Research Network (RDCRN). CEGIR addresses eosinophilic gastrointestinal diseases (EGIDs), the most common and well studied of which is eosinophilic esophagitis (EoE).[1] Strandburg, Frischmann, and Cui (2014) previously studied the Urea Cycle Disorder Consortium (UCDC), while the North American Mitochondrial Disease Consortium (NAMDC) is the subject of the previous chapter in this book. While there are many similarities between the goals of these consortia and their general structures, there are also significant differences in the underlying challenges they face and the approaches they take to those challenges. These studies also provide snapshots at different stages of consortium development: The UCDC, funded in 2003, was among the first RDCRN consortia and was well into data collection at the time of our study. NAMDC began operations in 2011 and is engaged in constructing its pool of research subjects, patient data, and biospecimens. CEGIR was funded in 2014 and had been in operation for less than a year at the time of this study.

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[1] EoE is about 10 or 15 times more prevalent than the other EGIDs, eosinophilic gastritis and eosinophilic colitis (Jensen et al. 2016).

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16.1 METHODOLOGY

Our study follows the *Governing Knowledge Commons* (GKC) framework described in Chapter 1. Specifically, we

- Reviewed public documentation about CEGIR and other materials about EGID research.
- Interviewed 23 individuals representing various CEGIR constituencies and other relevant groups, including 10 out of 22 CEGIR clinician researchers representing six out of nine CEGIR clinical sites (including CEGIR's consortium principal investigator (PI) and administrative director), a non-US-based CEGIR-affiliated clinician researcher, a dietician and biostatistician at CEGIR's lead site, two CEGIR study coordinators, three representatives of the two major patient advocacy groups, three pharmaceutical company representatives, one non-CEGIR-affiliated researcher and one non-CEGIR-affiliated study coordinator. The semi-structured interviews ranged in length from 45 minutes to more than an hour;[2]
- Attended Digestive Disease Week 2015, the "world's largest gathering of physicians and researchers in the fields of gastroenterology, hepatology, endoscopy and gastrointestinal surgery."[3]
- Analyzed the documents and interview transcripts using the GKC framework.

16.2 CEGIR'S BACKGROUND ENVIRONMENT

CEGIR, and the research community from which it emerged, are nested within a background environment that includes the biological realities of EGIDs as well as the general context of rare disease medical practice and research in the United States and internationally. Patients, represented by patient advocacy groups, are also important actors in this environment. The first three parts of this section briefly describe the EGID research context. The final part discusses relevant patient advocacy groups.

16.2.1 *EGID Basics*

Eosinophilic gastrointestinal diseases cause inflammations involving eosinophils (a type of white blood cell) that affect the esophagus (eosinophilic esophagitis, EoE),

[2] We maintain an archive of interview transcripts, which we rely on and quote from throughout this chapter. To preserve confidentiality as much as possible, we ordinarily do not cite particular interviewees. Readers may assume that unattributed quotations are taken from our interviews.

[3] www.ddw.org

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the lining of the stomach (eosinophilic gastritis) or the colon (eosinophilic colitis). Adult EoE patients usually have difficulties swallowing, which may become so severe that the esophagus is physically obstructed. Food refusal and failure to thrive are common manifestations in children. If left untreated, EoE can result in fibrosis, esophageal dysfunction, and permanent changes to esophageal tissue. EoE is a chronic disease that nearly always recurs if treatment is discontinued. While the exact causes of EoE are unknown, many patients also have other atopic diseases, such as asthma, food allergies, or atopic dermatitis, suggesting that EoE is allergy related (Cianferoni and Spergel 2016: 160).

EoE was first observed in the 1980s and appears to have been a truly new disease at the time (Schoepfer, Simon, and Straumann 2011: 632). The first systematic scientific descriptions of EoE, by Stephen Attwood of the UK and Alex Straumann of Switzerland, were published in 1993 and 1994 (Attwood et al. 1993; Straumann et al. 1994). Initially, EoE researchers encountered significant resistance from other medical professionals. One interviewee recalled giving a conference presentation on the disease in the early 2000s: "The chairman introduced me as follows: 'Now we hear a contribution about a disease which does not exist.' I can understand. It was new. It was from his own area." Today, EoE's existence is accepted, but questions about what causes it and how best to diagnose and treat it remain open (Straumann 2013).

Studies estimate that between 50 and 100 per 100,000 persons have EoE (Dellon 2014: 203). A study using 2009–2011 data estimated 150,000 US cases (Dellon et al. 2014). Annual incidence[4] is estimated at 6 to 13 new cases per 100,000 persons per year (Dellon 2014: 206). EoE has now been reported in children and adults across the globe, although it is more prevalent in Western countries than in Asia and no cases from sub-Saharan Africa or India are known (Dellon 2014, Cianferoni and Spergel 2016: 160). EoE affects three times as many males as females and is most common in Caucasians (Cianferoni and Spergel 2016: 160).

Both prevalence and incidence of EoE have increased dramatically over the past two decades (Dellon 2014: 207–210, Giriens, Yan et al. 2015: 1636). A Swiss study found a 10-fold increase in EoE incidence when comparing the period from 2010 to 2013 with the period from 1993 to 2009 (Giriens et al. 2015: 1633, 1637). A Minnesota study found a 27-fold increase in incidence between the 1993–1995 and 2001–2005 periods (Prasad et al. 2009). These increasing numbers cannot be fully explained by increasing awareness of the disease and improved diagnosis, but they appear to reflect a true increase in affected individuals (Giriens et al. 2015: 1636; Dellon 2014: 667).

EoE's increasing prevalence, combined with the nascent scientific understanding of the disease, has generated an active research effort. As Figure 16.1 illustrates, the number of EoE publications has skyrocketed in recent years. Entire academic careers can now be built on research into EGIDs.

[4] *Prevalence* indicates the total number of individuals exhibiting the disease at a given time. *Incidence* indicates the number of *new* cases occurring during a given time frame (Dellon 2014: 206).

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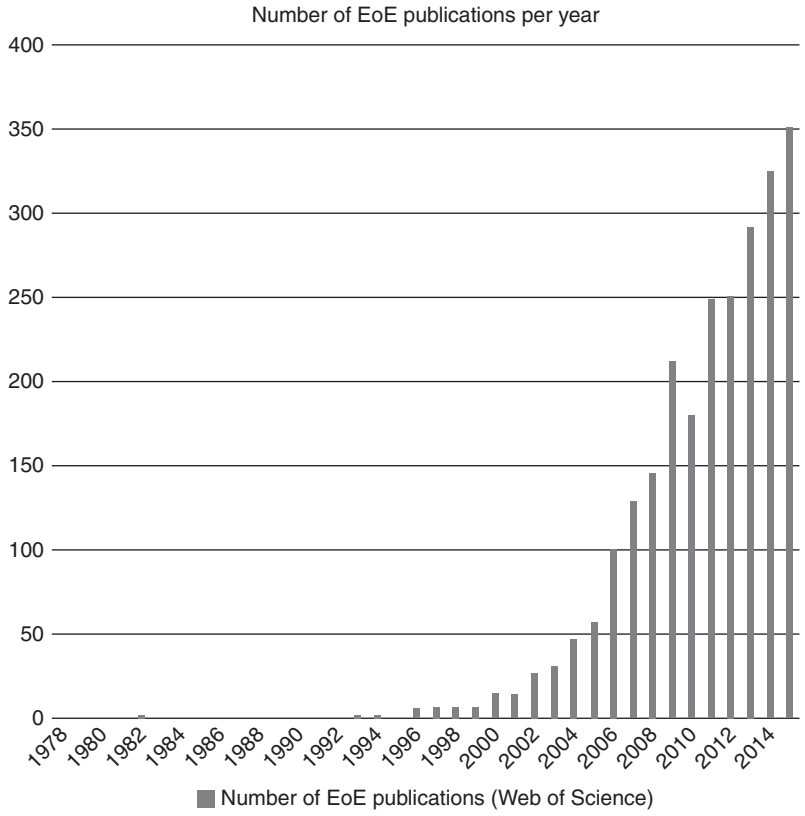

FIGURE 16.1 Number of EoE publications per year.
Note: These figures are based on a citation report for articles identified in a September 2016 Web of Science (Core Collection) search for the topic "eosinophilic esophagitis" (September 2016 EoE Articles).

16.2.2 *EGID Research and Treatment: An Interdisciplinary Endeavor*

EGID research is interdisciplinary in at least two respects: it involves specialists from medical disciplines spanning allergy, gastroenterology, pathology, and other fields, and it afflicts both pediatric and adult patients. To be effective, and take advantage of potential synergies, CEGIR must bridge these potential divides.

16.2.2.1 Allergy, Gastroenterology, and Pathology

The interdisciplinary nature of EGID clinical research brings both challenges and opportunities. Specialists from different backgrounds may have different expectations and view similar phenomena differently, which could lead to conflict.

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Interdisciplinarity also creates opportunities for synergies, however. As one interviewee explained:

> I think the field of EoE has gotten close to where IBD [inflammatory bowel disease] has in 20 years, as opposed to almost 100. That, I think, is directly attributable to the collaborative nature about it, and part of it is the disease itself. You need the pathologist. You need the gastroenterologist. You need the allergist . . . The cross-disciplinary nature has, I think, led to much quicker insights.

Interdisciplinary interactions also can be intellectually stimulating, as one gastroenterologist interviewee told us: "I have learned a lot of things and I'm still learning about immunology, things that happened in the tissue, cytokines, all these mechanisms. I have learned a lot about allergy . . . If I attend any session, I always learn new things. It's challenging."

16.2.2.2 Pediatric and Adult

EGIDs affect both adults and children, so that clinical researchers come from both adult medicine and pediatrics. In the United States at least, "a lot of the major players in the EoE world came from the pediatric world." Pediatricians and adult doctors bring different training and perspectives to EGID research.

16.2.2.3 Diet versus Drugs

One place in which these disciplinary divides have played out is in the choice of treatment. Currently, there are two alternative standard treatment options for EoE: daily topical steroids and strict food elimination diets (Cianferoni and Spergel 2016). According to our interviewees, treatment preferences have tended to split along the allergist-gastroenterologist and pediatric-adult divides. The elimination diet approach requires knowledge about nutrition and, because compliance is difficult for patients, support from a dietician, as an interviewee explained:

> You need a dietician at the back end to enforce the diet, to explain to them clinical contamination, how do I avoid milk, . . . what are the foods that contain it, processed foods and all these contaminants. It requires an effort, whereas steroids are very easy. The majority of the physicians go the steroid route because they don't understand diet.

Allergists are more inclined to use diet-based treatments, in part because they have more training in nutrition and in part because they ordinarily have better access to the dietician and nutritionist resources necessary to implement them effectively. As one gastroenterologist told us:

> I think the issue is for practicing docs with GI [gastrointestinal] training, we literally learn nothing about nutrition on the adult GI side. Literally, nothing. That's not true, obviously in pediatric GI; nutrition's a huge part of what they do. But even so,

> trying to direct the patient yourself, as a gastroenterologist, as to these food elimination diets, they won't work. You just can't answer the questions ... I think most practices with GI docs don't have any access to nutritionists, and so many will use the topical steroids. And of course, you look at the diets, they're not that easy. You have to be a very motivated person to try to do those diets.

Pediatricians, whether they specialize in allergy or gastroenterology, are more inclined toward the diet approach because of concerns about long-term use of steroid drugs by children and because parents "care more about their kids than themselves, so they take their therapies more seriously" and "enforce compliance with their kids a lot better, than they would otherwise do for themselves."

At one time, these differences in training and perspective were exacerbated by skepticism about the effectiveness of the diet approach on the part of many steroid proponents. Most of our interviewees told us that these divisions have lessened over time, as the effectiveness of elimination diets has become more clearly established, and because it appears that less draconian dietary approaches may be effective. Standard dietary treatment eliminates all milk, eggs, soy, wheat, nuts, and fish products (six-food elimination diet). Adhering to such a restricted diet is difficult and has a significant impact on quality of life. Ongoing research is isolating the foods most likely to cause eosinophilic esophageal inflammation, in the hope that more palatable dietary treatments, such as the elimination of cow's milk alone, will be effective for most patients (Kagalwalla et al. 2012).

Several interviewees thus told us, in essence, that food elimination diets and steroid drugs "both work, so I let the patient decide," based on the patient's willingness and ability to comply with the necessary dietary restrictions. Nonetheless, interviewees agreed that clinicians' preferred treatments continue to vary, largely along the disciplinary lines discussed earlier.

16.2.3 *Patient Advocacy Groups*

CEGIR partners with several patient organizations, the two largest of which, the American Partnership for Eosinophilic Disorders (APFED)[5] and the Campaign Urging Research for Eosinophilic Disease (CURED)[6] are described here. APFED and CURED representatives are heavily involved in CEGIR.

16.2.3.1 APFED

APFED was formed in 2001 by a group of mothers of EGID patients. Early on, APFED focused primarily on education and advocacy. Beginning in 2008, it began to fund some research. From 2012 to 2014, about half of its expenditures of about US$500,000 per year were devoted to research, primarily through pilot grants.

[5] http://apfed.org/ [6] https://curedfoundation.org/

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APFED has a paid executive director and both the chair and president of its board of directors are physicians. It is part of the lay organizations committee of the American Academy of Allergy, Asthma & Immunology (AAAAI). In 2013, APFED launched the Eosinophil.Connect Patient Registry to "capture self-reported, de-identified demographic and medical information for patients who have eosinophil-associated diseases into a central database so that it could be shared among researchers" (American Partnership for Eosinophilic Disorders 2014: 10). APFED has long-standing relationships with EGID researchers. About half of the members of APFED's medical advisory board are CEGIR investigators and several CEGIR investigators have been associated with APFED since its founding. APFED currently provides US$50,000 per year to CEGIR.

16.2.3.2 CURED

CURED was founded in 2003, also by parents of a child suffering from eosinophilic disease. One of its founders still serves as president of its executive board and as a volunteer executive director. Like APFED, it is part of the lay organizations committee of AAAAI. Though CURED organizes and participates in some educational and advocacy activities, it is dedicated primarily to raising money for research. Virtually all of its annual expenditures, averaging about US$370,000 for 2012 to 2014, go to research grants. CURED also has long-standing relationships with CEGIR researchers, particularly with Dr. Marc Rothenberg's group at the Cincinnati Children's Hospital Medical Center. Initially, all of CURED's research funds went to the Cincinnati center. In 2008, CURED began making smaller grants to a few additional institutions, nearly all of which are now CEGIR sites. Five CEGIR investigators serve as members of its honorary board, which includes medical professionals and others. CURED currently provides US$25,000 per year to CEGIR.

16.3 THE CEGIR CONSORTIUM

As explained in the previous chapter, the RDCRN aims "to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing."[7] Each consortium must have two clinical research projects (including a longitudinal study), a training program for junior researchers, at least one pilot project, a website, and a collaboration with a patient advocacy group.[8] Though CEGIR shares its general structure and goals with other RDCRN consortia, it is shaped by its own particular goals and history, by the

[7] www.rarediseasesnetwork.org

[8] See, e.g., Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Diseases Clinical Research Network (U54) – RFA-OD-08–001, http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08–001.html#SectionI

individuals who make up the community, and by its own governance structure and choices, some of which are described in this section.

16.3.1 *Goals and Objectives*

CEGIR[9] is dedicated to "improving the lives of individuals with eosinophilic gastrointestinal disorders through innovative research, clinical expertise and education via collaborations between scientists, health care providers, patients, and professional organizations." CEGIR pursues its mission through its clinical research projects, pilot study program, and training program. CEGIR also plans to "partner with industry in order to improve the lives of patients with EGIDs, including conducting clinical trials."

CEGIR's goals for its longitudinal study are both typical and tailored to the particular diagnostic and evaluation challenges posed by EGIDs. The study aims to "determine the correlation of clinical outcome measures (COMs), including patient-reported outcomes (PROs), with the histological disease activity as measured by mucosal eosinophil counts"; "test a series of related hypotheses concerning secondary histological parameters that may correlate with clinical and phenotypic measurements, potentially leading to a new gold standard for EoE, EG, and/or EC diagnosis and monitoring"; and "determine the correlation of the molecular profile for EoE, EG, and EC with COMs and mucosal eosinophilia."

CEGIR's second major project is an interventional study comparing the efficacy of the standard six-food elimination diet with that of a milk elimination diet and studying whether patients who experience diet failure remain responsive to swallowed glucocorticoids therapy. Eventually, CEGIR hopes "to develop a personalized medicine approach based on a biomarker analysis that can predict the best treatment for individual patients." All nine CEGIR sites are expected to participate in these major clinical research projects.

16.3.2 *CEGIR's History*

CEGIR's leaders, Drs. Marc Rothenberg and Glenn Furuta, were among the first researchers in the US to study EoE after it was identified in the 1990s. In October 2006, they were instrumental in organizing the First International Gastrointestinal Eosinophil Researcher Symposium (FIGERS), convened under the auspices of the North American Society of Pediatric Gastroenterology and funded by the NIH. The patient advocacy organizations also played a part in encouraging the researchers to meet.

[9] Information about CEGIR quoted in this section is taken from www.rarediseasesnetwork.org/cms/cegir/About-Us

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FIGERS instituted the production of so-called consensus guidelines for diagnosis and treatment, which review and evaluate the state of the art based on the available literature. The first set of EoE consensus guidelines was published in 2007 (Furuta et al. 2007). Coauthors of the 2007 consensus guidelines formed a group of about 13 senior researchers, which eventually became known as TIGERS. TIGERS was described by one of our interviewees as "essentially [an] unfunded consortium of concerned people who really wanted to work together and identify areas of need and so on. We work well together. It was quite natural." TIGERS "maintained monthly meetings to talk about things relevant to the field and perform small research projects, had collaborations, participant education, advocacy efforts." Though TIGERS received some private funding beginning in 2008, it has not had significant research funds but has served mostly as a forum for discussing scientific issues and organizing collaborative efforts.

TIGERS was instrumental in the development of updated consensus guidelines in 2011, though the group of coauthors for those guidelines was substantially larger (Liacouras et al. 2011). Over time, the consensus guidelines have become important references for the EoE community.[10]

Consensus guidelines, while useful for both clinicians and researchers, do not provide sufficiently standardized diagnostic and efficacy metrics for use in large-scale, multi-site clinical research or to provide clinical end points for FDA assessment of potential drug therapies. To address these needs, TIGERS also "engage[d] with the FDA to say, 'How do we talk about getting new treatments in place?'" and began to work to develop end points for clinical trials. TIGERS organized the development of both pediatric (Franciosi et al. 2011, Martin et al. 2015) and adult (Schoepfer et al. 2014) assessment tools incorporating laboratory tests and patient-reported outcomes (Nguyen et al. 2015).

To validate the tools, "people who were leading the efforts enrolled subjects at their own institutions as well as at TIGERS institutions" for a "multi-institutional effort that required a couple hundred patients." Validation was accomplished "without much backing, but [with] a lot of unfunded efforts on people's parts."

The decision to apply for NIH funding to create CEGIR was "simply an evolution" of this history of collaboration between senior researchers in the field: "Basically, we took the expertise from TIGERS, laid it into the grant application of what we had been doing for a while, teamed with the patient advocacy groups we were pretty engaged with already, and put the application in."

Many CEGIR investigators, including CEGIR's two primary leaders, are TIGERS members or were otherwise involved in the consensus process. Nearly every CEGIR site has at least one TIGERS member. Moreover, 15 of CEGIR's 22 investigators were coauthors of the 2007 consensus guidelines, FIGERS participants,

[10] This is evidenced not only by our interviews but also by citation patterns. The consensus recommendations are the most heavily cited EoE-specific articles on Web of Science (Core Collection). By September 2016, the 2007 and 2011 publications had received 692 and 561 citations, respectively.

or coauthors of the 2011 consensus guidelines. In this respect, CEGIR resembles the UCDC, which also grew out of a close-knit community of researchers.

16.3.3 *CEGIR's Participants*

16.3.3.1 Consortium Leadership

CEGIR has two primary leaders: Marc Rothenberg, of Cincinnati Children's Hospital, who serves as overall consortium principal investigator and hosts consortium administration at his institution, and Glenn Furuta, of Children's Hospital Colorado, who serves as consortium administrative director and is the named principal investigator for CEGIR's longitudinal study. Rothenberg and Furuta were the initiators of the 2007 consensus process and the primary founders of TIGERS. Their leadership of the consortium flows directly from these earlier leadership roles.

Rothenberg, a specialist in pediatrics, allergy, and immunology, is the founder and director of the Cincinnati Center for Eosinophilic Disorders, the first US center dedicated to eosinophilic disorders. Rothenberg spends about 80 percent of his time on research, much of which is basic, rather than clinical, about 5 percent of his time seeing patients, and the rest of his time on administrative duties. As he explained: "Now, if someone asks me, 'What do I do?' I don't consider myself a clinician. I consider myself a professional researcher so I'm coming to work every day to do research." Rothenberg is the most highly cited researcher of eosinophilic diseases; the next two most cited are also at the Cincinnati Center.[11] In addition to Rothenberg, the Cincinnati Center includes four other CEGIR investigators (including CEGIR's lead pathologist), CEGIR's lead study coordinator (effectively, a project manager) and other administrators, two biostatisticians, an informatics analyst and CEGIR's lead dietician.

Furuta, a pediatric gastroenterologist, is director of the Gastrointestinal Eosinophilic Diseases Program at the University of Colorado School of Medicine. One of CEGIR's three pathologists, a CEGIR study coordinator, and the recipient of CEGIR's first pilot project funding are also located at Colorado. Furuta is the fifth most highly cited researcher in the field, following the Cincinnati researchers and pioneer Straumann. Furuta views himself as "mostly [a] physician" and his program at Colorado focuses primarily, though not exclusively, on clinical research.

[11] In December 2015, we searched Web of Science (Core Collection) for the topic "eosinophilic esophagitis." We used HistCite to calculate how often these "December 2015 EoE Articles" by a particular author are cited by other articles (a "Global Citation Score" (GCS)). According to this calculation, the most important EoE authors are Marc Rothenberg (Cincinnati, GCS: 6909), Philip Putnam (Cincinnati, GCS: 4759), Margaret Collins (Cincinnati, GCS 4439), Alex Straumann (Switzerland, GCS: 3967), and Glenn Furuta (Colorado, GCS: 3202). The high scores of the three Cincinnati Children's Hospital authors reflect their frequent coauthorship. For some general information on HistCite and other bibliometric software tools, see van Eck and Waltman (2014).

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16.3.3.2 Other CEGIR Investigators

CEGIR's investigators are located at nine NIH-funded sites at US academic medical centers. All but one of CEGIR's 22 clinician researchers have medical degrees, while the other has a PhD. Three of the MDs also have PhDs. CEGIR investigators range in experience from those who obtained their medical degrees in the 1970s to those who obtained their degrees in the 2000s. Fourteen are gastroenterologists, six specialize in allergy and immunology (one with a dual specialization), and three are pathologists. About two-thirds are pediatricians. As one interviewee explained:

> We all play in the sandbox really well together. It's adult. It's pediatric. It's allergy, GI, pathology. It's basic and clinical researchers ... At the end of the day, we're mostly physicians. We're mostly people who are looking at how can we take care of patients better. What are new treatments and how are we going to get those treatments in place?

16.3.3.3 Study Coordinators

Study coordinators do much of the day-to-day implementation of clinical research projects. They obtain informed consent from patients, ensure that the appropriate tests are done and specimens collected, and enter data. They also "get to know the patients well, because they're seeing them for the study visits, they're on the phone with them to coordinate stuff. They're recruiting them, explaining the studies, the whole nine yards. Their job is really valuable." Study coordinators also bring a practical perspective to study design:

> They will go through and edit and write protocols that make sense. If they don't have the buy-in, then nothing is going to work. I think the group of coordinators, especially the ones who are really running logistics, they're so engaged in doing everything. It's not the usual thing that you find, I think ... To this point, they've been involved in the logistics of the study design, and the instruments, and they'll be like, "Look, we have all these instruments, do we really need every single one of these questions and data points?" We've gone through on a very painful call, and multiple forms, and like, nope, nope, nope, yes, nope, this has to be changed ... If you have a study that you did by yourself, and you're like, "Okay, here it is, implement it," it wouldn't go well.

16.3.3.4 Dieticians

Consistency in diet protocol between sites is crucial to the success of CEGIR's study of the comparative efficacy of six-food versus one-food elimination diets. CEGIR employs a coordinating dietician at the Cincinnati lead site and a dietician at each site to administer and monitor the protocol. As one interviewee put it, food elimination diet therapy requires "a very talented dietitian."

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16.3.3.5 Patient Advocacy Group Representatives

Patient advocacy group representatives are full-fledged members of CEGIR and are involved in CEGIR activities in many ways, such as serving on committees, reviewing the CEGIR website, attending meetings and conference calls, and commenting on study protocols and other issues. They are expected to be pivotal in recruiting patients to participate in CEGIR's studies.

16.3.3.6 NIH and DMCC Representatives

RDCRN grants are so-called U54 grants, meaning that NIH representatives take an active role in consortium activities, participating in conference calls and meetings and providing input at various stages. Because CEGIR is funded through three NIH institutes, several NIH representatives are regularly involved with its activities. NIH also funds a centralized RDCRN Data Management and Coordinating Center (DMCC), which provides various services related to collecting and managing consortium data. DMCC representatives also work closely with CEGIR. Interviewees called the DMCC "a huge, huge resource" of "enormous" value, describing it as "unbelievably responsive," "very helpful," and noting that it "operate[s] pretty quickly." Even though some observed that DMCC involvement "add[s] one extra layer of review and time involved," they concluded that "the value that it adds is probably quite significant."

The DMCC has assisted CEGIR in setting up a central Institutional Review Board (IRB). IRBs review and monitor study compliance with ethical requirements for human subject research. Traditionally, each institution's IRB reviews each study protocol, perhaps suggesting revisions, and then decides whether to approve it. Central IRBs are intended to make this process more efficient for multi-site studies. Most interviewees were convinced that the central IRB approach would "streamline things . . . in the end," but getting the necessary inter-institutional agreements in place to the satisfaction of all local IRBs can be a complicated matter. The DMCC "ha[s] all sorts of experience with setting up IRBs and central IRB models and just working with a lot of different groups with a lot of different types of study structures. In a lot of ways they can provide a lot of creative solutions to different things you want to try to do."

16.3.4 *CEGIR Governance*

16.3.4.1 Leadership

As in our previous studies, interviewees confirmed the importance of consortium leadership to consortium success. One interviewee described the importance of Rothenberg and Furuta's leadership in getting CEGIR started:

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> It would've been difficult for any of the other ones in the group to have pulled this off. I mean, they've had the NIH funding the longest in the group. They've made really seminal discoveries in the field. They're incredibly collaborative. Glenn [Furuta] has a wonderful personality of bringing people together and developing consensus, in a very understated way. I think probably everybody who is involved recognizes those would be the two natural people to do it. They foster the collaboration and stuff, but they also have the connections. They were able to work back door, and find out all the details and the whole nine yards, and get the thing put together. It was an enormous undertaking. They also have the infrastructure administratively to help to do that.

Having leaders who are so well known in the field also will be important to CEGIR's future interactions with pharma companies. Pharma sector interviewees explained that once a company identifies EoE drug development as a business opportunity, it begins reaching out to well-established experts in the field to get their input and advice on study designs, drug development, and regulatory approval:

> First, there is the compound and the business development opportunity. Then starts the networking with [the] experts . . . We work with well-known experts in the field who are very well connected, who are thought leaders, and who are either treating patients themselves or are connected with investigators and physicians who have very good knowledge and experience with treating this disease.

Their input is also influential in discussions with the FDA about suitable end points for the drug approval process (Fiorentino et al. 2012).

Interviewees described CEGIR's leaders as "great mentors," "pioneers in the field," "generous," "delegative, "passion[ate]," "motivating," "goal oriented" and "a great team." One noted: "[The research] means so much to them that they make everybody so interested in it or so excited about it. They pull everybody in. They listen to everybody. It's not just their way or the highway. It's they want input from every single person who's on the call." Another interviewee was of the view that CEGIR's leaders were adapting well to the transition from running a single lab to leading a multi-site consortium:

> I think like everybody else they're learning as they go and going from a one-man show to incorporating opinions from a lot of people I think has been a learning experience for all of them. They have done a really good job at it and they are seeing the value in the team . . . They do a very good job of making people feel included, making sure opinions are heard, do their best, of course, to ensure things are fair . . . I think they've been very open and open to new ideas, open to looking at things differently.

Interviewees also noted that "personality-wise, [CEGIR's two leaders] are very different people" with distinct leadership roles. They emphasized Rothenberg's

devotion to scientific productivity and to "getting the job done in the right way" and his "analytical mind," while emphasizing Furuta's role in "bringing people together and developing consensus," in taking "a global view of things" and "making sure [all the various projects in the consortium] are actually moving forward." Interviewees saw Furuta's community-building skills as essential. As one interviewee put it:

> I think it's the strength of his personality and his charisma, if you will, which is very quiet. It's not showy, it's not flashy, it's very steady and his ability to navigate choppy waters and smooth things over when they need to be that has resulted in a very long ongoing relationship among a lot of us . . . I'm not sure there would be a consortium if there hadn't been a Glenn [Furuta].

Another explained: "Dr. Furuta, he's a great leader. He's very open for discussion, very appreciative for everybody's input. I'm literally talking from the secretaries up to the pathologists."

Despite these generally very positive views of CEGIR's leadership team, a few interviewees expressed concern that CEGIR's leadership "is not inclusive, it's exclusive" with regard to those outside the inner circle, suggesting that the criteria for determining insiders and outsiders lacked transparency and that NIH's funding of CEGIR might serve to "validate that structure, that hierarchy that we have" in the field.

16.3.4.2 Conference Calls, Committees and Decision Making

CEGIR's primary governance institutions are regular conference calls and committees. Many interviewees commented on the sheer number and frequency of calls involved in getting CEGIR up and running. Bimonthly conference calls involve all CEGIR participants. Because these calls involve so many participants, they serve mostly for updates, for providing feedback, and for final approval of proposals hashed out in smaller working groups and committees. There also are monthly study coordinator calls and calls involving participants in particular committees and activities. For example, dieticians from the various CEGIR centers have been in frequent communication to work on standardizing the diet instructions for the food elimination comparison study.

Interviewees generally believed the calls were well run and served important purposes. As one interviewee explained:

> I think the calls . . . keep you on your toes. It's like a built-in deadline. There's a CEGIR call coming up, I better get this thing . . . straightened out before the next CEGIR call, because they're going to ask me about it. It's a reminder to keep the ball rolling about what needs to be set up next and so on. It's a good way to keep informed of what's happening, how many subjects have been enrolled and where the various studies are in the IRB process and the NIH review process, and so on. I think they're generally informative. The CEGIR-all call, certainly the advocacy

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> groups are called on to voice what their meanings, desires, or wishes are. They're very helpful in terms of helping to recruit people to sign up for registries, and from registries we potentially can recruit people into clinical trials. That aspect is very helpful. I think [the calls] serve a good purpose. They are numerous, but I don't miss them – if I'm here, I'm on the call – so it's not like they're that painful to have that I'd do anything to not be on the call.

CEGIR has a number of committees, including a Steering Committee and committees focusing on each of the main research projects, the pilot projects, the training program, the contact registry, data monitoring, publication policy, and various other aspects of CEGIR's activities. An ethics committee eventually will deal with issues such as intellectual property and cooperation with pharmaceutical companies. These committees include not only researchers but also, depending on the committee, may include patient representatives, dietitians, study coordinators, statisticians, or other administrators. Most committees are composed of volunteers.

The expectation is that, for most issues, the PIs and the Steering Committee will serve primarily as a "red stamp," so that, in essence, "decisions are being made locally by the committee." As one interviewee described the process:

> It's hard, I think, to make major decisions in [the large conference call], so I think what happens is that there are a lot of smaller working groups that bring preliminary decisions to the bigger groups for discussion, and basically it's not, "Does everybody agree?" but "Does anybody have a problem with this?" is the way that it's usually presented. I'll give you an example for the Publication Committee. They said there's going to be a Publication Committee, who wants to do it . . . [Several people volunteered, then the committee] had multiple calls and hashed out some of the details, and then [drafted] guidelines . . . [that] got sent out to the group. They said, "Here's a draft. Give comments." [There were] no comments, and so [it was] like, "Okay. Here it is" . . . [S]ame thing for protocol design, there are smaller working groups for the protocols . . . One or two of the people drive the bus. Those are PIs. They do the initial protocol, and then a smaller group gets on the phone to review it, and go through it . . . [Changes are made based on that small group discussion] and then that goes back out to the group. Sometimes . . . when you get a lot of feedback, it's just too many cooks in the kitchen for stuff. There's no way that a real major decision can be made on a call with 120 people, but it is a place [where] people . . . can voice their opinions, and everybody gets a chance to get heard.

16.4 CEGIR'S PRIMARY ACTION ARENAS: FORMING A CONSORTIUM COMMUNITY

As discussed in the previous chapter, an action arena is "the social space where participants with diverse preferences interact, exchange goods and services, solve problems, dominate one another, or fight (among the many things that individuals

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do in action arenas)" (Ostrom 2005: 13).[12] Because CEGIR was at such an early stage at the time of our study, it was too soon to observe how some of its action arenas would function in practice. We thus focus here primarily on action arenas related to CEGIR's start-up: community building within CEGIR and interactions between the CEGIR community and "outsiders."

16.4.1 *Building the CEGIR Community*

Clinical research requires the participation and cooperation of clinical researchers, supporting research personnel, such as site coordinators, dieticians, administrators, and patients. To be most successful, an RDCRN consortium must leverage the motivations of these various participants to build trusting, effective collaborative relationships.

16.4.1.1 Motivating Participation

Clinical researchers generally have both intrinsic and extrinsic motivations for their work. Researchers' extrinsic motivations, such as career incentives and reputation among colleagues (rewarded, e.g., by invitations as keynote speakers or invited contributions in prestigious journals) are somewhat competitive and may thus have ambiguous implications for community building. Interviewees emphasized how the intrinsic rewards of engaging in EGID research motivate collaboration. The satisfaction of solving a complex medical problem is one such reward. As one interviewee explained: "The main driving force is enthusiasm. We need money for all these research projects. We cannot work without any money, but it is not the main motivation ... My main motivation is to improve the understanding of this disease." The desire to help patients is also an important motivator. Several interviewees suggested that the prevalence of pediatricians in the EGID community in the United States played a role in facilitating and encouraging cooperation because "in general, pediatricians can collaborate and come together in things like a consortium, more easily than adult physicians can"[13]:

> Well, there are children involved. It's easier to let go of one's ego or at least to keep it under a little tighter rein when you've got a sick kid, then when you've got an adult who won't stop smoking, or an adult who won't take the blood pressure medicine. Noncompliance among adults is a large part of internal medicine whereas in pediatrics, they didn't do anything wrong, just got sick by bad luck or bad genes or whatever and you really want to help and make a difference. The motivation is a little different in pediatrics than in adult medicine generally. It shows in the ability to collaborate and then to get results.

[12] For further explanation of the "action arena" concept, which is central to our GKC framework, see Chapter 1 of this volume.

[13] UCDC interviewees made a similar observation (Strandburg et al. 2014).

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Supporting research personnel also will be driven by a mix of intrinsic and extrinsic motivations. With some exceptions, their career incentives are likely to be concentrated primarily on their local sites and less concerned with reputation and status within the larger EGID research community. Their intrinsic motivations may depend on how much impact they perceive their efforts as having on research progress and on whether they find their social interactions with other consortium participants rewarding.

Patients will be motivated to participate in clinical studies if they believe that the studies are designed with their needs in mind and will lead to progress in treatment and that participation is not too burdensome. Sometimes, the community can take active steps to shape the factors motivating participants. As a patient advocacy group representative who organizes meetings between researchers and patients explained:

> It's . . . amazing for the researchers to get to meet the patients, to get to see the patients' families and actually see the tears of those families and to know the pain those families are suffering . . . One of the things we said at our conference, we want to have a tour of the lab. I want the lab workers to be part of the tour. I want them to meet the patients. I want the patients to meet the lab workers. They're like, "No, it's a Saturday. They don't really work that much on Saturdays." I'm like, "It's going to work both ways. It's going to drive your people to work harder and it's going to drive the patients and families to help fundraise so please" . . . When they meet us and they hear stories, they're floored. They have no idea. It's all that they know; it's a blood slide or a rat or a mouse or whatever they're doing. They don't know the emotions.

A researcher made a similar observation:

> Meeting with patients also gives you perspective about why you're doing all the research. It's easy to kind of get lost in who's going to be on the paper; who's going to do this; who's going to do that. Then when they're like, "We've got these kids, and we don't know what to do with them, we don't know what the treatments are." That's actually the goal for all this stuff, and it kind of keeps everybody grounded, I think.

16.4.1.2 CEGIR's TIGERS Roots

CEGIR builds upon the collaborative relationships already established in the relatively small, close-knit TIGERS research community. The community was described by interviewees as "generous," "friendly," and "incredibly collaborative." As one interviewee explained:

> We're very lucky in that most everyone in this community is very collaborative and productive and wants to see the field move forward and wants to help patients, wants to improve their lives. So I think it's been very effective . . . I don't know what it is

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> about the EoE community. I do think it is very, very unique, because I hear some of my colleagues experiences with other areas of GI where it might be much more competitive and not as collaborative.

The trust among researchers that has been established through preexisting cooperation plays an important role. As one interviewee put it: "In my personal experience, I don't know a colleague before I have done a project with him. Working together, you get familiar with his personality. Once you can trust this person, then I don't need many legal rules."

As CEGIR expands out from TIGERS, it confronts two primary challenges. First, it must integrate its non-TIGERS researchers into the community. Second, it must transition from a community of researchers to a community that also includes patient representatives, dieticians, study coordinators, and others. In addition, since the NIH funding for CEGIR must be renewed every five years and may eventually be discontinued (whereas TIGERS is a collaborative project with no clear time limit), CEGIR has to maximize collaboration within a given time period so that the collaborative research network is stable enough to survive in post-CEGIR times.

16.4.1.3 Integrating Non-TIGERS Researchers

Our study suggested four strategies that may help extend the TIGERS collaborative culture to additional CEGIR researchers. First, CEGIR has expanded slowly from its TIGERS foundation, attempting to select participants with strong intrinsic motivations who "are really committed and the amount of ego is on the low level" so that they can "appreciate each other's strengths and weaknesses and not get too aggressive." Second, CEGIR has attempted to provide a high degree of transparency into decision making, including budgetary matters. Third, CEGIR attempts to be fair and transparent in various ways, the most salient of which at this early stage is its approach to allocating funding between sites. Fourth, CEGIR is focusing its research efforts on two projects that involve all of its sites in presumptively equal roles and, particularly in the case of the elimination diet/steroid interventional study, cross specialty boundaries and exploit the synergies of its interdisciplinary group of investigators.

16.4.1.3.1 A CAUTIOUS APPROACH TO SITE EXPANSION

On the whole, while CEGIR has expanded somewhat from its TIGERS roots, it has not expanded very far: most CEGIR's researchers are either TIGERS members or colleagues at the same institutions as TIGERS members. As one interviewee explained:

> It's a bigger group in CEGIR. [W]e all pay in the sandbox really well together. It's adult. It's pediatric. It's allergy, GI, pathology. It's basic and clinical researchers. To have that synergy in people who work well together, we really wanted to make sure we had that synergy. When we were going to do the [CEGIR proposal], we said "All

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> right, this is going to change some of the dynamics a little bit and we need to think about what that's going to do, but we need to [expand], and we will, but we also are going to be a little bit particular about how that happens." There are more people involved in it now, but it's worked out well.

Interviewees foresaw the need for further expansion but noted the potential trade-offs involved and the importance of "keeping it in centers that . . . would be able to accomplish the research and also work well together," and "focus[ing] on success from within," rather than "expanding it too broadly." Some were concerned about "overextending and diluting out the efforts" given the consortium's limited resources and about having the infrastructure needed to handle a larger effort. Others worried about the potential difficulty of finding additional researchers willing to put in the necessary effort, in light of the limited funding associated with CEGIR participation: "I think the people involved [so far] are willing to do it without getting much money. I think if we expand out more, I'm not sure what the willingness is to do things. Maybe some, but not a lot."

Unlike our interviewees in the NAMDC and UCDC studies, CEGIR interviewees did not generally articulate a goal of including all or nearly all EGID researchers in the consortium. This difference may stem from the growing prevalence of EoE. Higher prevalence generally means that each site sees more patients, reducing the need to aggregate patient participants from many centers to obtain a useful sample size. Indeed, one of our interviewees mentioned that CEGIR might need to add more sites if it intensifies its focus on the rarer forms of EGIDs. Increasing prevalence also attracts more researchers to the field, making the goal of incorporating all active researchers in a single consortium less feasible. As one interviewee explained:

> I don't think it's feasible that there's just one single massive research network that controls every researcher in the world . . . There's just not enough funding to support that type of structure. So for that reason it's absolutely necessary that people do small little things or even large-scale things on their own separate from the consortium, because competition is always good. Competition drives ingenuity and invention. That is just a fact of life.

While interviewees generally viewed it as "very positive that more people are engaged" in EGID research, one interviewee expressed concern that an influx of money related to growing prevalence would attract more competitive individuals to the field. Many interviewees emphasized the advantages of the currently small size of the EGID research community, which promotes "collegiality" and "friendliness" and helps "break down what could be contentious rivalries." The small size also gives younger researchers "the opportunity to get to know the big players, as opposed being a small fish trying to wade through the really big ocean." CEGIR's cautious approach to growth reflects an appreciation of the trade-offs involved in expansion.

16.4.1.3.2 TRANSPARENT DECISION MAKING

CEGIR's leadership has attempted to put a thumb on the scale toward transparency, even at the cost of a potentially overwhelming number of conference calls:

> We're exhausted from the number of calls, but we said, "The first year is the hardest because we got to get everything together." We kind of overdid the communication almost because we wanted to make sure that people felt at least engaged, they weren't excluded, that there was a good synergy of people. If people said it's too much, that's okay, but we don't want them to say, "What's going on? We don't have access."

Our interviewees generally seemed satisfied with their level of engagement in consortium decision making, at least so far. As one told us:

> Usually, when Glenn [Furuta] and Marc [Rothenberg] run the meetings, they're actually good at being, "Okay, NIH, anybody want to say anything?" "Patient advocacy groups, want to say anything?" I think it's a way that everybody feels like they're included, and there's certainly no shortage of phone calls for people to be included in the first year of planning. It's nothing but phone calls. I think the decision making has been working okay, and they've made an attempt to be transparent with budget stuff, and decision making, and who theoretically is in charge of the different subareas and everything.

16.4.1.3.3 ALLOCATION OF CONSORTIUM FUNDS AND OTHER POLICIES

RDCRN consortia must allocate grant funding among sites and researchers, manage publication credit and access to and use of data collected through its longitudinal and other studies, and eventually may need to make decisions about intellectual property. The perceived fairness and transparency of a consortium's approach to allocating resources and rewards may affect its success in forming a collaborative community. While CEGIR had developed a publication policy, tasked a committee with managing data use, and formed an ethics committee to deal with intellectual property questions and other matters, these issues had yet to attract much attention from CEGIR members at the time of our study. Thus, the most salient allocation question concerned the distribution of consortium funding among CEGIR sites.

CEGIR's budget was determined through a proposal-writing process in which members from all current CEGIR sites were involved. While the Cincinnati and Colorado sites receive larger funding allocations because of their administrative responsibilities, funding is otherwise divided roughly evenly among sites. As an interviewee explained:

> Basically, there's a number of different models that one could use for [allocating funds among sites]. You can have pay as you go or pay as you perform – you do some work, you get some money. Or you can divide it up, equal divisions depending upon what you're expected to do. We've taken the latter model.

About 20 percent of CEGIR's US$1.25 million grant is allocated to the administrative costs of the lead site, consistent with the administrative budgets for the two other consortia we studied.[14] Additional moneys, totaling about 20 percent of CEGIR's grant, are allocated to pilot projects and the training program for junior researchers. The remaining 60 percent or so is divided between CEGIR's two primary clinical research studies, in which all of the sites participate. On average, CEGIR's budgets for the longitudinal and food elimination/steroid comparison studies amount to about US$50,000 and US$35,000 per site, respectively.[15] The majority of CEGIR's funding allocation for each site goes toward "the salary of the investigators and the clinical research coordinators and a couple of other people like the statisticians. We divide [the funding] up so each site is going to get the same approximate amount of effort for each [category of] individual. It's a 5 percent effort of an investigator, 20 percent effort on a CRC [study coordinator]." The remaining site allocations support "the clinical processes that are basically just for research purposes and the research procedures and assays and the biochemical and molecular analyses that are done," as well as "a small amount of money for administrative issues like travel and meetings and things like that." None of our interviewees voiced complaints about CEGIR's funding allocation model, suggesting that the allocation was perceived as reasonably fair and transparent.

16.4.1.3.4 MULTI-SITE STUDIES THAT BRIDGE DIVIDES

Both of CEGIR's primary research studies involve all of its sites in relatively equal roles. The UCDC study noted that "the longitudinal study formed a backbone for . . . developing collaborative practices" (Strandburg et al. 2014: 206) simply by providing a structured platform requiring group interactions. We hypothesize that the same will be true for CEGIR's two major projects. Indeed, the standardizing of diet instructions for the studies seems already to have played a community-building role for CEGIR's dieticians. Moreover, CEGIR's interventional study comparing treatment options across disciplinary perspectives not only exploits the possible synergies of CEGIR's interdisciplinary membership but may also promote community cohesion across specialization lines.

16.4.1.4 Integrating Other CEGIR Participants

Building a trusting and committed community that extends beyond researchers to include patient advocacy group representatives and site personnel such as study coordinators and dieticians is likely to enhance CEGIR's effectiveness. Beyond

[14] Budget information quoted here was obtained from NIH RePORTER, https://projectreporter.nih.gov/reporter.cfm, to facilitate comparison between consortia.

[15] The UCDC consortium, which adopts a similar funding approach, budgets a similar amount per site for its longitudinal study, while the NAMDC consortium, which employs a "pay as you perform" model, budgets less than a third as much.

mandating the involvement of patient advocacy representatives, who generally sit on consortium steering committees, the RDCRN framework does not address this issue, so each consortium must determine how it will go about integrating its non-researcher participants.

16.4.1.4.1 PATIENT ADVOCACY GROUP REPRESENTATIVES

Our interviews suggest that CEGIR has been successful so far in integrating patient advocacy group representatives into the community. Though most CEGIR researchers were involved with the patient advocacy groups before CEGIR was established, interviewees of all stripes stressed the benefits of the RDCRN patient participation model, which one interviewee described as "a whole different level of collaboration in terms of planning studies and sort of the back and forth."

Researcher interviewees emphasized the value of patient advocacy group input in designing and conducting studies that will successfully recruit and retain patient participants. As one explained:

> I think the patient advocacy groups are actually incredibly important, and a very unique aspect of [CEGIR]. First of all, there's several reasons. There's the obvious one where they can say, "This is important to our patients. It's not important to patients." That really can help drive some of the stuff, and actually some of the major study decisions, they were giving feedback on, so for [the interventional study] there was debate about which of the eliminations diets we were going to use. It came down to . . . asking them, "Is this something that a patient would agree to be randomized to? Is this realistic?" It's a real practical input that you don't get when you're just designing this stuff theoretically in a room. If you can't get patients into it, you're kind of hosed.

Suggestions from patient representatives already have led CEGIR to change a study protocol "in a dramatic way." The changes made the dietary information provided to patients "much easier to follow and read and much more patient friendly" and gave "practical advice" about "ensuring adherence" to study protocols."

From a researcher perspective, patient advocacy group involvement does "have its challenges in terms of we all tend to speak a common language, and then you bring somebody in who doesn't and that's hard. Sometimes there may be things that don't seem worthwhile or equitable or whatever that are scientifically necessary, and that can be a hard discussion to have, but probably still a valuable one." Nonetheless, the overwhelming view expressed by interviewees was that the advantages of patient advocacy group involvement make it well worthwhile to deal with the challenges.

For their part, patient representatives emphasized how participating in CEGIR had connected them to into the community in a way that their association with TIGERS had not. As one interviewee explained:

> For me, I think it's a lot like . . . a collaboration because . . . there's so many different committees and we're part of every one of them, and there's a different mix of

> physicians at each committee . . . The patient advocacy groups are eligible to be on every one of those committees. We're just very fortunate.

Another told us that "I saw minds change after listening to me. I'm totally impressed with the way they care about what the patients feel."

CEGIR faces one potential challenge in dealing with patient advocacy groups that we did not encounter in our two earlier studies: the two major national patient advocacy groups dealing with EGIDs. As discussed earlier, the two groups take different approaches, with CURED emphasizing that it is volunteer run and that "Only CURED Donates 100% of Profits to Research for CURE,"[16] and APFED emphasizing its "future and long-term vision . . . to become an all-encompassing eosinophilic advocacy organization."[17] These groups generally do not work cooperatively and compete for funding and volunteer time. In 2014, the Coalition of Eosinophil Disease Patient Advocacy Groups (C-EOS) was formed,[18] in part to support CEGIR's application for RDCRN funding. The coalition now meets on a monthly basis.

It is not yet clear what effect, if any, the patient advocacy group coalition, or CEGIR itself, will have on relationships between the patient advocacy groups. Both CURED and APFED are devoted to CEGIR's success, however, believing that "at the end of the day, everybody's got to work together or we're not going to get anywhere." As a result, differences between the patient advocacy groups had not led to "any complications to date" for CEGIR:

> In general, [any differences between patient advocacy groups haven't] stalled out the research. It's just like in patient care what we always try to come back to is what's best for the patient, what's best for making those decisions. In this, it's what's best for the research and completing the mission of the grant. That usually works. People are able to come back to the mission and say, "Okay, yep."

16.4.1.4.2 SITE PERSONNEL

There are at least two possible participation models for supporting personnel. In a hub and spoke model, site personnel interact primarily with others at their sites, as they would during a single-site research project, and occasionally with the project manager or others at the lead site. They may also sit in on monthly consortium conference calls. In a more thickly connected model, site personnel interact more directly and more often with members at other sites. Cross-site interactions between the personnel responsible for the nitty-gritty of running consortium studies may benefit a consortium in various practical ways, for example, by helping ensure uniform implementation of study protocols and surfacing practical problems at an earlier stage. Less tangibly, cross-site relationships between site personnel may benefit the consortium by fostering a sense of

[16] http://curedfoundation.org [17] http://apfed.org [18] www.c-eos.org

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belonging and responsibility to the larger community and enhancing intrinsic motivations. CEGIR's dieticians already appear to relate to the consortium through the more connected model, while it is too early to assess how CEGIR study coordinators will relate to the consortium.

16.4.1.4.2.1 Dieticians

By the time of our study, CEGIR's dieticians had already engaged in significant cross-site interactions in preparing for CEGIR's elimination diet study, in consultation with CEGIR's researchers and patient advocacy group representatives. While much of the work was carried out by email and teleconference, CEGIR's dieticians also met in person for a daylong session at CEGIR's annual meeting. As a dietician interviewee explained:

> Of course, one big issue of the study is that we all need to give the same advice. That's something interesting, because if you put 10 dietitians in a row . . . and you say, "What do you say about wheat avoidance? How do you handle 'may contain traces'? What do you say about milk avoidance?" you get ten different answers . . . I knew that one of the biggest issues of this trial would be that we have a standardized approach. It may be not exactly what you would do in clinical practice, but we all need to do exactly the same thing. Otherwise, we can't compare outcomes across the different sites.

The sites' geographical dispersion created challenges because "people eat very differently in different states. We had to take all of that into account, which once again was why it was so good to have dietitians from all the sites on board."

Like CEGIR's researchers, most of CEGIR's dieticians already knew one another reasonably well, which presumably facilitated community building. Many were involved in a working group aimed at producing standardized dietary recommendations to implement the EoE consensus guidelines. Most also had worked closely with CEGIR's researchers in the past. As a result, "There were never contentious issues. We all like each other. We know each other. It wasn't a big deal to make a decision."

16.4.1.4.2.2 Study Coordinators

CEGIR's funding allocation approach means that each site has a study coordinator who dedicates a fraction of his or her time to CEGIR activities. In principle, CEGIR study coordinators can form cross-site relationships through CEGIR's monthly consortium-wide conference calls and study coordinator calls. At the time of our study, however, only the lead coordinators at Cincinnati and Colorado had been significantly involved in CEGIR teleconferences and other cross-site activities. Study coordinators at other sites generally had not yet participated regularly. Interviewees anticipated that their participation would pick up, however, once patient enrollment for CEGIR's studies, in which coordinators play a major role, kicked into gear.

Even after patient enrollment and participation begins, however, eliciting study coordinators' full participation in cross-site dialog may be challenging, in part

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because they may be more reticent than investigators and dieticians about speaking up:

> I think, in general, study coordinators are a little bit less vocal than the investigators. For example, if you're on a big conference call when you have investigators and coordinators, you're going to hear primarily from the investigators and not as much from the coordinators. Even when we're on just a coordinator call, they're just a lot less vocal than the investigators are.

Unlike CEGIR's researchers and dieticians, study coordinators generally do not have preexisting relationships with CEGIR participants at other sites, which may exacerbate this reticence.

Cross-site interaction between study coordinators may be valuable, however, and thus worth facilitating. As one interviewee explained:

> I do think it would be helpful sometimes for the coordinators to have a better opportunity to be able to work together besides the email and the conference call . . . Every site is different, and the way things are done at every site is a little bit different. Sometimes it's hard when you're not talking with them face-to-face to figure all those things out; to design the study in a way that really accommodates all of the idiosyncrasies of how each site has to do things.

This interviewee suggested that occasional face-to-face meetings might help strengthen bonds between study coordinators.

16.4.2 *Relationships with Outsiders*

In addition to building its community from within, CEGIR must manage its relationships with non-CEGIR research entities and researchers. Two aspects of this management task surfaced during our interviews: relationships between TIGERS, CEGIR, and US-based outsiders, and relationships between CEGIR and the international EGID research community. We discuss these issues briefly here, with one important caveat: most of our interviewees were CEGIR members, which means that our view of these boundary matters is unavoidably one sided.

16.4.2.1 CEGIR, TIGERS, and other US-Based EGID Researchers

When the TIGERS group of a dozen or so EGID researchers was formed in the mid-2000s, the EGID research community was considerably smaller than it is now. At that time, the group may have included all the most active US researchers in the field. That is no longer the case. TIGERS has added only a few new members over the years, intentionally opting to remain a small, self-selected, close-knit group. While there are obvious advantages to such an approach, our interviews suggested that TIGERS may be perceived by some as exclusive and clique-ish, particularly

because the criteria for membership are, as one of our interviewees described them, "nontransparent."

Though CEGIR is distinct from and larger than TIGERS, its membership also is limited. Even though 19 of the top 23 US-based EoE researchers are at CEGIR institutions[19] and 8 out of the 10 most influential EoE research centers in the United States belong to CEGIR,[20] many EGID researchers are not included. Thus, when asked what fraction of US EGID researchers were included in CEGIR, one interviewee responded: "If you'd asked me that five years ago, it probably would have been the majority. If you ask me that now, I would say probably less than half, but it's hard to know." CEGIR's cautious approach to expansion, along with its deep roots in TIGERS, may lead to perceptions of exclusion. As one interviewee put it:

> From my perspective, there is a trade-off. It's going to be the ins and the outs and the haves and the have-nots. There would be groups, you surmise, that are going to be wanting to get in and maybe feel that they should be in and maybe deserving to be in but aren't in and then they can say, "That's an elite group," or, "They didn't give us a chance. They don't have a fair policy to spread it out."

To some degree, such trade-offs are endemic to consortia that do not incorporate essentially all active researchers in a field. EoE's increasing prevalence may put CEGIR in a particularly tricky position, however. When a disease has a small researcher base, as is the case for most rare diseases, it may be possible to include nearly "everyone" (in some sense of the term) in a single consortium. Both UCDC and NAMDC adopted that goal, at least in principle. When a disease is sufficiently common to have a large patient and researcher base, including everyone in a single consortium is both impractical and unnecessary. Instead, multiple research groups compete with one another for funding and publication credit in the traditional way. As EoE prevalence increases, CEGIR may find itself uncomfortably in the middle, in that the EGID patient and researcher base may grow too large for a single consortium but remain too small to support multiple effective research groups.

As CEGIR becomes more established, it will face additional boundary management questions related, for example, to data access and sharing. Despite the substantial overlap in membership, CEGIR is distinct from TIGERS and from the preexisting close-knit EoE community. For example, our interviews suggested some tension over the scope of CEGIR's rights to use assessment tools developed at particular sites and validated with TIGER participation. These tools consist, in part, of questionnaires addressed to patients, in which questionnaire developers may assert copyright. As one interviewee explained: "It's a property. It's a five-year

[19] To determine the most-cited authors, we used HistCite to calculate how often December 2015 EoE Articles by each author had been cited by other articles in the group. We then checked whether the institutions associated with the top 30 authors were CEGIR members. Seven of the top 30 authors were from institutions outside of the United States, which are not eligible for RDCRN funding.

[20] Here, we identified the most influential institutions in EoE research as those institutions as those with the highest GCS based on our December 2015 EoE Articles.

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process. You have shed blood, sweat, and tears for that. It's like your baby and you're going to keep a little bit track of your little baby, I guess." The norm seems to be to make the assessment tools available for free or at low cost to academic researchers, while charging considerably higher fees to commercial companies. The scope of CEGIR's rights to these assessment tools (as a matter of community norms, if not as a legal matter) is a potential source of conflict, particularly if CEGIR seeks to use an assessment tool for clinical trials involving pharmaceutical companies.

16.4.2.2 The International EGID Research Community

CEGIR's members are US institutions. EoE research has international roots, however, and cross-border cooperation may be important for research progress. Europeans authored the first articles documenting EoE. Soon after, the center of gravity for EoE research shifted mostly to the United States, which played an important coordination and catalyst role in the medical community's recognition of the disease. While pioneering EoE research was performed in Europe, acceptance in the United States apparently served as a worldwide credibility signal.

Though Swiss pioneer Straumann has been a part of TIGERS since the beginning, his relationship with the US EGID research community is unique. Straumann's clinic is CEGIR's only "collaborating site" abroad.[21] When asked whether TIGERS was an international group, one of our interviewees explained: "To be honest, Alex [Straumann] was the international group. Now, we're starting to expand out a little bit more from that, but he was the international part." Indeed, Straumann was the only non-US EoE researcher that some of our interviewees could name.

If this US myopia was ever excusable, it certainly is no longer appropriate. An active, high-quality research scene exists outside the United States. About 45 percent of all EoE publications are authored in other countries,[22] some of which have significant EoE research programs. Average citation rates for papers produced in Switzerland, Belgium, and Canada are higher than the average for US papers,[23] and interviewees mentioned important work being done in Spain and Australia. One interviewee suggested that international collaboration may be particularly important for EoE research because differences in diet across the globe could provide interesting avenues of investigation. Moreover, there seem to be fewer pediatric EoE patients in Europe than in the United States. Such cross-country differences may provide important clues to understanding and treating the disease.

[21] www.rarediseasesnetwork.org/cms/cegir/Learn-More/Participating-Clinical-Centers

[22] A total of 1448 of the 2624 (55%) September 2016 EoE Articles were written by US-based authors. Other important countries include Spain (6%), Switzerland (4%), Canada (3%), Australia (3%), Germany (3%), as well as the United Kingdom and Japan (2% each).

[23] The average December 2015 Article from Switzerland, for example, is cited 36.5 times, while the average US publication is only cited 19.6 times. The Swiss result may be largely driven by Alex Straumann's prolific publication record. Other countries with high average citation rates include Canada (21.2) and Belgium (26.2), although the number of papers originating from these countries is smaller.

While CEGIR's leaders recognize the importance of global research cooperation, international research collaborations face distinctive organizational problems. Several interviewees pointed out that funding structures may impede international collaboration. As one interviewee put it:

> I think it would be a good thing to collaborate, I think logistically the way that the funding is developed it's for US centers, and that's the issue here. I don't think that [the smaller amount of international collaboration] is because there are questions about research integrity, or research quality. Logistically, I will tell you, in terms of just conference calls, it's very hard with time zones to get it all organized.

Data sharing across national borders also was reportedly more rare than sharing between US centers.

While funding structures and logistical difficulties may impede transatlantic collaboration, competition with research centers in the United States may incentivize collaboration among European researchers. European single-site studies are typically smaller than those administered by US centers. Cross-site collaboration among European sites is a way to compete more effectively. As one interviewee explained:

> Switzerland is relatively small ... For a long time, that was recognized as a disadvantage because you were never able to have large patient sets to publish. This was really a limitation if you are located at an institution in Switzerland. You never reach the large scale of US size. Of course, you also publish less well, because it's the large patient numbers that give your results more creditability. I think that was one additional motivator to draw all together, basically to also have the possibility to publish better.

The smaller sizes of hospital teams and patient cohorts in smaller countries generally limit specialization. It is much harder for Swiss physicians to dedicate themselves only to the esophagus than it is for physicians at large US academic hospitals. Whether this lack of specialization is an advantage or a disadvantage remains unclear. On the one hand, researchers in smaller countries run the risk of superficiality, given the lack of opportunities for deep specialization. On the other hand, working with patients with a wider spectrum of diseases may produce beneficial research spillovers.

CONCLUSIONS

CEGIR is a new RDCRN consortium that focuses primarily on EoE, an eosinophilic gastrointestinal disease discovered in the early 1990s whose prevalence and incidence have increased substantially since then. In the past, a relatively small, close-knit interdisciplinary community that has tackled the disease with great motivation and enthusiasm and achieved remarkable progress has driven EoE research. As research on EoE advances, the research community grows and the prevalence of EoE increases, CEGIR is attempting to move the EoE community from a loose

network of researchers in which personal connections provide the only social glue necessary for collaboration to a more formal way of collaborating at a larger scale.

Like the UCDC, the CEGIR research community evolved from a consensus recommendation process. The consensus process not only served its intended purpose of standardizing definitions, diagnostic tools, and treatment options but also catalyzed ongoing cooperative activity, in the form of TIGERS. TIGERS, in turn, was instrumental in CEGIR's creation.

CEGIR benefits, as did the other consortia we studied, from the ongoing leadership of pioneers in the field. It differs from the other consortia in the way that it divides leadership between individuals with different strengths. As one interviewee described it, the CEGIR community functions well because of its members' diverse skill sets. Some community members are incredible for their publications and scientific productivity; some can engage well with people and are charismatic; some are doers who make sure that things get done; and some have particularly novel ideas. So far, at least, CEGIR seems to have mostly avoided, or successfully dealt with, the conflicts that one might anticipate from such a divided leadership structure.

Various aspects of CEGIR's governance appear to contribute to community cohesiveness and stability. As with the UCDC, CEGIR's multi-site projects seem likely to serve as an infrastructure for community building. Limiting consortium growth may also help build a cooperative culture among CEGIR members.

While both the EGID research community in general and CEGIR in particular look like success stories so far, they may face various hurdles in the future. First, as the EGID research and patient communities continue to grow, CEGIR may find it increasingly difficult to balance inclusiveness with manageability. Second, as the EGID research community becomes more global, research activities concentrated in the United States will become less and less comprehensive. Third, while intellectual property issues have not been very important so far, they may become more contentious in the future. Indeed, some of our interviewees raised concerns about maintaining ownership interests in assessment tools in the consortium context. Finally, and especially if EoE continues to increase in prevalence, new players – including pharma companies – may enter the field. When more money is on the line, social ties and norms that successfully managed collaborative activity in the historically small community of highly determined, intrinsically motivated researchers may be put under stress. Conversely, if EoE eventually loses its official status as a rare disease, but remains relatively uncommon, pharma company interest in developing EoE treatments may decrease again, as pharma companies would lose the benefits governments grant developers of rare disease drugs (such as smaller patient groups in phase 3 clinical trials, tax incentives, or orphan drug exclusivity). Only time will tell whether and how a transition of EoE into a non-rare disease will impact the EGID research environment.

We close by noting how efficient the RDCRN approach appears to have been in promoting large-scale collaboration, in light of the relatively small size of RDCRC grants, which must be shared among many sites. The RDCRN approach seems to

reduce barriers to cooperation primarily by providing institutional infrastructure that leverages physicians' intrinsic motivations to advance science and treat patients and builds on preexisting community relationships to catalyze large-scale collaboration.

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