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The Rare Diseases Clinical Research Network and the Urea Cycle Disorders Consortium as Nested Knowledge Commons

Katherine J. Strandburg, Brett M. Frischmann, and Can Cui*

I. Introduction

Concerns about the productivity of the pharmaceutical industry, the accessibility of treatment, and the expense of healthcare have led to numerous experiments with “openness” at various stages of research. “Open” approaches are particularly attractive in the rare disease context, given the small numbers and geographical dispersion of potential research subjects and the inapplicability of the “blockbuster drug” business model.

Estimates suggest that there are between 5,000 and 8,000 rare diseases (Field & Boat 2011), where, in the United States, rare diseases have been defined legislatively as diseases affecting fewer than 200,000 individuals.1 In the aggregate, rare diseases affect millions of Americans. Moreover, as scientific understanding of disease advances, it appears that more and more diseases may be “rare” for treatment purposes. For example, while one

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used to speak of a “cure for cancer,” it now seems evident that there will, if we are lucky, be many and various cures for the various forms of the disease, perhaps tailored to the characteristics of individual patients. Moreover, some adverse reactions to trauma and to interventions such as chemotherapy and surgery also appear to be driven by genetic variations similar to those underlying many rare diseases.

These developments make it all the more pressing to find effective approaches to rare disease clinical research. Information sharing, collaboration, and community building among researchers, doctors, and patients are critical to rare disease research. It is very difficult to do clinical research on rare diseases; rareness means small numbers of patients, who usually are dispersed among geographically scattered medical centers. As summarized in a National Academies Report, Rare Diseases and Orphan Products: Accelerating Research and Development:

Because the number of people affected with any particular rare disease is relatively small and the number of rare diseases is so large, a host of challenges complicates the development of safe and effective drugs, biologics, and medical devices to prevent, diagnose, treat, or cure these conditions. These challenges include difficulties in attracting public and private funding for research and development, recruiting sufficient numbers of research participants for clinical studies, appropriately using clinical research designs for small populations, and securing adequate expertise at the government agencies that review rare diseases research applications or authorize the marketing of products for rare conditions.

The Rare Disease Clinical Research Network (RDCRN) is a program of the National Institutes of Health (NIH) which aims to develop infrastructure and methodologies for rare disease clinical research by creating a network of rare disease research consortia. Each RDCRN consortium (RDCRC) creates a collaboration involving researchers, other healthcare professionals, and patients at a group of geographically dispersed clinical sites that focuses on a cluster of at least three related diseases. Essentially, the RDCRN constructs a commons (or, more precisely, a nested set of commons arrangements). The RDCRN also includes a Data Management Coordination Center (DMCC), tasked with developing databases and other information technology for coordinating the research of the consortia.

Knowledge about medical treatment is an inherently nonrivalrous resource, which can be used to treat any number of patients without diminishing its value to the next patient. RDCRCs nonetheless face resource governance challenges, including (1) managing some rivalrous resources, such as research funding, that are necessary inputs to producing knowledge about medical treatments; (2) managing some rivalrous resources, such as authorship credit, that incentivize and reward members’ work; (3) overcoming potential “anticommons”-type problems arising from researchers’ incentives to respond to the scarcity of research subjects by hoarding access to patients and their data; (4) reducing the
transaction costs of cooperation between widely dispersed researchers; and (5) managing interactions with outsiders, such as pharmaceutical companies and the NIH.

There is a tension inherent in all scientific research between the need to apportion scarce resources (such as funding and the time and attention of good researchers) and the value of sharing research results and certain infrastructural data and research tools as broadly as possible. The general mechanisms developed by society and by scientific research communities for managing this tension include public funding, reputation-based systems of peer review and publication for disseminating knowledge and apportioning funding, and scientific norms encouraging what Merton famously described as communism (better described today as openness or sharing), universalism, disinterestedness, and organized skepticism. In the clinical research context, there is further tension between the potential value of the research and potential risks to research subjects, which is addressed by measures such as informed consent regulation, medical profession ethical requirements prioritizing duty to patients, and various institutional review boards (IRBs). These general governance mechanisms form part of the backdrop of the specific resource management strategies of the RDCRN and its associated consortia.

This chapter reports on a case study of the RDCRN’s Urea Cycle Disorders Consortium (UCDC) that employed the knowledge commons framework described in Chapter 1 of this volume. This case study is a step toward understanding whether and in what ways the RDCRN contributes to progress in combating rare diseases. Government funding for research is limited, and it is important to try to understand how various ways of structuring that funding influence the outcomes. Moreover, a government program such as the RDCRN inevitably interacts with preexisting collaborative arrangements, strengthening or undermining them. Observations from close study of the UCDC generate hypotheses about the RDCRN approach that can be tested in comparative studies of other consortia.

The UCDC is considered one of the most successful RDCRN consortia. One important indicator of its success is that it has created and continues to build a relatively large pool of research subjects and patient data through a longitudinal study of urea cycle disorder patients at all fifteen of its clinical sites. The common pool of patient data facilitates both collaborative and individual research projects by consortium researchers. It also reduces the expense and difficulty of clinical treatment trials. The UCDC’s strong relationship with the National Urea Cycle Disorder Foundation (NUCDF), the patient advocacy group for those with urea cycle disorders, has been critical to this effort. The UCDC also appears to have been reasonably successful in pursuing several other important objectives: sustaining and growing a community of researchers with expertise and interest in urea cycle disorders; promoting knowledge and idea sharing within the community; cooperating with patients in framing research and disseminating research results to patients; and translating research into treatments by interacting with pharmaceutical companies.

Our case study suggests that several factors have contributed to the UCDC’s success thus far. Trust in and respect for the consortium leadership appears to facilitate informal
decision making and avoid conflict. Shared goals and norms, arising in part from the fact that the consortium grew out of a long-standing and close-knit group of researchers, serve similar purposes. The study also identifies several aspects of the RDCRN structure that appear to have been particularly important to the UCDC’s successful operation, including the longitudinal study requirement, the mandate for involvement of the patients advocacy group, the requirement of regular monthly teleconferences, and the DMCC’s provision of data aggregation services. Finally, the study identifies several areas on the horizon that may pose challenges to the UCDC’s current approach to governance in light of its heavy dependence on informal interpersonal relationships, including pending leadership transitions, the need to incorporate a growing number of new researchers and clinical sites, and data sharing and intellectual property issues that may arise out of increasing interactions with pharmaceutical companies.

Part II explains the methodology of this case study. Part III briefly sets out the background contexts for the UCDC, focusing primarily on the RDCRN. Part IV describes the UCDC’s goals and objectives and its history. Part V describes the various participants in the UCDC and their roles. Part VI identifies some of the important resources used, generated, and disseminated by the UCDC and touches upon some of the governance challenges they pose. Part VII describes the UCDC’s overall approach to governance and decision making. It also explores how the UCDC handles the governance issues that arise in some specific action arenas. Part VIII concludes by setting forth several hypotheses about factors that may contribute to consortium success, which can be tested in future comparative studies.

II. Methodology

Our overall approach follows the modified version of the Institutional Analysis and Development (IAD) framework described in Chapter 1. Specifically, we:

- **Conducted a literature review.** We reviewed available public documentation about the RDCRN and UCDC, using the knowledge commons framework to structure our observations. Based on what we observed, we identified questions to investigate as we continued our research by interviewing various participants. We later obtained permission to review some documents available on the UCDC’s members-only website, including Publication and Data Use Policies, executed Industry Agreements, and minutes of consortium meetings.

- **Conducted a series of semi-structured interviews.** We interviewed sixteen professionals involved with the UCDC: four NIH officials, including the head of the Office of Rare Diseases Research, the director of extramural research for the Office of Rare Diseases Research, and the science and program officers for the UCDC; the three UCDC consortium principal investigators (CPIs); the UCDC program manager; a principal investigator at one of the UCDC
clinical sites (SPI) in the United States; an SPI in Europe; a former SPI in the United States; a site study coordinator; a neuropsychologist at one of the clinical sites; an attorney at Children’s National Medical Center; the Director of U.S. Commercial Operations for one of the pharmaceutical companies involved with the UCDC; and the executive director of the associated patient advocacy group, the NUCDF. NUCDF is a volunteer organization with activities ranging from education, research, and fundraising to support groups.

The interviews ranged in length from 45 minutes to 120 minutes, with average duration of about 85 minutes. Though interview questions were tailored to each interviewee, we used the modified IAD framework to structure the interviews, keeping them focused on relevant issues. Our analysis procedure focused on organizing information provided by interviewees according to that framework.

- **Attended a UCDC conference as observers.** During the course of our interviews, the UCDC researchers invited us to attend their annual conference in July 2012. We attended a pre-conference dinner, where the UCDC CPI Mark Batshaw introduced us to the attendees. The first day was a scientific research workshop during which, for the most part, we sat in the back of the room as silent observers and took notes. We also spoke informally with various participants about their interactions and experiences with the UCDC. Our aim was to observe the interactions among researchers, their methods of communication and interaction, the social dynamics, and anything else relevant to the UCDC’s stated objectives of facilitating research collaboration.

The second day of the conference was sponsored by the NUCDF for the benefit of urea cycle disorder (UCD) patients. During much of the day, UCDC researchers, as well as one of the NIH officials we interviewed, gave presentations to clinicians, patients, and their families about the state of research and treatment, responded to questions, and engaged with patients and their families informally. Again, we acted mostly as silent observers.

- **Conducted an online survey of UCDC researchers and administrative staff.** The survey was designed to supplement our interviews, both by obtaining additional perspectives and by testing some of our observations. We used the e-mail list from the UCDC website to solicit responses. After eliminating those who were no longer associated with the UCDC or whose roles (such as research assistant or volunteer) limited their familiarity with the issues addressed by the survey, we were left with 95 potential respondents, 56 of whom began the survey. The average number of responses to a question was 51. Somewhat more respondents answered earlier questions, so that the number of responses tapered off to about
45 near the end. Though our sample sizes are quite small, the fact that they represent a large fraction of the entire population gives us some confidence in the accuracy of our results. In analyzing the survey results, we included data from partially completed surveys, since the questions were generally independent of one another. Unless otherwise noted, all percentages reported here were calculated in terms of the number of respondents to the given question.

For the most part, we broke down the responses by role for comparison. We received an excellent response rate from principal investigators and study coordinators. Fifteen out of twenty principal investigators responded, representing ten out of the fifteen research sites to which the survey was sent. Seventeen of twenty-five study coordinators responded, representing fourteen of the fifteen sites to which the survey was sent. The remaining respondents included thirteen other researchers, eight providers of clinical or testing services, and three with other responsibilities. While it is possible that there were selection effects based on the fact that the survey was voluntary, we would expect such effects to be fairly minimal for principal investigator (PIs) and study coordinators, given the very high response rate. The response rate for other categories appears to have been considerably lower, though we were unable to determine with certainty whether non-respondents who were not PIs or study coordinators remained active in the UCDC. Nonetheless, for purposes of this qualitative study, we believe it is useful to consider respondents in all categories in generating hypotheses.

III. The UCDC’s Complex Environment

The UCDC is shaped by a larger context, which includes the biological realities of urea cycle disorders, the cultural contexts of medicine and academic research, and the more specific contexts of rare disease research and NIH research funding. The UCDC also is nested within the RDCRN and constrained by the requirements of the consortium grants. The complexities of the background environment in which these consortia “live” inevitably affect the degree to which and means by which these commons-type approaches can produce the desired result—improved medical treatment.

A. THE BIOLOGICAL CONTEXT: UREA CYCLE DISORDERS

A consortium’s progress in understanding and treating its focal diseases depends unavoidably on the underlying biology of the diseases and on the extent of current scientific understanding. UCDs result from inborn errors of ureagenesis, a metabolic process. Thus far, eight different enzyme deficiencies have been linked to inborn errors of ureagenesis. UCDs range in severity and may be fatal when not detected and treated quickly enough. Symptoms may begin at birth, during childhood, or in adulthood. Ammonia, which is
produced during protein digestion, accumulates to toxic levels in the bodies of individuals with UCDs. While elevated ammonia in the blood is a strong indication of a UCD, definitive diagnosis requires a combination of family history, clinical presentation, and a battery of laboratory tests, which may include amino acid and orotic acid measurements, molecular genetic testing (lab tests), and measuring enzyme (arginase) activity from a liver biopsy specimen or red blood cells. Treatments employ various methods for reducing the amount of ammonia in the blood or attenuating the effect of hyperammonemia, such as special diet, medication to assist in the excretion of ammonia, interventions aimed at reducing the risk of brain damage by hyperammonemia, and, in some cases, infant liver transplant. Research regarding treatment options, diagnostic methods, and diagnosis for newborns and children is ongoing. Gene therapy may be possible, an option which provokes some controversy within the consortium.

B. THE MEDICAL RESEARCH CONTEXT

The medical research context in which the RDCRCs are situated lies at the intersection of at least three background systems of laws, norms, and regulations. First, RDCRCs are situated in the medical environment. They involve patients, physicians, and other caregivers, invoking medical norms and practices guided in part by physicians’ ethical duties toward their individual patients and toward their fellow physicians. Some of our physician interviewees suggested that the norms of the pediatrician community are particularly important to UCDC researchers’ ability to collaborate successfully for the benefit of their patients. The medical environment also involves health insurance and healthcare regulation, including concerns with patient privacy and the costs of treatment.

Second, RDCRCs sit in the academic research environment. The consortia are funded by the NIH and the research mostly is performed at academic medical centers, which are governed by additional regulations and practices, including the requirements of their IRBs, which must approve all human subjects research. Academic research is both cooperative and competitive by nature. Practices regarding when and with whom to share data and results vary among academic disciplines.

Third, because RDCRCs seek to develop drugs and other medical treatments, they interact with the pharmaceutical environment, which includes the commercial sector, with its norms and practices of proprietary control of data and patenting of discoveries, and the regulatory regime of the Food and Drug Administration.

C. THE RARE DISEASE CONTEXT

The rare disease context involves a number of publicly and privately funded projects and organizations. It is importantly shaped by patient advocacy groups, which engage in political advocacy, education of physicians and patients, and research promotion and
funding. Many patient advocacy groups, including the NUCDF, long preexist the NIH’s establishment of the RDCRN.

Within the NIH, rare disease research is coordinated by the Office for Rare Diseases Research (ORDR), but funding comes from many of the NIH’s twenty-five institutes and centers, each of which focuses on a particular field of disease research. Many other NIH initiatives also contribute to rare disease research. According to one of the ORDR officials we interviewed, ORDR recently has calculated that approximately 10 percent of NIH research spending, or about $5 billion, goes toward research on rare diseases, though only about $12 million of that funding is dedicated to clinical research.

D. THE RDCRN CONTEXT

The Rare Disease Act of 2002 mandated the establishment of “Rare Disease Regional Centers of Excellence.”2 The NIH responded to this mandate by creating the RDCRN in 2003. The RDCRN is funded by contributions from relevant NIH institutes and centers, along with direct funding from ORDR. Though there are thousands of rare diseases, funding is limited and RDCRN consortia cover only a small fraction of them. In 2003, ten RDCRCs were funded, along with a Data and Technology Coordinating Center (DTCC).3 In a second round of funding in 2009, the NIH selected nineteen consortia,4 including five of the original ten.5 The DTCC was reconfigured and retitled DMCC at that time. Another round of proposals, peer review, and funding is scheduled for 2014.

1. RDCRN Goals and Objectives

The overarching goal of the RDCRN is to address obstacles that hamper clinical research in the rare disease context as a result of the small numbers and geographic dispersion of rare disease sufferers. The RDCRN thus is designed to promote research collaborations across multiple sites. Interviewee Stephen Groft, head of the NIH ORDR, explained the considerations that went into the design of the RDCRN:

[W]e were facing a lot of perceptions about research on rare diseases. One, it couldn’t be done; two, you couldn’t get enough patients; three, you can’t get researcher interest; and four, if you did, you could not get grants to do research on rare diseases.

2 Rare Diseases Act of 2002, §§2(a)(6), 2(b)(1), 3 and 4. According to one interviewee, “The ideas of funding of creating consortia have been circulated amongst our [UCDC] community for a long time but nothing serious has happened until the RDCRN had been established.”
5 For a list of former RDCRCs, see https://rarediseasesnetwork.epi.usf.edu/about/rdcrn.htm#bmfc.
So, we thought with a little bit of money... we get a critical mass of investigators together under one consortium from different sites around the country. We also want an active role for the patient advocacy group in a patient community because again we felt they were essential to whatever we do. We felt there’s the tremendous need for a training component that we had to train the next group of investigators who got to get ready for it so that was a requirement. And then we had the requirement of natural history studies and we’ve realized that for most rare diseases... we don’t have good information and so [for the consortia we had the] requirement to do natural history studies. [A consortium also gives us] the potential to do clinical studies, clinical trials that if we discover a compound that... industry could contribute money for research studies. We would have the investigators on board. We’d have the patients on board ready to go... [T]o prepare the way to start these clinical trials, we needed to have this infrastructure in place, which we didn’t have back in 2000.

Groft emphasized the importance of involving the entire rare disease community in the research:

[We] call them rare diseases community because it involves everyone. [You] need all the partners working together to effect the best treatment and best care... [T]he group of urea cycle disorder [researchers]... had been able to affect the care even... before there were [pharmaceutical] interventions coming[,]... Even if you don’t have an intervention, just getting that clinical picture, getting the clinicians, getting the nursing staff, the respiratory therapists, the physical therapists, all the partners together, all the specialists, they’ll say, “What is the best thing for the patients with this disease? What’s the best thing for this disease? How can we manage this better?... Why do some patients seem to be doing better? Is there a genetic mutation or genetic difference? [What] is this center or consortium site doing that this site may not be doing and how do we extend the knowledge from here to here to here then out to the entire community?” [Then] that knowledge of how best to treat the patients comes in to place. A lot of these thoughts were running through our minds as we [put] [the RDCRN] together....

These general ideas led to a set of specific objectives:
The purpose of each RDCRC is to facilitate clinical research in rare diseases through support for

- collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies and/or phase I, II and II/III trials;
- training of investigators in clinical research of rare diseases;
- pilot/demonstration projects; and
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- access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the lay public. (Website resource for education and research in rare diseases)\(^6\)

The RDCRN seeks not only to develop treatments for the focal diseases of the funded consortia\(^7\) but also to develop a shared body of knowledge and experience about the problems involved in rare disease clinical research and approaches to solving them. While the NIH thus views the RDCRCs partly as pilot programs exploring the effectiveness of the consortium approach, we did not uncover much evidence of inter-consortium sharing of methodologies and resources, with the exception of the DMCC. One interviewee suggested that perhaps there could and should be more “cross-fertilization” among consortia, but that it might be difficult to pull off without additional NIH support:

To be specific, they could, if they wished to, encourage neural imaging. Because many of these diseases affect brains especially the pediatric diseases. So the NIH could create and could invest in a series of neural imaging facilities that will furnish services at a subsidized cost to registrants or participants in each of these consortia. It could do the same in the world of genetics. It could consider, I don’t know if it will work, creating tissue banks. It could offer expertise in experimental design. But so far it’s not done that. It hasn’t been invested in. Perhaps they think it’s enough to just get Penn and Hopkins and Harvard on the same page.

2. RDCRN Structure

The basic structural components of the RDCRN, illustrated in Figure 5.1, are the individual consortia, the DMCC, a Coalition of Patient Advocacy Groups (CPAG), and various institutions with network-wide governance responsibilities. Grants for RDCRCs provide a maximum of $1.25 million per year over a five-year period and are intended to facilitate collaborative efforts beyond the small-scale collaborations typical of individual research projects. The NIH uses two basic mechanisms to try to ensure that RDCRCs meet NIH goals: mandating certain activities as a condition of funding and structuring the funding so as to ensure cooperation between researchers at different institutions.

The “request for applications” (RFAs) for RDCRC funding required that each consortium’s proposed activities include the following components:

1. Clinical Research Projects for Observational/Longitudinal Studies and/or Clinical trials (At least two projects are required, one of which must be a longitudinal study)


2. Pilot/Demonstration Projects (At least one project is required)
3. Training (career development) Component
4. Website resource for education and research in rare diseases
5. RDCRC Administrative Unit
6. Collaboration with Patient Advocacy Group

The DMCC is an important central infrastructure for the RDCRN. All consortia have access to and are in some respects required to use the DMCC for data collection and management, website management, maintaining a patient registry, and various other functions, including audits of each site’s compliance with data collection protocols. The DMCC has been housed at the University of South Florida since the initial funding round in 2003. The site was chosen via a peer review process similar to that used to select the consortia. We discuss the DMCC’s role in more detail in the section on resources used by the UCDC.

RDCRC grants are implemented by the NIH’s “U54” funding mechanism for Specialized Center-Cooperative Agreements, for which “[t]he spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical

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A key feature of the U mechanism is substantial programmatic interaction between the NIH and the grantee. As one interviewee explained:

Normally you have a single investigator doing an RO1 in a single institution, and there is no relationship to patient advocacy group or to pharmaceutical industry. But this U54 mechanism [collaborative research projects] allows you to do team science in a broader sense. [The NIH Science Officer] is part of the group. She contributes scientifically, and she is our advocate in the NIH, which you don't normally have…. [The] combination of philanthropy, NIH, advocacy groups, and the pharmaceutical industry and then the team scientists and investigators is quite extraordinary for a single NIH grant.

Unlike the standard “R” funding mechanism for individual grants, U funding ensures cooperation between different institutions. As one principal investigator explained:

[T]he advantage of a U is that they will force the different centers to cross-fertilize and cross-collaborate more, which is akin to the example of UCDC. Because what happens now is in [a differently funded consortium] the money goes to core laboratories in each center. What that means is everybody winds up with a genetic center and everybody winds up with a statistics center and it's inefficient. So the NIH insists upon centralization and more cross-fertilization in terms of access to clinical populations….

When asked why a special funding mechanism is needed to facilitate this kind of collaboration, the interviewee continued:

Quite honestly the R [individual NIH grant] mechanism is inherently competitive. It disfavors collaboration because it goes to each center. It says here is a million dollars. Do with it what you want. There is no incentive to share populations or anything. It’s the opposite because we know we are competing with one another for renewal so you want to be the best. There is no incentive to cooperate… [Under the U mechanism], the measure of our success in NIH’s eyes is our ability to realize a collaboration of major medical centers. Without that collaboration we fail.

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Each RDCRC must include at least one patient advocacy group. Currently, there are more than eighty-five patient advocacy groups associated with the RDCRN, which together form the CPAG. The NIH has not specified the extent or type of “collaboration” that individual consortia are to have with patient advocacy groups. ORDR director Groft told us that patient advocacy groups are “the hub of all activities related to rare disease” because “[t]hey touch everybody:” “the patients are so few and scattered many times and you have some group that coordinat[es] that patient aspect. You also need them to bring in the scientific and medical experts and the other medical advisory boards and technical advisory boards.” Groft also noted that patient advocacy groups are crucial “research partners” who contribute, among other things, to understanding and communicating rare disease patients’ “willingness to accept risk” in medical research “because for many diseases, there are no treatments and there’s a very, very low hope of survival over X number of years.”

Groft further expounded on the importance of patient advocacy groups to consortium success:

For the most part, I would say the successful consortia are the ones who have a good working relationship with the patient advocacy group. Their staffs are responsive to the patients and the families. They have a way to answer questions when [they] come[] in. They share information and extend information out to everyone and so I think that’s one of the keys. I mean, there are a lot [of] keys we can click on depending on what we’re talking about but it’s a sharing of information and knowledge so that people—families and patients—know how to respond if a situation develops. As the disease moves forward, they know how to respond if something starts happening. I think it’s part of what we’re trying to do, too: build up that knowledge about the disease and how to treat it so that as the disease progressed, the whole community would know and here’s what we have to do to address this complication that’s occurring.

Another NIH official noted that the relationships between patient advocacy groups and the research communities vary considerably across consortia. We discuss the relationship between the UCDC and the NUCDF below.

The RDCRN is governed by a Steering Committee composed of the CPIs, the principal investigator (PI) of the DMCC, representatives from the NIH’s in-house scientific staff and the ORDR, and the chair of the CPAG. Research protocols for all consortia are overseen by an NIH-established Protocol Review Committee (PRC), which “provides in depth scientific review of protocols developed by the consortia,” and a Data and Safety Monitoring Board (DSMB), which “monitors study protocols, ensures the safety of study participants and the integrity of studies” (Seminara et al. 2010).
IV. UCDC History, Goals, and Objectives

The UCDC is one among many RDCRCs and necessarily shares characteristics with other RDCRN consortia. The UCDC is also a very particular organization, with its own history and community. In this part, we discuss the UCDC’s goals and objectives, which are reflected in its significant action arenas. We then briefly describe the UCDC’s history.

A. UCDC Goals and Objectives

To understand a knowledge commons such as the UCDC, we must understand its goals and objectives. The makeup of a knowledge commons, the resources it creates and employs, and its governance structure all tend to be centered on its goals and objectives. The UCDC’s goals and objectives generate specific action arenas, which in turn generate a need for governance. Meeting UCDC objectives requires cooperative efforts among UCDC members, who may differ as to how best to accomplish those objectives, how to apportion responsibility and credit, and so forth. Moreover, constraints on funding, time, and attention mean that the UCDC must prioritize and make trade-offs between efforts addressed to the various objectives. The determination and updating of goals and objectives is itself an action arena, for which formal or informal decision-making procedures are needed. The group’s goals and objectives also provide metrics for assessing success. The UCDC’s Mission Statement explains that:

The Urea Cycle Disorders Consortium is a group of health care professionals and researchers dedicated to improving the lives of patients with urea cycle disorders. . . . The UCDC strives to provide current and useful information on urea cycle disorders to health care professionals and families. The Consortium is also dedicated to research in clinical and scientific issues in urea cycle disorders. To better understand the nature of these diseases, the Consortium has established a National Registry for patients, and is conducting long-term studies on the outcome of patients with urea cycle disorders. The Consortium also has laboratory researchers working to develop new treatments and new understandings for urea cycle disorders. With better understanding of these diseases, we hope to improve the future for our patients and their families.

Our interviews, survey, and document review all suggest that UCDC members are focused on the substantive goal of treating patients with urea cycle disorders, while meta-questions of how to conduct rare disease research play a decidedly secondary role. Nonetheless, NIH requirements and the specific challenges of rare disease research necessarily influence the UCDC’s approach. As a result, the overarching goal of patient treatment is resolved into five main objectives: (1) creating a pool of research subjects
and patient data; (2) sustaining and growing a community of researchers with expertise and interest in urea cycle disorders; (3) promoting knowledge and idea sharing within the community; (4) cooperating with patients in framing research and disseminating research results to patients; and (5) translating research into treatments by interacting with pharmaceutical companies. We consider each of these objectives in turn.

1. Creating a Pool of Research Subjects and Patient Data

The primary action arena through which the UCDC pursues its goal of creating a pool of research subjects and data is the longitudinal study of patients with urea cycle disorders, which tracks various biological, mental, and behavioral indicators of how the disorders affect patients over time. Longitudinal study data collected at various UCDC sites is pooled using the data management facilities of the DMCC. Data from the longitudinal study may be used in several distinct ways. It may be mined to obtain better understanding of the disorders, to identify and characterize participants for research studies involving further patient testing or intervention, or used to reduce the costs and increase the efficiency of clinical trials of pharmaceuticals or other treatments.

All UCDC sites take part in the longitudinal study, which is the activity that most closely binds UCDC members. Nearly 90 percent of our survey respondents were actively involved in the longitudinal study in some fashion. Though the longitudinal study is required by the NIH, its importance is enthusiastically endorsed by UCDC members. For example, nearly 80 percent of survey respondents agreed or strongly agreed (and none disagreed) that every rare disease research consortium should conduct a longitudinal study, while more than half agreed or strongly agreed that the longitudinal study is the UCDC’s most important project. Indeed, the UCDC’s growth over its ten-year existence seems to have been organized for the most part around adding clinical sites so as to obtain larger numbers of patient participants in the longitudinal study.

2. Sustaining and Growing a Community of Researchers with Expertise and Interest in Urea Cycle Disorders

The rarity of the UCDs means limited funding for research and some degree of isolation for researchers. Even the most involved UCD researchers spend only part of their time studying UCDs and treating UCD patients. UCDC leaders are quite cognizant of the need to sustain the research community as some of the pioneers approach retirement age. Researchers may be drawn to particular research topics by various factors, including the availability of funding, the sense of excitement afforded by participation in cutting-edge research, and the opportunity to work with colleagues in similar situations. The UCDC provides a mechanism for researchers to network and collaborate on projects of mutual interest.

research, the support and mentorship available from a particular research community, and the perception that a particular research area has the potential to lead to a successful and fulfilling career. Long-time UCD researcher interviewees discussed the importance of providing mentoring, training, and pilot funding to new UCD researchers. While pilot funding and research fellowships are most clearly directed toward new UCD researchers, other UCD activities, such as monthly telephone conferences and annual face-to-face meetings, are intended in part to promote a sense of community and inclusiveness among UCDC members.

Sustaining a growing community of UCD researchers presents a variety of challenges, ranging from obtaining and managing additional funding to dealing with the logistics of organizing face-to-face meetings and teleconferences for a growing number of participants to maintaining a collaborative culture within an increasingly large and dispersed community.

3. Promoting Knowledge and Idea Sharing within the Community

Sharing knowledge and ideas internally is one of the most basic reasons to form a research consortium. In the ordinary course, informal knowledge sharing is most likely between researchers at the same institution, between collaborators, and at conferences and workshops that bring researchers together. The challenge for the UCDC is to provide structures and an atmosphere that promotes informal sharing of knowledge and ideas among a group of widely dispersed researchers, study coordinators, and others, only some of whom know each other well.

4. Cooperating with Patients in Setting Research Objectives, and Communicating Research Results to Patients

Several of our interviewees discussed the importance of involving patients as research partners in the consortium’s activities. Several UCDC structures and activities are focused on this objective. Probably most importantly, the executive director of the NUCDF participates in many of the UCDC’s decision-making processes. UCDC researchers also serve on the NUCDF’s advisory board and participate in an annual NUCDF meeting, at which they update patients on research and treatments, answer questions, and socialize informally with patient attendees. Many interviewees also emphasized how their clinical relationships with patients and their families, especially as pediatricians, motivated and shaped their research.

5. Translating Research into Treatments through Interactions with Pharmaceutical Companies

In general, UCDC members are focused on bringing treatments to patients, a goal for which pharmaceutical company interactions are essential. Indeed, interactions with pharmaceutical companies are growing in importance to the UCDC as its research progresses. Involvement with pharmaceutical companies also is mandated implicitly by
the NIH’s inclusion of phase II and phase III clinical trials among the RDCRN’s goals. Cooperation with pharmaceutical companies raises a variety of issues for a consortium such as the UCDC, including issues of intellectual property policy, conflicts of interest, and treatment costs.

B. UCDC History

The UCDC has its roots in a community of collaborators that preexisted the RDCRN’s establishment in 2003. As Mendel Tuchman, one of the three CPIs, described it, “Our cohesive group was formed way before the Rare Diseases Clinical Research Center.” Similarly, when asked whether he has “previously collaborated with other members of the UCDC,” another CPI, Marshall Summar, replied: “Absolutely, since the 1980s. Mendel and others, we [had] been working together for over 10 years. It’s a very collegial community.”

Several current UCDC CPIs and SPIs spearheaded an effort to develop standardized treatment guidelines for UCDs several years before the establishment of the RDCRN. A “consensus conference” held in 2000 resulted in a series of treatment protocols and documents describing what then was the state of the art. Those consensus guidelines, which have been updated in subsequent years, have been very important for treatment of

12 One important incident, though not described by our interviewees as having a direct impact on the UCDC’s governance, occurred during the time the UCDC was being established. In 1999, Dr. Batshaw was associated with a highly publicized tragedy in urea cycle disorder research. Jesse Gelsinger, a UCD patient with ornithine transcarbamylase deficiency, died during a gene transfer trial conducted at the University of Pennsylvania by Batshaw in collaboration with Drs. Steve Raper and James Wilson. The FDA immediately began an investigation. Jesse’s family later filed a lawsuit against those involved. The family’s suit settled almost immediately in 2000. Charges stemming from the government investigations were finally settled in 2005. The most serious sanctions stemmed from conflict of interest allegations against Wilson, who had financial interests in a gene therapy company with connections to the trial. Batshaw and Raper agreed to a three-year period of restrictions on their human subjects research and to various forms of supervision and oversight. The Gelsinger case is discussed regularly in health law and bioethics classes and was one impetus for a series of institutional changes in the regulation of gene transfer trials and of human subjects research more generally during the early 2000s. See, e.g., Johnson et al. 2009: ch. 11; Steinbrook 2008.

None of our interviewees mentioned the Gelsinger case as a significant factor in UCDC structure and governance, except in relation to the UCDC’s reluctance, thus far, to engage in gene therapy research. (Batshaw continues to conduct NIH-funded gene-therapy related research outside of the UCDC framework.) To probe more deeply, after some readers of a draft of this chapter asked about the apparent absence of impact, we conducted follow-up interviews of Mark Batshaw, Marshall Summar, Stephen Groft, and Jennifer Seminara. Seminara’s observations are particularly relevant because her initial interactions with Batshaw were in an oversight capacity during the monitoring period required by the settlement. We did not uncover any significant impact of the Gelsinger case on the structure and governance of the UCDC in particular, which is the focus of this study. In part, this is because the changes in the oversight and conduct of human subjects research that the tragedy inspired have become part of the background environment at the NIH and in the researchers’ universities in which the UCDC operates. It is, of course, possible that there are effects that our interviewees did not share with us or of which they themselves are unaware. Having done only this single case study so far, we cannot comment on how likely it is that our study missed any such effects.
UCDs. The 2000 conference also was an important precursor to the RDCRN. UCDC CPI Marshall Summar explained the connection:

The nucleus of the idea came in 2000. A company acquired a main drug in our field and asked around different centers what they should do. We decided to have those consensus conferences because there was no industry protocol at that time and no one had come up with a consensus protocol. Mendel had this idea and it… was a great success. When the RDCRN came into being three years later, Mark [Batshaw] said that this was obviously the way to put all these groups together. [E]veryone had their own recipe until we got together and pulled all the information together. Some of it was guess work. We wanted to set a baseline. This doesn’t mean that it can’t be modified. The idea “once you get it down in writing you can’t deviate from it” is actually not the way to do it. We got the idea that longitudinal study would be useful. I spoke with someone at NIH and several years later, it worked. We were so far ahead at that point being used to working together that Mark wrote grants. That’s one of the reasons ours was the top scoring grant among the initial grants.

As the informal collaboration of UCDC researchers has become formalized into the UCDC, the original group of researchers has remained deeply involved, as explained by CPI Mark Batshaw:

All the people who were there at the beginning are still there. There is very little turnover over the years. But we have been able to add people. The nice part about that is we now have three generations of investigators. I am the grey-haired in his 60s; Marshall Summar is a less grey-haired in his 50s. And we have junior investigators who are 35–40 to carry this on. So it’s really important.

Since its establishment in 2003, the UCDC has grown substantially. At its inception, the UCDC involved ten investigators at five clinical research institutions. By 2009, it had grown to “43 faculty investigators and 26 research staff members” (Seminara et al. 2010). Today, there are fifteen sites, twelve dispersed throughout the United States, one in Canada, and two in Europe.

One interviewee described this growth:

So as we have started with these five sites that we got a terrific score and we got funded, we started adding soon thereafter other sites because we quickly realized that we have to have a geographic coverage of most of the United States in order to be effective because these diseases are distributed all over the country and patients have a hard time traveling, right? So you don’t expect somebody to come frequently flying from California to for example Tennessee or something like that.
So we wanted to make sure that we have coverage, and the only way to have coverage with respect to having patient access these sites would be to have them in as many places.

The UCDC’s expansion beyond the original five sites has meant the inclusion of researchers who are less focused on UCDs. As Tuchman explained:

[Some of the more recently added sites] have a general interest, not a specific interest. They had patients with these disorders at their location, but they didn’t do primary research in these disorders. But nevertheless, they have agreed [to participate] because of the need of the patients who joined this consortium. And so they have basically collaborated with us on executing the studies that we have.

V. UCDC Community Members and Their Roles

The UCDC includes fifteen dispersed clinical sites. Consortium-wide leadership is provided by three CPIs and a Program Manager. The programmatic NIH involvement central to the U funding mechanism is provided by a science officer and a program officer. The NUCDF and its director are critical participants in the UCDC. The UCDC also interacts with the DMCC and with several pharmaceutical companies.

A. UCDC CONSORTIUM-WIDE LEADERSHIP

The UCDC’s central leadership team, located at Children’s National Medical Center (CNMC) in Washington, D.C., is composed of CPIs Mark Batshaw, Mendel Tuchman, and Marshall Summar, all of whom are physician researchers, and Program Manager Jennifer Seminara, MPH. The CPIs take primary responsibility for the overall scientific direction of the consortium and for grant-writing and fundraising. They also lead and manage the consortium in other ways, discussed in the section on governance below. Program Manager Seminara participates in consortium decision making at a high level and has overall administrative responsibility. She also plays a particularly important role in training and managing the study coordinators at UCDC clinical research sites.

All three CPIs are well-established and well-funded researchers, with significant additional responsibilities at CNMC and long-standing relationships with the NIH. Dr. Batshaw has been the UCDC’s project director since its inception and is its acknowledged leader. He is a pioneer (indeed, “the” pioneer) in urea cycle disorder research. Drs. Tuchman and Summar are part of the core group of researchers who started the UCDC and both were heavily involved in the 2000 UCDC consensus conference. Summar was SPI at the UCDC’s Vanderbilt University site before moving to CNMC.
B. PARTICIPANTS AT UCDC CLINICAL RESEARCH SITES

The UCDC today is composed of fifteen clinical research sites. As explained in Seminara et al. 2010, “each consortium site is led by a principal investigator, who is a board-certified metabolic specialist, with a team consisting of a study coordinator, a neuropsychologist, and at some sites a co-investigator, research fellow, and/or nutritionist.”

1. SPIs

The PI for each UCDC research site has overall responsibility for UCDC research performed at the site and provides scientific direction for the site’s UCDC-related research. All UCDC SPIs are medical doctors and some also have PhDs. According to our survey, about half had performed UCD research before joining the UCDC, while 75 percent had performed research on closely related subjects. In addition, 80 percent of SPIs had treated UCD patients clinically before joining the UCDC. Of about a dozen potential motivations for joining the UCDC, top choices of PI survey respondents were interest in researching UCDs, metabolic disorders, or rare diseases generally and desire to participate in a research community. SPIs are for the most part highly published. Nearly three-quarters of PI survey respondents reported more than fifty publications. Most have published about UCDs, though only 40 percent had more than twenty publications focusing on UCDs, while 20 percent had three or fewer UCD publications. Though all SPI respondents had co-authored with other UCDC members, most reported that only about a quarter of their publications were co-authored with other UCDC members.

Our survey responses reflect the extent to which the UCDC has grown out of preexisting relationships between PIs. All fifteen PI respondents reported some type of prior relationship with another UCDC member, with about half of PIs reporting prior personal friendship and/or collaboration. Nearly all were professionally acquainted with other UCDC members before joining.

2. Site Study Coordinators

Study coordinators at the clinical research sites are critically important to UCDC activities. One UCDC leader went so far as to say that “[t]he key to the success is the site coordinators, not the doctors” and that “[s]tudy coordinators are the guts of this thing, without whom nothing happens.” Study coordinators are centrally involved in recruiting patients and have major responsibilities for patient contact, arranging appointments, following up with patients about participation in the longitudinal study, and so forth. Nearly half of survey respondents agreed that “patient recruitment is primarily the responsibility of site coordinators,” while more than half agreed that “making sure that patients continue participating in the longitudinal study is primarily the responsibility of site coordinators.” Study coordinators also are responsible for ensuring that
data are entered into the DMCC databases correctly, completely, and in accordance with DMCC protocols, obtaining informed consent and otherwise ensuring IRB compliance at their study sites, and handling general administrative duties.

Study coordinators tend to be relatively young, most are female, and their professional backgrounds include genetic counseling, public health, and nursing. About half of site coordinator survey respondents had previous experience in medical research. Less than a third reported any kind of relationship with another UCDC member before joining the UCDC, with few of those reporting anything other than professional acquaintance. While interest in metabolic disorders and in participating in a research community were important to study coordinator decisions to join the UCDC, the top factors selected were “UCDC activities are part of my job responsibilities” and “I was recruited to work on the longitudinal study.” Most, but not all, study coordinators reported few or no publications.

3. Other Researchers and Clinicians

As noted in the quote above, at many sites non-PI researchers and clinicians are involved in UCDC research. Some are PhD scientists, some are MDs, and some have other relevant degrees. Most of the UCDC’s MD researchers specialize in pediatrics and are experts in metabolic disorders generally or in genetics. Some non-PI researchers are graduate students or postdoctoral researchers, while others are more established. Clinicians are involved in various aspects of UCDC activities. For example, testing by neuropsychologists is an important part of the longitudinal study. Because diet is a central aspect of UCD treatment, nutritionists and dieticians are involved. Because UCDs are genetically triggered, genetic counselors also are important members of the healthcare teams at UCDC sites.

C. NIH REPRESENTATIVES

The UCDC interacts closely with two NIH officials, a program officer, and a scientific officer, as required by the U54 grant mechanism. Both work with multiple consortia. The scientific officer is effectively “embedded” in the research community, participating in monthly telephone calls, helping to develop research protocols, and even assisting with grant proposals. One PI interviewee explained:

When I tell you we have a monthly phone conference, there is an NIH person who is on the phone and she is a participant. So there is an ongoing relationship with them. They are part of the project…. [The scientific officer participates] in every sense. In other words, they have the right to voice an opinion. And actually we often solicit their advice. Again, these are people whom we’ve known for a long time. It’s an enabling relationship, not paternalistic or adversarial. They are part of the group.
The program officer’s role focuses mostly on administrative oversight, though it also involves assisting the consortium with its interactions with the NIH. The program officer gives the “official [ ] approval for protocols.” As the UCDC’s program officer explained:

They say they are going to go ahead and do this. This is the plan, but then they have to submit a detailed protocol… that has a description of what they’re going to do, how much blood they’re going to take, or what they’re going to give the patient or whatever, and then they also have to submit the consent forms because to me, that’s really important. It is what they do to the patient or get from the patient or ask the patient or test with the patient, and then how they explain what is the risk, can it be done, and what have they told the patient as an educated lay person, would I be able to understand, and do the patients understand whatever risk there may be to them and are they willing to do that…. [U]sually, I’ll have questions and so it goes back and they respond and until I’m completely comfortable with the fact that they’re not asking too much from the patient. Then I approve it. It gets the NIH watermark and then it goes to the IRBs and their institutions.

The program officer emphasized that in reviewing protocols she considers ethical issues and feels responsible “for making sure the patient’s perspective is taken into account.”

The program officer also assists junior researchers in attempting to obtain individual NIH grants of their own:

I’ve interacted with some of the more junior investigators to look and to discuss with them their grant applications. I see my role as sort of oversight for the consortium, but also a mentor for the more junior investigators…. [S]ome of them will turn to me and I’ll talk to them and help them both with the administrative ways of getting things coming in to the NIH and submitting a grant and those kinds of administrative issues. I will take a look at their grant. If they send it to me, I’ll review it and see if it’s structured correctly. I do this for all. It’s not just for UCDC.

D. THE NUCDF PATIENT ADVOCACY GROUP

The UCDC collaborates with a single patient advocacy group, the NUCDF, which undertakes a wide range of activities, including education, research, fundraising, and organizing support groups. Both the NUCDF and its relationship with many of the UCDC’s PIs predate the RDCRN. Currently seven out of nine members of the NUCDF’s Medical Advisory Board are UCDC PIs. The NUCDF reaches out to patients to inform them about clinical research studies and hosts an annual conference for patients, families, healthcare professionals, and researchers. The NUCDF’s website (which is independent of the UCDC’s public website) summarizes research results for patients and contains information about ongoing UCDC studies and patient registries.
Pharmaceutical company clinical trials also are listed on the NUCDF’s website. Though not performed under UCDC auspices, these trials often are offshoots of research by UCDC members. NUCDF also helps match patients to UCDC sites that will fit their needs. As NUCDF’s executive director, Cynthia Le Mons explained: “It’s almost like a personality match sometimes to make sure [patients] are going to communicate with someone who is [ ] going to be able to help them.”

NUCDF executive director Le Mons is a voting member of the Steering Committee of the UCDC. Primarily through her involvement, NUCDF has a role in a wide range of UCDC activities and decisions, including setting the research agenda, designing the longitudinal study, developing study protocols, and deciding whether to add new clinical sites to the UCDC. As one of the NIH officials explained, “Don’t forget that the patient advocacy groups are on every call, on a monthly call, and their comments are solicited…. Cindy is extremely involved and her point of view is solicited and listened to.”

Interviewees stressed the importance of Cindy Le Mons’s leadership in facilitating effective interactions between the UCDC and the NUCDF. As one researcher explained:

Fortunately for us, by the way, the patient parent group is very well organized. The NUCDF, the credit to that belongs really to Cynthia Le Mons [ ]. She made it her lifetime work to advocate for these children and provide support to these families. She’s been very successful.

The UCDC’s NIH program officer also noted that “leadership personality” is important to the success of a patient advocacy group:

You’ve met Cindy and so you know that she will speak her mind and she will speak for the needs of the patients and the different concerns and issues that they have, and actually she is right on target because if patients complain, they know their illness, what they’re feeling, etc., really, really well. And so if there is enough noise, there must be a reason for it and you listen to it and you begin to examine so that’s why this was just a fantastic idea when it was established. And so the urea cycle has been particularly successful in harnessing the families, the researchers both the M.D. types and also the Ph.D. types, all of your other clinical personnel, and the companies.

Annual joint meetings between the UCDC and NUCDF facilitate relationships between researchers and patients. As one PI explained: “When we do meet, we make an effort to meet in concert with the patient group. So I’ve actually become friendly with families not only in Philly but also in LA…. When we have the Philadelphia meeting, the social part was in my home, not just here at the institution. The association is very gratifying for both sides.”
A site coordinator interviewee noted other ways in which the NUCDF helps to bridge the gap between patients and physicians, while at the same time hinting at some tensions that can arise between researchers and patient advocacy groups:

I talk to [NUCDF executive director] Cindy fairly frequently. If I have a patient whom I am unable to help I reach out to her. I usually give out information to new families, information about our conference. [The patient advocacy group] is good and bad. It’s generally good to have other patients who are going through the same thing. It’s really good for the kids, I think, to meet other kids who are like them. The bad is the discussions that happen regarding medical things amongst themselves instead of talking to doctors, as with any other internet thing, which is going to happen. They have groups and forums and whatever and they talk about “oh you should try this and this.” It would be better for you to call your doctors and nutritionists than asking these other moms who may have a completely different situation or what have you. If you hear those things, I still think going back to the doctors or nutritionists is the right thing to do….I think Cindy generally makes sure that people talk to the doctors. I think it’s hard to put her in such a position that she can help fix everything. But generally she encourages them to go see the doctors and succeeds in doing that.

Finally, at least one interviewee believed that the NUCDF’s involvement had been important to the UCDC’s selection as an RDCRN consortium:

I think the presence of that advocacy group made it a certainty that we would be included as a consortium. Because let’s face it. NIH is sensitive to public pressure. Here you have a very articulate and forceful advocacy group who insisted that their children get a hearing.

E. PHARMACEUTICAL COMPANY REPRESENTATIVES

While pharmaceutical company representatives are not members of the UCDC, they are important enough to UCDC activities to warrant discussion here. It was our expectation going into the study that there would be little interest from pharmaceutical companies in developing treatments for these rare diseases. The UCDC, however, is cooperating with six different pharmaceutical companies working on UCD treatments. When asked about the reason for pharmaceutical company interest in developing treatments for diseases with such a small number of patients, many of our interviewees emphasized the importance of the fact that the UCDC, through its longitudinal study, has data on a large number of potential research subjects, cutting the costs of clinical trials.
These are not “Big Pharma” companies, but smaller companies focusing on rare and orphan diseases. These specialized companies are much more integrated into the rare disease community than would be likely for a large pharmaceutical company focusing on more prevalent diseases. For example, representatives from these companies attended both days of the annual conference and gave presentations at the research workshop. At least some of these specialized pharmaceutical companies have been involved with the UCDC from close to its inception. As one pharmaceutical company representative explained:

I don’t know when we [Orphan Europe] started collaborating with [the UCDC] but it’s probably not from inception but very close. [For the study of UCD drug] Carbaglu…we’ve always collaborated with [the PI] for the development and marketing approvals specifically in the U.S. He has accompanied us for the approval in the U.S. which we actually got approved based on the European data. We want to develop Carbaglu into other indications that are also urea cycle disorders so we’re doing this study together where [the PI] does the study and we provide the study drug and we provide some financing. So we’ve always been present at the consortium meetings. Scientifically, we leave them alone pretty much. I mean of course with this trial because it’s [an] improved [drug], we want to use [the data] for the approval afterwards. There has been some back and forth on the timing of the whole thing on what data you could use when for approval.

VI. Resources Used, Generated, Shared, and Disseminated by the UCDC

The UCDC uses, generates, shares, and disseminates a variety of resources, most of which it must manage in some way. This section describes many of these resources and identifies challenges and social dilemmas involved in their creation, use, sharing, and/or dissemination.13 To organize our discussion we have divided the resources into four categories: (1) resources obtained from outside sources; 2) resources generated by the UCDC primarily for internal use; (3) resources generated by the UCDC for both internal and external use; and (4) resources generated primarily for external use. These categories are somewhat blurry. In part, this is because of the nonrivalrous nature of many of the resources, which means that it is possible to provide external access to them even if

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13 In analyzing the resources generated and used by the UCDC, we began by making as comprehensive a list as possible. We then analyzed the ways in which various resources were used to pursue particular UCDC objectives. We found it helpful to distinguish resources along various axes: (1) level at which the resource is shared (i.e., across medical research generally, across rare disease researchers generally, across the RDCRN generally, within the UCDC, etc.); (2) locus of generation (e.g., outside of the UCDC or within the UCDC); (3) locus of use (e.g., outside of the UCDC, within the UCDC, or both). We then narrowed the list to those discussed here, which our study suggests are most important to UCDC objectives. This preliminary step was critical, as scrutinizing a wider list of resources helped us to move beyond preconceived notions based on more traditional research contexts.
they were generated for internal use. In part, it is because some of the UCDC’s activities require collaboration with outsiders. It is also possible for resources to migrate from one category to another, particularly if external uses grow in importance over time.

A. RESOURCES OBTAINED FROM OUTSIDE THE UCDC

1. Research Funding

The UCDC obtains research funding from the NIH and from private donors. Many of its researchers also have individual grants that support UCD or related research. Importantly, the amount of funding distributed through the RDCRN U54 grants is relatively small—only about $1.25 million per year per consortium. As an interviewee explained, “The RDCRN funding is essential but not sufficient.” Philanthropic funding, much of which comes from a few donors with family members suffering from UCDs, accounts for a proportion of UCDC funding on a par with NIH funding. The NUCDF also raises money for the UCDC. As one of the site PIs explained:

There are families who will raise money for us. By the way that’s not only for UCDs but for many [rare disease research activities]. We must be getting 50–100K a year, very moving, from families who organize bake sales, from marathon racers to help us do our research. I can’t tell you it [ ] compare[s] with the millions of dollars from NIH but it plays a role and does help to support [young researchers especially]. On an emotional level that’s very gratifying…. We meet these people once a year in July…and it’s a very important morale boosting event.

Pharmaceutical companies also “supplement the funding of the government and the philanthropy” in various ways. The relationship with these companies is complicated, as it is in medical research generally, by concerns about conflicts of interest. Therefore, companies do not provide research funding directly to the UCDC. Some of the senior PIs consult with the pharmaceutical companies and, in accordance with conflict of interest policies, fees are returned to the UCDC general coffers. Pharmaceutical companies also support clinical trials stemming from UCDC research by donating the drugs being tested and other support services.

The UCDC deploys its funding in three primary ways, all of which are closely connected to the goals and objectives identified above. First, each research site is allocated funding for its participation in the longitudinal study, which pays for the time of study coordinators, neuropsychologists, and other clinicians involved in the study, among other things. Second, UCDC funding supports certain central consortium functions, such as the project manager, annual meetings, biostatistics support, and so forth. Third, the UCDC funds a few pilot projects intended, as one interviewee explained, to support “new program project development…to specifically enable research by younger
people because younger people with no track record have a lot of trouble getting grants at NIH.” UCDC pilot funding advances the goal of recruiting more researchers into UCD research not only directly but also because researchers hope that UCDC participation will serve as a “springboard for future research funding.” Indeed, that possibility motivated many researchers to join the UCDC. Nearly 60 percent of PIs and about 30 percent of other researchers responding to our survey rated this factor “very important” or “essential” to their decision to join.

Because funding is limited, the UCDC faces challenges in allocating it among sites, researchers, and uses. Funding limitations also drive decisions about whether to add new clinical sites and continue to fund existing ones.

2. DMCC Services

The RDCRN’s DMCC provides a number of resources to the UCDC, including a central repository of study data for the consortium’s geographically dispersed sites; support for data analysis and biostatistics, enforcement; and auditing services for data collection protocols, assistance with the creation and structuring of data collection protocols, training and assistance for study coordinators, assistance with the human subjects research requirements of IRBs, and a patient contact registry.

The DMCC also maintains an online registry of patients who might be interested in participating in research studies. Based on our literature review, we expected that the DMCC Patient Registry would be a very important resource for patient recruitment. However, multiple interviewees told us that the DMCC patient registry has played a rather minor role in patient recruitment. As one interviewee explained to us, “only 14% of our patients actually came through the [DMCC] registry.” On average, survey respondents gave the DMCC patient registry about the same ranking, somewhat below “important,” that they gave to IRB compliance assistance.

Interviewees varied in their conjectures about why the DMCC patient registry had not worked very well for the UCDC thus far. The initial design of the registry relied on notifying patients by e-mail about relevant studies, but did not permit researchers to contact patients directly. According to one interviewee, that approach was premised on an overly restrictive interpretation of the Health Insurance Portability and Accountability Act (HIPAA) privacy regulations. In an attempt to improve its effectiveness, the DMCC’s patient registry procedure was modified to permit patients to give researchers permission to contact them directly about studies.14 However, that option was not endorsed by the NUCDF. At one point, its website stated:

At the end of registration, you may consent to allow a researcher or institutional representative to contact you directly, which may result in outside access by third

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parties to your contact information. NUCDF recommends you do not give consent to release your contact information.15

Currently, the NUCDF website does not mention the DMCC patient registry, referring patients to the UCD International Patient Registry,16 which promises that “[t]he Registry will not release your name to the researcher.”17

The DMCC also performs various other information technology functions. For example, it maintains a members-only web-based e-mail communication platform and document repository and public-facing websites for the RDCRN and for each individual consortium.

B. RESOURCES GENERATED PRIMARILY FOR INTERNAL USE

1. Pool of Research Participants and Data about Them

As already discussed, creating a pool of research participants and data about them is one of the UCDC’s most important overarching objectives. Creating this resource is a cooperative effort involving patients, UCDC researchers, study coordinators and clinicians, and the DMCC. The longitudinal study is the most important part of this effort. It is the primary source of the data in the common pool and is also the main way in which patients become involved in UCDC research. The longitudinal study tracks many indicators—biological, mental, and behavioral—of how the disorders affect patients. As explained by one of the SPIs:

The data includes biochemical markers (ammonia and amino acids and so forth) and it includes demographic information (age, height, weight and so forth), and it includes neuropsychological profile of the child. The funding provides that each kid enrolled undergoes a very detailed series of tests that can take as long as six hours depending on the child’s age. We identify IQ and specific areas of weakness, difficulties in spatial relationships or mathematics. They have emotional problems, anger, hostility and all sorts of things. All of that is resident and deposited in the databank in South Florida.

To generate a pool of research participants and patient data, the UCDC must overcome challenges in three main areas: patient participation, researcher cooperation, and data aggregation and management. The UCDC also must manage internal use of the

pooled data and determine whether and under what circumstances to make the data available to external users (including those in the private sector). Sharing data with outsiders, especially for-profit companies, raises issues of informed consent and patient privacy.

2. Human Capital and Tacit Knowledge

The purpose of attracting additional researchers to the UCDC is to create a growing pool of human capital focused on UCD research. UCDC members contribute and continually generate important human capital, in the form of knowledge about and skills related to many aspects of rare disease research, which includes specialized medical and scientific knowledge, knowledge about and skills in methodologies for dealing with the particular challenges of rare disease research, clinical knowledge and skills, knowledge about and skills in interacting with patients and their families, and so forth. As the UCDC grows and new researchers, site coordinators, and clinicians are brought on board, the UCDC must pass on this knowledge, some of which is, and is likely to remain, tacit. As already discussed, the NIH requires each consortium to have a plan for training young investigators. Researchers are only one part of the picture, however. Site coordinators are critical in obtaining patient participation over time and in ensuring the accuracy and standardization of the UCDC’s pool of patient data. Training study coordinators is a challenge that the NIH framework does not address. The UCDC appears to have recognized the importance of this challenge, however, and recently has appointed one of its experienced site study coordinators to head up study coordinator training.

C. Resources Generated by the UCDC for Both Internal and External Use

1. Knowledge and Ideas about Research, Treatment, Clinical Trials, and Other Related Subjects

Knowledge and ideas are the lifeblood of all scientific and medical research; indeed, generating them essentially defines research. A wide variety of knowledge and ideas generated by UCDC activities are important resources for internal use in ongoing consortium activities. Some of the knowledge and ideas generated by the UCDC also are intended to be disseminated to outsiders, including outside researchers, treating physicians, and patients, in the guise of “research results.” Individual researchers will, of course, share some knowledge informally with colleagues and associates outside of the UCDC. Before being disseminated more widely, research results are reviewed and validated internally and generally are codified and translated into publications, treatment guidelines, research reports, newsletters, and the like intended for particular types of audiences.

Examples of such codified forms of knowledge are scientific publications and treatment guidelines for physicians. The UCDC website lists seven scientific articles stemming from the longitudinal study, thirteen articles coming out of other UCDC protocols, and
an article about the design of the consortium itself. The earliest of these were published in 2008, five years after the consortium’s inception in 2003, evidencing the considerable start-up time required to obtain publishable results. Managing publication of UCDC research results raises issues of authorship and credit, as well as the need to decide when research findings are ready for external release.

As already discussed, the development of consensus treatment guidelines played a very important role in the UCDC’s history. The community continues to develop and refine treatment guidelines that can be used not only by its members in treating their own patients but by physicians who are less familiar with the disorders. A section of the UCDC website specifically aimed at physicians includes information about the diagnosis of UCDs and detailed treatment guidelines. As Mark Batshaw explained:

In terms of education we have a website where we go all out to the peripheries. We talk to neonatologists about all these kinds of things. We standardized care. We held a series of consensus conferences in five-year intervals. We published that and it’s on our website so that everyone can have a standard therapy. They are generally followed. So I can now get the person on our website and walk them through the treatment process, which wasn’t something that was done because people didn’t know who to call. There is the website and the Internet.

Knowledge generated by the UCDC also may be brought to bear on interactions with pharmaceutical companies aimed at developing, validating and gaining regulatory approval for new or improved drugs. Each of these three dissemination contexts brings its own set of challenges for UCDC governance.

D. RESOURCES GENERATED BY THE UCDC (MOSTLY) FOR EXTERNAL USE

1. Educational Materials about Urea Cycle Disorders for Patients and the General Public

The NIH requires each consortium to maintain a website information resource aimed at basic and clinical researchers, academic and practicing physicians, patients, and the lay public. The public-facing websites maintained by the DMCC for each consortium fulfill this requirement. The UCDC website provides information about urea cycle disorder symptoms, diagnosis, and treatment. Much of this information also is available through the NUCDF website. The UCDC and NUCDF websites reinforce and refer to one another. However, the UCDC website does not provide information for patients about support groups, coping, and the experiences of others, which are an important

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focus of the NUCDF’s website and activities. The NUCDF website provides more extensive educational materials than the UCDC website, and it seems likely that the NUCDF’s website plays the more important role in patient education.

2. Diagnostic Tools and Tests

Diagnostic methods for UCDs range from clinical assessments of symptoms to genetic tests. To be useful, a diagnostic test must be developed and validated, based upon basic and clinical research. Developing diagnostic tests is not the whole story, however, since these tests must be made available to physicians outside of the UCDC.

Dissemination of diagnostic methods poses several particular challenges in the rare disease context. Some diagnostic methods can be (and are) disseminated effectively simply by educating physicians, by means such as the UCDC website. According to one interviewee, however, it can be difficult to communicate diagnostic methods to general practice physicians effectively because they do not have experience with rare diseases. Moreover, to use diagnostic information, physicians first have to know both that the disease exists and may be relevant for their patients and where to find information about it, both of which are difficult for rare diseases.

In addition, to disseminate some diagnostic tests, it may not be enough to inform physicians about them. Testing for genetic disorders such as the UCDs often requires specialized laboratory expertise. To make these tests available for patients, then, the UCDC must transfer technology and expertise to commercial laboratories. For example, an interviewee explained that the UCDC developed expertise in gene sequence testing for mutations associated with UCDs and then passed the relevant information on to an industry partner so that it could provide the test commercially. The potential for commercial involvement in providing diagnostic tests raises the question of whether a particular test can, or should, be patented. The UCDC PIs we interviewed had differing views about whether diagnostic methods should be patented and there did not seem to be a consensus policy on the subject.

The dissemination of newborn screening tests involves a further wrinkle. Undiagnosed UCDs can be fatal during the neonatal period. At the urging of the patient advocacy group, the UCDC has worked to develop and validate newborn screening tests for the UCDs. However, outside authorities, including the Department of Health and Human Services (HHS), define the standard suite of newborn screening tests. If screening is to be broadly available, UCD screening must be included in this standard suite. As a result, UCDC also is engaged in advocating that testing for UCD to be included within the HHS standard newborn screening suite.

VII. UCDC Governance

In this part, we explore the ways in which the UCDC governs its various activities. We begin by discussing the UCDC’s general governance structure, which affects the way
that decisions are made in virtually all of the UCDC’s action arenas. We then discuss some specific action arenas related to the UCDC’s primary objectives. We focus in most detail on the governance of the creation and use of the pool of research participants and patient data created by the longitudinal study. This action arena appears to be particularly central to the UCDC’s goals and objectives and structure. It raises a number of important and interesting challenges and dilemmas, and illustrates several different aspects of UCDC governance. We also include brief discussions of UCDC approaches to knowledge sharing within the consortium, interactions with pharmaceutical companies, and interactions with patients in setting research priorities and sharing research results. Notably, overcoming the standard “free rider” problem that dominates discussions of intellectual property policy is only a small piece of the governance picture for this knowledge commons.

A. GENERAL GOVERNANCE STRUCTURE

The UCDC is formally governed by a Steering Committee “composed of the UCDC directors [CPIs], the principal investigator from each site [SPI], the executive director of the National Urea Cycle Disorders Foundation, the NIH scientific and program officers, the DMCC director, the project manager, and the grant manager” (Seminara et al. 2010). Yet our interviewees and survey respondents did not emphasize this formal structure. Instead, they overwhelmingly emphasized more informal aspects of governance and, in particular, the importance of leadership and the collegiality of the community. This is not entirely surprising; while the UCDC is not a purely “grassroots” commons, it grew out of and takes advantage of grassroots relationships between research collaborators, and between researchers and the NUCDF. The UCDC’s governance practice reflects the interplay between these relationships and the structure imposed by the RDCRN.

1. Leadership

The importance of the UCDC’s current leadership to its success was one of the most definitive findings of our study. Virtually every interviewee emphasized the importance of Mark Batshaw’s leadership to the success of the UCDC. Batshaw is highly respected, not only for his pioneering scientific work on UCDs but also for his organizational and people skills. One interviewee, for example, described Batshaw as the “glue that holds everyone together.” Another described him as a “master” of leadership. Still another stated that Batshaw “may be the best administrator I’ve ever known. He is very aggressive, very smart, and very fair, always in possession of himself and never loses his cool.” More abstractly, our survey asked respondents to rank collegiality, funding, leadership, patient advocacy group, relationship with the NIH, and the DMCC in order of importance to UCDC success. Each subgroup of respondents ranked leadership, collegiality, and funding highest, with leadership receiving the largest number of first place votes overall.
In light of this affirmation of the importance of leadership, we attempted to ascertain what aspects of leadership characterized the current UCDC leaders and which of those aspects were deemed important by UCDC members. When asked to choose three words that “best describe the current UCDC leadership,” approximately 75 percent of respondents included the word “dedicated” among their choices, making it by far the most popular choice. There was somewhat less agreement about other characteristics, though “trustworthy” and “determined” were chosen next most often overall. We asked respondents to consider which characteristics they thought would be most important in choosing leaders for a new rare disease consortium. “Dedicated,” selected by more than 80 percent of respondents, topped the list of desired characteristics, while “trustworthy” and “determined” solidified as second and third choices. Respondents put more emphasis on trustworthiness when considering a hypothetical new consortium.

Our interviews also suggested that certain leadership skills, including grant writing, fundraising, scientific insight, communication, organization, and community building, also were important to UCDC success. Our survey asked respondents to rank these skills in order of importance to the success of the UCDC. There was little overall consensus as to the ranking, with different subgroups appearing to emphasize different skills. One possibility is that all of these skills are necessary for a successful UCDC leader.

The UCDC expects to undergo a leadership transition before long, since Mark Batshaw plans to retire (or at least step down from his role as project director for the UCDC) sometime in the next few years. Leadership transitions may be especially difficult for institutions, such as the UCDC, that rely heavily on informal governance and on the skills and personality of a strong leader. Our survey did not inquire specifically about concerns about the impending leadership transition, though two answers to an open-ended question about the UCDC’s growth raised the issue. One respondent expressed the view that “it will depend on the future leadership if [growth of the UCDC] will work,” while the other more bluntly referred to the “leadership transition,” commenting that “there are few Mark Batshaws in the world.”

The UCDC leadership has taken specific steps to prepare for the upcoming transition. At the July 2012 conference, Batshaw announced to the group that Marshall Summar eventually would be succeeding him as project director. Bringing him into the official UCDC leadership as a CPI was part of a plan for leadership succession. As Batshaw explained:

The other thing is you need to have a succession planning. Marshall is my successor planning. When I talked to the NIH I said I wanted Marshall to be a co-PI so that when I run off to the sunset he will be here.

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19 Respondents were given a list of ten positive descriptors and “other” to choose from. Those choosing “other” were given the opportunity to write in some other characteristic. The ten terms were: articulate, confident, decisive, dedicated, determined, friendly, outgoing, trustworthy, perceptive, and persistent. We selected positive descriptors because our interviewees overwhelmingly expressed positive views of the UCDC leadership, and the goal of this question was to determine which leadership characteristics were considered most important.
Though Summar is the most recently appointed, and youngest, CPI, he has considerable experience as a leader of the UCD research community and in research involving genetic and metabolic disorders more generally. He is the Chief of the Division of Genetics and Metabolism at CNMC and plays a major role in the clinical research center at CNMC, working with Clinical and Translational Science Award grants. Before becoming a CPI in 2012, Summar was the SPI at the UCDC’s Vanderbilt University site. As mentioned earlier, he was part of the core group of researchers who participated in the 2000 consensus conference. Though he thus has much in common with the other two CPIs, Summar has what he described as an “unconventional” approach to research funding, with an emphasis on the private sector. He told us that he receives approximately 60 percent of his individual research funding from tech transfer. He is an inventor on a number of patents and patent applications filed since 2000. While all of the PIs we interviewed emphasized the importance of working with the private sector to deliver treatments to patients, Batshaw, Tuchman, and the substantial majority of SPIs obtained and filed for no patents during that period.

2. Collegiality and Inclusiveness

Our interviewees and survey respondents also agreed on the importance of collegiality to the UCDC’s success. The UCDC’s roots in a close-knit community of colleagues are important in understanding its present structure and governance. The PIs we interviewed all had been in this original group and most emphasized the collegiality of the UCDC research community as the first or second (depending on the interviewee) most important factor in the consortium’s success (with leadership generally taken the other slot). Interviewees also emphasized the importance of personal relationships to the UCDC’s success, explaining that they had visited one another’s homes, attended celebrations such as weddings and bar mitzvahs, and so forth. Interviewees also emphasized that shared commitment to the patients brought the group together. Several interviewees suggested that the researchers’ common backgrounds as pediatricians made collaboration more successful (the implication apparently being that pediatricians are more caring and less self-centered than those in other specialties because their patients are children). Interviewees also mentioned the mutual respect between researchers that had developed over a long period of interactions.

It is well known that close-knit communities sometimes can govern themselves effectively through systems of informal norms. The UCDC would not be a success, however, if it had not expanded beyond its original group of five institutions. In light of the priority given to expanding the number of sites and researchers involved and the perceived importance of collegiality to the success of the UCDC, it is important to understand whether, and if so how, the group has maintained the sense of collegiality and community as the number of research sites has expanded. Unfortunately, because our selection of interviewees was made before we realized the importance of understanding how new members are incorporated into the consortium, our interviews were for the most part conducted with core UCDC members. We thus have two primary sources of information about the way
in which the growth in research sites and consortium members has affected the collegiality of the group: interviews with core members about efforts made to incorporate newer members into the group and responses to some of our survey questions.

The original members of the UCDC we interviewed all reported conscious efforts to be inclusive, in part because the research itself demands widespread geographic coverage. For example, when asked whether there are researchers who work on UCDs but are not included in the UCDC, Batshaw indicated that there “are a few, but we have about 90%. If I had more money I would get the other 10%. We wanted to make sure that we cover the entire U.S. The northeast tends to have more academic institutions than do other areas. So there are a few areas that are not covered.” Another PI responded to the same question:

Very few and I think that’s an important point because our psychology has always been to be inclusive. I would actually be curious if that’s typical of all of the consortia. I think for some people there is the tendency when they get the money, make it an old boys’ club. We have avoided that…. From the beginning our goal was to enroll every person in the world in our studies, every patient in the world. So today I think we have 350 people out of probably a few thousands.

Several of the UCDC’s activities (some required by the NIH) provide opportunities for interaction among UCDC members and presumably provide opportunities for newer members to be integrated into the collegial group. The UCDC now holds face-to-face meetings annually, though they were held more often in earlier years. Our observations at the 2012 meeting suggest that the face-to-face meetings facilitate collegiality between consortium members in various ways. We observed a general sense of engagement and community within the group attending the meeting. The NIH program officer also noted her experience of the openness of the UCDC:

I’ve only been part of UCDC for a year. In fact, my first real contact with the UCDC was that meeting in Colorado last year when I was brand new, and this last meeting was amazing because it’s like I’d known them all my life.

We also noted several times when Batshaw took actions that seemed designed to facilitate collegiality and inclusiveness. For example, at a dinner prior to the substantive meeting, Batshaw made a point of going around the room so that each attendee could introduce himself or herself to the group. This same ritual was repeated at the beginning of the research meeting the following day. We also observed him leading several discussions about potential research directions. During those discussions, he sometimes solicited input from particular researchers in what appeared to be an effort to ensure that all views were heard.

Our survey asked how the value of face-to-face meetings had changed with the consortium’s expansion. More than 85 percent of the PIs reported that the value of face-to-face
meetings had increased with consortium growth, though other respondents were most likely to report no change in the value of face-to-face meetings. Unfortunately, our survey did not ask about the absolute value of face-to-face meetings (but only about whether the value had changed), so we cannot assess whether members of these other groups believed that face-to-face meetings were valuable and remained so or were not particularly valuable and remained so. Two of the responses to our open-ended question about what respondents would change about the UCDC did address face-to-face meetings, with one PI simply suggesting “more face to face meetings” and one site coordinator advocating “more opportunity for face-to-face meeting, especially for site coordinators and individuals involved in the research who are not the PIs (young physicians, dieticians, genetic counselors, etc.).” This second response suggests at least some concern about the integration of non-PIs into the UCDC community.

The UCDC holds regular monthly conference calls, which are attended by PIs and study coordinators, along with the NIH science officer and the executive director of the NUCDF. It appears from our interviews and review of the minutes of these calls that the monthly conference call is a very important venue both for scientific discussion and for deliberation about decisions and issues facing the UCDC. It seems likely that these calls also help to integrate newcomers into the group, but we did not address that question directly in our interviews or survey. Certainly, the survey confirmed that UCDC members value the monthly calls. Only about 7 percent of the PIs and 20 percent of study coordinators agreed that “participating in monthly conference calls takes too much time from my other responsibilities.” Given that these individuals are all extremely busy, with many responsibilities, this is a fairly resounding endorsement of the value of the conference calls. While they apparently value the monthly calls, only 43 percent of the PIs agreed that the calls contribute to their research, suggesting that the conference calls are valued for other reasons, perhaps including reinforcing the collegiality of the group.

We also asked survey respondents to assess the effects of consortium growth on the monthly conference calls. Most respondents believed that the value of monthly conference calls had been unaffected by the growth in the number of consortium sites and most were not at all or only slightly concerned that as the UCDC continues to grow, the monthly phone conferences would become less effective.

In the next section, we consider how the emphasis on leadership and collegiality is reflected in UCDC decision making.

3. UCDC Decision Making

While the UCDC formally is governed by a steering committee, our interviews suggested that many (perhaps most) decisions are made by a much more informal process involving discussion among UCDC members, often during the monthly teleconferences, with final decisions made by the CPIs (and especially Mark Batshaw) in consultation with the Program Manager. Interviewees repeatedly described a process of active
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(sometimes even “loud”) discussion of issues followed by general agreement. Several interviewees also noted, however, that if push came to shove Batshaw’s decisions would carry the day because of his “status” as a pioneer in the study of UCDs. Our observations at the UCDC conference also suggested a kind of hybrid approach. Though votes were occasionally taken, it was not evident to us, at least, that voting was limited to steering committee members or to formal members of the UCDC. Voting seemed more like an informal show of hands than a formal process. We did not observe any votes on contentious issues. According to our interviewees, however, this informal approach was taken even on issues that might have been expected to be contentious, such as allocation of funding among sites or even dealing with sites that were not succeeding in recruiting patients to participate.

We also asked a number of survey questions aimed at characterizing UCDC decision making. The responses gave a mixed, and apparently contradictory, picture. On average, respondents were slightly inclined to agree that “most UCDC decisions are made by the leadership” and that “the UCDC is hierarchical.” Yet they also were inclined to agree that “UCDC decisions are based on consensus” and that “UCDC decisions are made by majority vote.” Looking at responses by subgroup or excluding responses from those who selected the option “neither agree nor disagree” did not resolve the apparent contradiction. In light of our interviews and observations, we believe that the most reasonable interpretation is that the survey responses reflect the complexity, variability, and informality of UCDC decision-making processes. One interviewee’s description nicely captured this sense of what one might call hierarchical democratic governance:

It’s all majority type of decisions. Mark then makes the final decision but he makes it based on the discussion…. I can think of several things that we voted the majority was completely wrong but they still adopted it because it is very hard to go against the majority…. And you want them to be dedicated to the mission of the consortium.

One apparent exception to the UCDC’s generally informal approach to decision making is its process for selecting among proposals for pilot funding. That process is somewhat more formalized. As one interviewee explained:

Mark Batshaw is in charge of a committee consisting of other members of the consortium. It will be anonymous. They will render a verdict. They read the proposal. There was a deadline. There will probably be I guess 3–6 proposals. I think two of them will be funded so we are spending 70K a year on two proposals.

We can speculate that this procedure is more formal because it would be undesirable for various reasons for the entire UCDC membership to debate the merits of these proposals,
and yet it is important that members perceive the decisions to be fair. A process of this sort is a means to give legitimacy to the pilot funding awards.

During our interviews, we also asked specifically about conflict resolution, a vital area of group decision making. We were told that although there is no formal conflict resolution procedure or policy for the UCDC, there are occasional conflicts, which are usually resolved amicably after discussion or “negotiation” with the parties involved, in which UCDC leaders play the role of “mediator.” As NUCDF’s Le Mons put it: “[T]hese are people that have worked together for a long, long time and have the mutual respect and are able to work out conflicts reasonably. So there’s nobody going to war.” When we asked one interviewee how conflicts were resolved, we were told about the following example:

A couple of years ago several PIs wanted to add organic acidemia to the diseases covered by the UCDC. The idea was presented at the annual meeting by the PI who felt most strongly about it. There was vigorous discussion and disagreement about whether doing so would dilute resources. The NUCDF representative said that patients would feel betrayed because they had been so supportive of the UCDC, including financially. There was concern about funding and where it would come from. In the end, there was a vote and the consortium decided, by majority, not to add it.

Our survey also gave respondents a chance to indicate their satisfaction with the present UCDC decision-making process. Despite the strong support for describing the UCDC as collegial, there was some dissatisfaction with the inclusiveness of the decision-making process. Thus, 33 percent of respondents agreed that SPIs should have more say in decisions, while only 8 percent disagreed (leaving 59 percent who neither agreed nor disagreed). Similarly, 33 percent agreed that non-PI researchers should have more say in decisions, while only 14 percent disagreed, and 40 percent agreed that site coordinators should have more say in decisions, with only 18 percent disagreeing. Responses to open-ended questions also indicated some concern about the inclusiveness of the decision-making process for those outside of the core group of PIs. One PI, for example, would want “more participation in decision making process at least for site PIs, ideally coordinators would also have a role, neuropsychologists have somewhat of a role.” Several site coordinators indicated a desire for greater involvement in decision making, particularly as related to data collection. One wrote, for example, that “study coordinators are rarely acknowledged, listed to or even allowed to contribute to a variety of decisions that involve data collection or contribution to the UCDC…. There is much disconnect between the site PIs involved in UCDC and the site coordinators.” Another suggested “greater reception and discussion concerning practical suggestions from site coordinators with UCDC investigators and leadership.” One respondent complained that “neuropsychologists were constantly undervalued (e.g. not invited to meetings, not funded adequately).”

In light of these findings, both the upcoming leadership transition and the UCDC’s growth may pose challenges to its informal approach to governance. As one survey
respondent wrote: “[C]onflict resolution is getting sticky because... when we were a small group of 20 people, [we would] literally just stand up and say anything reasonable and talk as a group. Now when there are 55 or 60 people, it’s not conducive to people standing up and saying, ‘Well, I don’t think that or I disagree with that.’ Some will, but I think people are intimidated by that.”

B. Governance of the Pool of Research Participants and Patient Data

Perhaps the most important resource created by the UCDC is the pool of research participants and patient data associated primarily with the longitudinal study. In creating this pool, the UCDC has to manage challenges associated with the need to recruit rare and dispersed patients to participate in the research and the need to overcome barriers to cooperation by researchers at geographically dispersed clinical sites. The UCDC also must have mechanisms for managing use of the pooled data internally and by external researchers, including those from pharmaceutical companies.

1. Patient Participation

In the rare disease context, recruiting study participants is both difficult and crucial to the objective of creating a pool of research subjects and patient data. The UCDC’s public website reflects this reality:

The purpose of this consortium is to provide a way for patients to join with doctors and researchers by participating in research studies. The greater the collaboration between doctors and patients, the more we can learn about Urea Cycle Disorders. This important first step is necessary if we are ever to find newer treatments.

To recruit study participants, UCDC researchers must identify and make contact with a small and scattered patient population. According to our interviewees, patients, rather than their physicians, institute most contacts with the UCDC. Patients most often learn about the UCDC and its studies through the NUCDF. Some patients also find about the UCDC through its own website (and, as discussed above, some come to the UCDC through the DMCC’s patient registry). The UCDC’s clinical sites, which have specialists who treat UCDs and other metabolic disorders, also bring some of their own patients into the studies.

Once identified, patients (or more often, their families) must be convinced that study participation is worthwhile, either because they expect to benefit directly or because they feel a commitment to other UCD patients. They also need to trust that the researchers will conduct the research in as safe and fair a manner as possible. The NUCDF has been critical to the UCDC’s success in recruiting patients to participate in UCDC studies. NUCDF staff makes direct contact with patients to determine their interest in
participating in UCDC research studies. NUCDF’s Le Mons emphasized in our interview with her that the NUCDF’s role is to inform patients, not to persuade them to participate in studies, “to make sure the patients understand the clinical trial, the risks, the benefits if any, and exactly what they’re getting before they jump.” Through its annual meeting of patients and researchers, the NUCDF also helps to forge the necessary trusting and reciprocal relationships between patients and researchers.

Unlike many clinical research studies, UCDC research depends on engaging patients’ participation over long periods of time. UCDs are chronic genetic diseases that run in families. Fortunately, current treatments often make it possible to avoid early fatalities. It is thus both possible and important for particular patients and families to participate in UCDC studies over significant periods of time. Long-term participation provides some direct benefits to patients, in that they are monitored by experts on the disorders, receive neuropsychological testing that may be used to obtain special education benefits, and so forth. Participating in the longitudinal study is time-consuming, however, often requiring travel. Though the tests are not very invasive or risky, which makes patients more likely to want to participate, long bouts of testing can be frustrating and unpleasant for patients and their parents, especially because inattentiveness is a common symptom of UCDs.

The RDCRN’s structure attempts to address the challenges of identifying UCD patients, recruiting them to participate in the longitudinal study, and sustaining their ongoing participation by involving geographically dispersed clinical sites, requiring patient advocacy group participation in the consortium, and providing IT infrastructure for a patient contact registry. In the UCDC’s case, by far the most important of these elements with respect to patient identification and recruitment seems to have been the involvement of the patient advocacy group, with the infrastructure provided by the DMCC playing a relatively minor role. Patients seem to prefer to engage with the UCDC through the NUCDF intermediary, rather than directly, suggesting that patient advocacy groups not only serve as easily findable hubs for information but also are important in establishing research legitimacy and trust.

The availability of dispersed clinical research sites reduces the costs of patient participation in research and thus facilitates sustained patient participation. Beyond that, however, the RDCRN structure does not appear to address the challenge of sustaining patient participation in research. Our interviews and observations suggest that maintaining long-term participation depends importantly on two factors: (1) the follow-up efforts of study coordinators and (2) relationships that patients form with UCDC researchers and study coordinators. Study coordinators are the front line for patient recruitment and follow-up. They are the most frequent point of contact with study participants who see participants every time they come for data collection and testing, phone them to remind them of their appointments, answer their questions, and work with the NUCDF to help them in various ways. UCDC researchers also are clinicians and most, as several interviewees emphasized, are pediatricians. They provide clinical care to some UCD patients.
on a regular, though perhaps infrequent, basis over long periods of time. The UCDC also fosters trusted relationships with researchers by partnering with the NUCDF at annual meetings in which researchers make themselves available to explain the results of their research and interact informally with patients.

It would be interesting to investigate the impact of these factors in more detail to determine whether the RDCRN should consider requiring consortia to participate in joint meetings with patient advocacy groups and whether study coordinators, in particular, should be given some kind of training aimed at making their interactions with patients more useful in sustaining participation.

2. Researcher Cooperation

A second challenge is to motivate researchers to contribute to a common data pool. Barriers to data pooling can arise out of the natural tension between researchers’ recognition that sharing data increase the pace of research and their interests in obtaining credit for their individual efforts. The small number of rare disease patients, along with the scarcity of funding to study any particular rare disease, creates particular incentives for researchers to “hoard” access to patients so that they can publish whatever they can learn from case studies of their own patients. As some of our interviewees noted, the NIH competitive individual grant process plays inadvertently into this dynamic because success depends on having one’s own group of patients to study. Because both funding and access to patients are limited in the rare disease context, competition for individual grants may well result in research concentrated at a few independent sites, with study participants drawn from a few local areas (or brought in from other areas at great expense and inconvenience). This situation is particularly disastrous for rare diseases because clinical research is critically dependent on involving enough patients to support sound statistical analysis. In essence, meaningful studies of rare diseases depend on collaboration between widely dispersed researchers, but, within the standard model of individual competitive grants, the scarcity of research subjects and of funding in the rare disease context erects barriers to cooperation.

The RDCRN’s structure addresses this problem head on by (1) mandating a longitudinal study, (2) monitoring and displaying each site’s progress in recruiting patients to participate in the longitudinal study, (3) providing funding targeted at facilitating the longitudinal study, especially for hiring study coordinators, and (4) providing infrastructure, especially through the DMCC, to make it easier for researchers to contribute to the common data pool.

Based on our study, we believe that there also are several inherent features of the longitudinal study that make it a particularly good foundation for overcoming barriers to

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20 Hoarding may be too strong a word, although we did hear it used once or twice during the interviews. The point is that without a consortium to bring people together, doctors tended to focus on their own patients and not work with others across the country.
researcher participation in creating a common data pool. First, once the protocols for data collection are in place and with the DMCC providing data management services, participating in the longitudinal study is a relatively low-cost way for researchers to become part of the consortium, enabling it to grow beyond a core group of researchers who are highly dedicated to the study of UCDs. Second, the pool of data produced by the longitudinal study can be used not only for consortium-wide research projects but also as a resource for independent research projects, through which researchers can establish individual competence and reputation.

Despite these features, the creation of the pool remains vulnerable to free-rider issues if researchers are permitted to use the pooled data and to be given authorship on consortium-wide publications without regard to their contribution of data. Aspects of the RDCRN structure seem designed to mitigate this problem, however. Most importantly, patient recruitment numbers are available to RDCRN participants on the members-only website. Cumulative and current year totals for each consortium are displayed to all participants, while totals for each clinical site are displayed to UCDC members. The availability of this information means that social norms can be effective in discouraging free riding. Monthly teleconferences involving UCDC members and NIH officials perform many functions, but one result of these frequent group calls may be to strengthen the effectiveness of norms against free riding. The availability of patient recruitment information also makes it possible for a consortium to de-fund a clinical site that is not pulling its weight, if necessary.

As the UCDC collects more and more data about more and more UCDC patients, it also becomes a self-reinforcing focal point for everyone interested in UCD research, including patients, researchers, and pharmaceutical companies, thus potentially creating an “if you can’t beat ‘em, join ‘em” dynamic for researchers.

3. Coordinating Data Collection and Entry

A third major challenge is to coordinate the collection and entry of data from a large number of clinical sites.

Standardizing data collection protocols requires coming to an agreement about what data should be collected and what test should be run. This is a challenging activity, because it requires the UCDC to balance factors including the desire to collect as much data as possible, different researchers’ views about what data is most important, the practical need for protocols that can be implemented by all UCDC sites, and limits on patients’ willingness to submit to a large battery of tests. Input from nearly every participant in the UCDC, including PIs, study coordinators, neuropsychologists, genetic counselors, and other clinicians, as well as from patients is important to getting the balance right. As a study coordinator interviewee explained:

The general idea across the board, the initial goal, not just for neuropsych, is to get as much data as possible, right? If there is a longitudinal natural history study, you
want to get everything. Over time, we adjusted things that we collected, because it
didn’t turn out as feasible or as logical as they thought it would be. So initially the
way they captured family history was totally crazy and clearly they didn’t involve
a genetic counselor in doing it. Right, you have to look at a pedigree where they
are assigning numbers, make a mathematical weight and analyze it. This doesn’t
really work. So it sort of shifted on how things were collected and there are a lot of
examples to that. When you are gathering so much data from so many patients that
over time we realize what works better just from direct experience.

The UCDC’s collegiality and informal democratic/hierarchical governance apply to the
making of protocol changes, such as this one. While participants seem generally satisfied
with the informal decision-making system, designing the longitudinal study protocol
may be the kind of decision for which complaints about lack of voice for study coordina-
tors and neuropsychologists have some force.

Besides establishing a standard study protocol to be used at all sites, challenges asso-
ciated with coordinating data collection and entry have to do with creating a shared
database with an interface that facilitates data entry and later data use and ensuring that
data is entered in a timely and accurate fashion. The RDCRN deals with these issues
by centralizing data management in the DMCC, thereby providing a central source
of database expertise and relieving individual consortia of many of the costs of data
management. There was widespread agreement among our survey respondents about
the importance of the DMCC’s role in “managing the central data repository,” with
thirty-four out of forty-five rating it as “very important” or “essential.” The DMCC
activity next most highly valued by survey respondents was “data analysis and statis-
tics support.” DMCC auditing and enforcement of research protocols, assistance
in protocol design, and site coordinator training and assistance also were considered
“important” on average. DMCC assistance with IRB compliance was ranked somewhat
below “important” on average, with some interviewees suggesting that IRB compliance
would be more effectively addressed by the establishment of a cross-institutional IRB
for RDCRN projects, so as to cut down on the time and expense of obtaining approvals
from multiple clinical sites.

We speculate that “outsourcing” certain enforcement tasks, such as auditing the clini-
cal sites’ compliance with study protocols and posting patient recruitment numbers
online, to the DMCC may have possibly unappreciated benefits in reducing conflict and
maintaining collegiality among consortium members.

4. Managing Internal Use of the Data

If researchers are permitted to use the data pool for individual research projects (which is
one of its major purposes), there is the potential for conflicts of two sorts. First, there may
be disagreements over data use, especially if more than one researcher wants to pursue a
similar project. Second, there may be disagreements over publication and authorship of publications reporting research based on the data pool. The UCDC has formal written policies dealing with each of these issues.

The UCDC’s Data Use Policy stipulates that all UCDC researchers have access to the data (stripped of identifying information, such as name, address, phone number) generated by the longitudinal study. However, data-mining studies must be approved by the CPIs “to ensure that there is not redundancy or overlap in concurrent analysis.” According to one CPI, “a request for data mining is expected to be accompanied by a reasonable research idea or proposal approved by the PIs, the request has to be approved by the steering committee, and relevant data needs to be extracted out of the DMCC database before it can be shared with others for mining.” Other uses of longitudinal study data do not require CPI approval. Consortium members wishing to use data generated by other UCDC research projects, such as the pilot projects, are to “work closely” with the PIs of those projects to “define roles for analysis and drafting a publication (or other use).” Informal norms appear to be important in implementing these policies. As the Program Manager explained, there is a concept of joint ownership of consortium data, but, nonetheless, researchers would not use data generated by projects at other sites if the researchers who collected the data objected.

Our survey asked about respondents’ familiarity with the UCDC data sharing policy. All PIs, about half of study coordinators, and smaller fractions of other respondents reported familiarity with the policy. About 70 percent of PIs reported that it was important to them to have input into the data sharing policy.

Publications are the primary means by which researchers gain reputation, which is the “coin of the realm” in scientific research. Thus, authorship credit is very important to researchers. A consortium in which a large number of members contribute to the collection and analysis of a pool of data also effectively creates a “pool” of authorship credit, which must be allocated among consortium members. The UCDC’s Publication Policy “addresses the coordination, development, and communications related to the orderly and timely release of information generated by the UCDC.” It “defines authorship roles and responsibilities—including communications and notifications among co-authors, other investigators, the consortium Principal Investigator, and relevant NIH science and project officers.” It provides that “[m] ajor publications resulting from the Longitudinal Study will include all UCDC Site PIs, UCDC leadership, project director (Jennifer Seminara), co-PIs [at certain sites] and [certain] former PIs [].” Major publications are defined to include “publications describing the Longitudinal Study or reporting on the overall results of the specific aims of the study.” Study coordinators are to be acknowledged by name. Authorship of individual analyses of longitudinal study data is to include those (including study coordinators where appropriate) who have “significantly contributed to the analysis and publication,” as defined in the policy. The author list for such individual analyses also must include “Members of the UCDC,” who are to be listed in a footnote. The publication policy defines the “first author” as
the researcher who takes primary responsibility for the project and gives the first author responsibility for determining the timeline of publication. The policy also provides for internal quality review of all UCDC manuscripts by UCDC leadership before publication and sets out various other requirements for acknowledgments and compliance with NIH policies.

All PI survey respondents expressed familiarity with the publication policy, while only about half of site coordinators and even fewer non-PI researchers and clinicians were familiar with the policy. Nearly all PIs reported that it was important to them to have input into the publication policy. Moreover, all PI respondents agreed that authorship of UCDC research was assigned fairly. Most respondents from other subgroups neither agreed nor disagreed with that statement, though a small number of site coordinators and clinicians disagreed.

The written data sharing and publication policies appear to be important for managing the use and publication of the UCDC’s data pool. But they do not appear to be deployed for conflict resolution in any formal way. Our interviewees emphasized that conflicts, including conflicts about data sharing, generally are resolved informally as described in the section on UCDC general governance. Interviewees also emphasized that researchers’ commitment to advancing knowledge about the disorders and helping patients tended to ward off conflict. As one of our interviewees explained:

> People in the consortium are collaborative and they have that in mind: yes everybody wants to be the first author on a publication, and things like that; but they are also thinking about the impact of the publication. It’s not just about being a lead on something. It’s about the impact of the work. It’s important not just for your own career advancement but for the impact. There are so many more pluses to collaborate.

The same interviewee also explained how belonging to the UCDC mitigated concerns about being “scooped” by competing researchers:

> There is an advantage to being in a large consortium. If you combine everybody, instead of having 100 subjects, you will have thousands of subjects and that’s going to make a much higher impact than a bunch of individual smaller papers.

5. Managing External Use of the Data

The NIH requires that, after a specified period of time (generally five years), data obtained by its funded projects be contributed to a data repository that is available to the scientific community. Over and above complying with this policy, the UCDC sometimes makes data available to particular outsiders, including pharmaceutical companies, in response to specific data requests. Data collected by the longitudinal study has been
critically important in interesting pharmaceutical companies in pursuing treatments for UCDs. As CPI Batshaw explained:

The last partner is really the pharmaceutical companies. We are involved with six pharmaceutical companies. Three of them were actually involved in, for a long period of time, very intensive ways. The fact that we have six pharmaceutical companies in a disease that occurs 1 on 30,000 is quite remarkable. And the reason this happened is because we provide to them 600 patients that represent the entire population. They are in Europe as well as in the U.S. They are all being treated in exactly the same way so that their clinical pathway is the same. And for natural history you have to pull a number of years, the cognitive function, biomarkers…. So the cost for them to do clinical studies is about 1/10 of what it would have been if they had to do this on their own. And it worked wonderfully.

Thus, sharing data with pharmaceutical companies is central to the UCDC’s objective of developing improved treatments for patients. While patients also welcome pharmaceutical company interest in developing treatments, however, they also are concerned about data sharing with pharmaceutical companies for privacy reasons and because of the extremely high cost of many treatments that are developed using patient data.

According to the UCDC Data Use Policy, all external uses of UCDC data must be approved by UCDC leadership. Moreover, “[t]o ensure that the confidentiality and privacy of study participants are protected, all external investigators seeking access to data from UCDC studies must execute and submit an appropriate standard data use agreement prior to obtaining UCDC data.” Unless research subjects have consented explicitly to the use of data that does not meet HIPAA’s definition of de-identified data, only de-identified data is made available to external investigators. Academic researchers may obtain access to UCDC data by collaborating with a UCDC member or by obtaining approval from UCDC leadership. Commercial users are given access only through specific service agreements, which set out a “scope of work” to be performed by the UCDC and deal with fees to be paid by the user, ownership of intellectual property, confidentiality, and so forth.

Though the Data Use Policy addresses the form of data sharing agreements with external parties, it has little to say about the standards for deciding whether to allow data to be shared. Nor does it address how issues of data ownership and intellectual property are to be handled in agreements with external data users, stating only (and rather opaquely) that “[e]ach site owns the data collected at their own site. The Urea Cycle Disorders Consortium owns the complete set of data collected at all sites (collective ownership).” The policy thus apparently leaves such questions to be resolved by UCDC leaders when they negotiate data use agreements. Despite its formal data use policy, UCDC’s approach to decision making about external use of data thus appears consistent with its general approach to decision making, which is strongly dependent on members’ respect
for UCDC leadership (and in particular, for Mark Batshaw) and on informal discussion and debate.

Up to this point, there appear to have been few conflicts within the consortium about the interactions with pharmaceutical companies. Our interviews suggest that this lack of conflict is due to a combination of factors: (1) relationships with pharmaceutical companies are handled according to general conflict of interest policies for medical research, which have become stricter in recent years, (2) the pharmaceutical companies involved so far are specialized companies, with which consortium researchers have interacted for many years, and (3) UCDC researchers are very pleased to have succeeded in attracting pharmaceutical company interest in developing drugs for these rare conditions. As UCDC research progresses toward the development of more treatments, however, issues of data sharing with pharmaceutical companies may become more pressing.

C. SHARING KNOWLEDGE AND IDEAS WITHIN THE UCDC

As far as we were able to ascertain, most UCDC members are intrinsically motivated to share their knowledge and ideas with other consortium members because they enjoy collaborating and see the benefits of the exchange for their research and for UCD patients. One interviewee described the core group of researchers, who had sought to work collaboratively even before the RDCRN was established as “just the type of people that were collaborative and wanted to work together and were committed and they were interested in science and they were also compassionate about patients.” As another interviewee put it: “[t]he whole reason people are in the consortium is because they are willing to collaborate.” Both interviewees and survey respondents agreed that the UCDC has succeeded in improving the exchange of knowledge between researchers. For example, in answering a question about how the UCDC affected his “day to day research or interaction with the other collaborators or researchers in the urea cycle disorders,” one interviewee explained:

The first thing I see is a great exchange of ideas. You see, I have a laboratory research portfolio, quite a good one, I think. I have like 12 people in the lab and have several NIH grants. But you know, the ideas that we exchange are mainly between us. Here, we have a consortium and any time we have some kind of an idea, we vet it out, among everybody, suddenly you get all kind[s] of perspectives. So exchange of ideas and new ideas is something that is clearly facilitated.

Along similar lines, another interviewee explained:

We meet often. We discuss treatments. Some issues puzzling patients, we talk about those. We have a couple of groups embedded in NIH. Peter McGuire, a fellow we trained, is now in NIH....A good case in point is the curiosity a few years back about vaccine safety in UCDs. I talked to other people in the group and wanted
to get vaccine records. We pulled 1,200 vaccine records and examined whether the patients fell sick after vaccination and it turned out they didn’t. The vaccines were actually quite safe. That’s a case where we were sitting down and just talking about some idea, asking for opinions and others thought it was a good idea.

More than 85 percent of survey respondents “agreed” or “strongly agreed” that without the UCDC UCD researchers “would have shared ideas less often” and “would have done less data sharing.” A similar fraction “agreed” or “strongly agreed” that “the UCDC has increased collaboration among urea cycle disorder researchers.” An equally large number of survey respondents “agreed” or “strongly agreed” that “without the UCDC, geographical dispersion would have been a much greater barrier to collaboration,” confirming that the UCDC has been effective in addressing this particular obstacle to rare disease research.

Interestingly, our interviewees suggested that the structure provided by the consortium, such as the regular monthly teleconferences and annual meetings was important in facilitating knowledge sharing, despite the fact that many, if not all, UCDC researchers are inherently motivated to share. Thus, for example, one interviewee told us that “[s]imply having the grant with leadership provides cohesion to the effort and people feel invested and responsible.” We speculate that a regular structure for communication, such as the required monthly conference calls, may be particularly important to promoting knowledge sharing in circumstances in which participants are separated geographically and have many responsibilities clamoring for their time and attention. In this respect, the consortium structure seems to serve as a mechanism for coordination and commitment, rather than as a mechanism for overcoming a collective action problem of the prisoner’s dilemma variety.

D. MANAGING INTERACTIONS WITH PHARMACEUTICAL COMPANIES

There are many facets to the UCDC’s interactions with pharmaceutical companies. We discussed some of the issues related to data access in Section A, above. Here, we briefly consider the issues raised by more direct involvement between UCDC researchers and pharmaceutical companies. Currently, for example, UCDC researchers are involved (though not always directly under UCDC auspices) with a UCDC-sponsored surveillance study of patients who are being treated with Orphan Europe drug, Carbaglu; with clinical trials of HPN-100, a drug produced by Hyperion Therapeutics, which drastically improves the palatability of treatment for certain UCDs; and with studies of a human liver cell infusion treatment sponsored by Cytonet GmbH & Co. KG; and with studies of additional UCD indications for Carbaglu.

As already discussed, the development of new drug treatments is an important goal of the UCDC’s research. When research results suggest new or improved treatments, UCDC researchers often interact with pharmaceutical companies as they develop and
test the drugs. UCDC researchers are also likely, because of their expertise in UCDs, to be involved with the development and testing of pharmaceutical treatments that do not initially stem from UCDC research. As already mentioned, perhaps the primary way in which the UCDC influences the interaction with pharmaceutical companies in the rare disease context is by creating a pool of data about potential research subjects that dramatically reduces the cost of recruiting and characterizing patients for clinical trials.

As interactions with pharmaceutical companies increase, there are likely to be more issues for the UCDC to address. While institutional conflict of interest policies address general concerns raised by interactions between researchers and pharmaceutical companies, they cannot address conflicts that arise out of differences of opinion between UCDC members about issues such as choice of appropriate pharmaceutical company partners, terms of data sharing and intellectual property agreements and so forth.

Patients may also want input on these issues. For example, in our interview, NUCDF’s Le Mons emphasized the importance of transparency in collaborations between pharmaceutical companies, the UCDC, and the patient advocacy group, describing a successful collaboration in which information learned in clinical trials was shared with researchers and led to advances in scientific understanding of the disorders.

Some of our interviewees suggested that the UCDC may need to develop policies for dealing with intellectual property issues that are likely to arise in interactions with pharmaceutical companies. At present, the UCDC does not have an intellectual property policy and there appears to be some significant disagreement about the issues among PIs. For example, researchers (both PI and non-PI) and study coordinators all were evenly split as to whether the decision to apply for a patent “should be up to the individual researcher” and close to evenly split as to whether “patents based on UCDC research should be jointly owned by all UCDC participating institutions.” While a majority of PIs agreed that licensing policy for such patents “is the business of that patent’s inventors and their institutions,” nearly 30 percent of PIs disagreed. Nearly all PIs agreed, however, that licensing policy should be established by the UCDC Steering Committee and that it was important to them to have input into the UCDC’s intellectual property policy.

E. INTERACTING WITH PATIENTS TO SET RESEARCH PRIORITIES AND SHARE RESEARCH RESULTS

Interactions with patients serve many important purposes for the UCDC. We already discussed the issue of recruiting participants for UCDC studies in Section A, above. Here, we consider interactions between patients and researchers that involve the setting of research priorities and the communication of research results.

As already mentioned, one of the goals of the RDCRN is to treat patients as “research partners.” Our study suggests that the UCDC has been relatively successful in that regard. NUCDF executive director Le Mons appears to take an active part in discussions of proposed research directions and protocol design. A CPI confirmed the importance
of NUCDF input: “Cindy is part of our steering committee so her input is critical. If we want to do something and she doesn’t think it’s a good idea, we listen very carefully because she knows…. She has her finger on the pulse of the patient. So she knows what the patients are interested in.” Le Mons herself emphasized the collegial relationship she has with UCDC researchers and especially with CPI Batshaw. As she explained: “I can pick up the phone any time and talk to Mark [Batshaw] and I have.”

At the annual meeting we attended, NUCDF’s Le Mons participated both in the NUCDF-sponsored gathering for patients and researchers and in the more technical research workshop that preceded it. NUCDF was acknowledged along with various researchers in many of the researchers’ PowerPoint presentations. One interviewee described a specific situation in which the NUCDF helped the UCDC identify patient needs and adjust research priorities:

[T]his U54 mechanism [collaborative research projects] …really allows you to do team science in a broader sense…. Cindy Le Mons has been extremely helpful, and not only helpful; she’s told us what’s important to parents. And she lets us know if we are not doing certain things. So for example, the grant did not tell us to do newborn screening, to develop screening for UCDs. We hadn’t focused on that; we really focused on natural history and developing therapies. The advocacy group’s point was: many of these kids were not diagnosed in the newborn period, and so they are dying without being diagnosed, without any treatment. And these parents keep having additional patients, additional children who were dying without diagnosis. And so newborn screening has to be part of this, even though you are not funded to do it; you gotta do it. And she was absolutely right. So that really impacted, changed the directions, and added to what we were going to do.

In communicating research findings to patients, the UCDC faces two main challenges: the difficulty of translating research results into terms that patients will understand and incentivizing the investment of time, energy, and other resources necessary to translate and disseminate research findings to patients. UCDC researchers’ concern for patient welfare, particularly as pediatricians, undoubtedly motivates them to invest time and effort in these activities, as do the longstanding relationships between UCDC researchers and the NUCDF’s director. Translating research results for rare disease patients may also be made easier by the fact that many patients and their families have invested heavily in self-education about the diseases and are extremely well informed.

The NUCDF plays an important role in ensuring that patients gain timely access to research results by reporting research results on its website, newsletter, and e-mail updates to patients. The NUCDF annual conference, which we attended in 2012, provides an important bridge between the research community and UCD patients and families. Researchers devote a day to presenting research findings to patients and their families who attend. As one interviewee explained: “[t]o her credit, Cindy Le Mons has been
extremely proactive in making sure when families get together every year in their meeting that scientists are there to sit down and answer questions and tell the families about what their studies have done.” Le Mons explained that the annual meetings can also play an important role in getting patients’ local physicians “into the fold.” Just as the consortium structures, and thereby encourages, communication between UCDC researchers, the NUCDF’s activities appear to structure, and thereby encourage, communication of research findings to patients.

VIII. Conclusion

The UCDC is considered one of the most successful consortia in the RDCRN, and we have largely taken that as a given here. From what we can tell at this stage, having performed only this single case study, the UCDC is effective, at least in so far as it has been successful in meeting many of its own self-professed goals, as well as those set by the NIH. Though we do not have independent metrics for assessing UCDC outcomes, the NIH peer review process in 2009 gave the UCDC its highest score. Because this is our first RDCRC case study, we cannot reliably identify the characteristics responsible for the UCDC’s success, nor can we entirely disentangle characteristics resulting from the structure imposed by the RDCRN from characteristics stemming from the UCDC’s particular community. Nonetheless, we believe that our study of the UCDC allows us to identify characteristics that seem to have contributed to the UCDC’s success and to posit hypotheses that such characteristics that may be important for consortium success more generally. We hope to expand our study to several more rare disease research consortia to allow us to perform systematic comparison and analysis. Our interviews thus far suggest that existing rare disease research consortia vary considerably along many dimensions, including their success.

To begin at a rather general level, our study suggests that the following have been important for UCDC success and may be important to the success of other consortia: strong CPI leadership, strong program manager leadership, a close-knit core researcher group coupled with inclusiveness/openness to new members, and a strong patient advocacy group with a good working relationship with the consortium leadership. Strong PI leadership in the UCDC seems to involve the following important characteristics: dedication, collegiality, trustworthiness, fundraising capability, respected decision-making capability, scientific credentials, and sincere interest in serving patients. While formal governance was not important in most respects, the UCDC’s publication policy and internal data sharing policies served to clarify and set consortium norms. Involving the patient advocacy group with the research community seemed to have several benefits, including better understanding of patient needs, more successful patient recruitment for research studies, and strengthening of researcher motivations to collaborate because of shared concern for patient welfare. We hypothesize that cooperation is more likely to
succeed when (1) the patient advocacy group is an empowered member of the consortium; (2) patient advocacy group participation is visible to other community members; and (3) the patient advocacy group is itself successful and has strong leadership. Along the same lines, we note that most UCDC researchers are pediatricians and most of the patients are children and hypothesize that collaborative research may be more likely to succeed when this is the case.

Certain aspects of the RDCRN’s structure also seemed to have been particularly important to the UCDC’s success. The longitudinal study formed a backbone for developing a shared data pool, developing collaborative practices, and facilitating consortium growth. Monthly teleconferences appeared to be extremely important both for scientific communication and for implementing the consortium’s informal governance approach. The DMCC’s data management activities provided important infrastructure for the creation of a shared pool of data, and its auditing and enforcement activities may have alleviated a potential source of conflict between consortium members.

Finally, the study identified several areas on the horizon that may pose challenges to the UCDC’s current approach to governance and decision making, with its heavy dependence on leadership style and informal, though hierarchical, decision making. As various interviewees noted, the UCDC will undergo a leadership transition in the next few years and such transitions can be difficult. Continued growth in the number of sites and community members may increase transaction and management costs and put additional pressure on the consortium’s informal governance mechanisms. Other loci for potential stress include pursuing research on gene therapy and various interactions with pharmaceutical companies.

Our list of potentially important contributors to the UCDC’s success is rather long and many of them may seem evident in hindsight. Nonetheless, the list is not quite what we anticipated after a reasonably extensive review of the UCDC website, RDCRN documentation, and other publicly accessible documents. We had anticipated, for example, that factors such as a formal conflict resolution policy or procedure, a history of involvement by all SPIs in UCD research, the DMCC patient contact registry, and the UCDC’s public-facing website would be much more important for the UCDC’s success than our detailed case study showed them to be. The difference confirms our view that structured and detailed case studies are needed to understand knowledge commons.

In our view, the modified IAD framework was an extremely useful tool for identifying and studying the governance issues faced by the UCDC and its approaches to managing them. Though RDCRN consortia aim to produce nonrivalrous knowledge, the study demonstrated that they have a variety of related goals and objectives. These goals and objectives produce action arenas involving the generating, sharing, and managing of many different types of resources—rivalrous and nonrivalrous, tangible and intangible. These action arenas involve a variety of social dilemmas, which governance systems must resolve. A superficial focus on knowledge sharing runs the risk of missing important facts on the ground that shape success or failure. The study also provided us with many ideas...
about how the modified IAD framework might be further adapted to better fit these research commons. For example, we found that the inquiry into goals and objectives is more foundational here than it might often be in the natural resources context because, to a significant extent, goals and objectives precede, generate, and organize both resources and community and define important action arenas.

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