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THE RARE DISEASES CLINICAL RESEARCH NETWORK AS A NESTED CULTURAL COMMONS

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ABSTRACT: 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. One issue of particular concern is the difficulty in applying the current "blockbuster drug" model to rare diseases and conditions. The Rare Diseases Clinical Research Network ("RDCRN") is an attempt by the United States government to overcome some of these difficulties and to foster a collaborative approach to rare disease clinical research and treatment development, essentially by constructing a commons. The basic idea behind the RDCRN is to construct a network of research consortia, with the dual aims of improving understanding of the disorders, improving diagnostics, and developing better treatments for the particular disorders represented by the funded consortia and developing infrastructure and clinical research methodology that may be used more broadly in studying rare diseases. This project will apply the constructed cultural commons framework to study the RDCRN and related patient advocacy groups. In this preliminary report, we begin by focusing on the structure of the RDCRN itself and on two consortia that have been part of the RDCRN since the beginning in 2003 – the Urea Cycle Disorders Consortium (UCDC) and Angelman, Rett & Prader-Willi Syndromes Consortium (ARPWSC). To date, we have conducted a literature review, using the cultural commons framework to structure our observations, which we present below. Based on what we have observed thus far, we have begun to identify potential hypotheses and questions to investigate as we continue our research into these initial cases by interviewing various participants.

NOTE TO READERS: This is a very early work-in-progress and we welcome your comments, suggestions, and critiques. We also apologize for the paucity of references in this draft.

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. One issue of particular concern is the difficulty in applying the current "blockbuster drug" model to rare diseases and conditions.

In the United States, rare diseases have been defined, legislatively, as diseases affecting fewer than 200,000 individuals. While "rare" when viewed individually, the cumulative impact of rare diseases is substantial. Various estimates suggest that there are between 5,000 and 8,000 rare diseases. In the aggregate, rare diseases affect millions of Americans. Moreover, as scientific understanding of disease advances, it appears that more and more diseases will be "rare" for some purposes. For example, while one 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 personal characteristics of individual patients. This situation makes inquiry into how to coordinate rare disease research all the more pressing.

Constructed commons is one form of coordination that is promising and worthy of systematic investigation. Information sharing, collaboration, and community building are (or at least, appear to be) critical to rare disease research. Most importantly, it is very difficult to do scientific research with very few research subjects; rareness means small numbers and that poses complications for researchers.[1] It is difficult to develop appropriate research protocols, attract funding, train researchers, and communicate and translate research findings into clinical practices, among other things. As summarized in a recent 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 Diseases Clinical Research Network ("RDCRN") is an attempt by the United States government to overcome some of these difficulties and to foster a collaborative approach to rare disease clinical research and treatment development, essentially by

1 A few additional definitional notes: First, consistent with the Orphan Drug Act, we use disease, condition, and disorder interchangeably. Second, it is worth noting that rareness can be defined in absolute terms, as done in the United States (<200,000 threshold), or it can be specified in terms of a prevalence rate (# of affected individuals / 100,000), as done in Europe. Third, rareness can be evaluated by genotype (# of people who have a genetic mutation) or phenotype (number of people who have clinically evident disease based on tests and symptoms).

constructing a commons. The RDCRN was established pursuant to the Rare Disease Act of 2002, which provided statutory grounding for the NIH Office of Rare Diseases and mandated the establishment of "Rare Disease Regional Centers of Excellence." RDCRN is funded by the National Institutes of Health ("NIH") and administered by the Office of Rare Diseases Research. The basic idea behind the RDCRN is to construct a network of research consortia, with the dual aims of improving understanding of the disorders, improving diagnostics, and developing better treatments for the particular disorders represented by the funded consortia and developing infrastructure and clinical research methodology that may be used more broadly in studying rare diseases. Each member consortium, structured according to NIH directions, creates a network of geographically distributed research sites and aims to facilitate collaboration among researchers, health care professionals, patients, and other interested parties. Increasing collaboration among researchers, doctors, and patients and fostering patient participation in research studies are (or at least, appear to be) critical to rare disease clinical research.

In 2003, the NIH, after reviewing proposals, funded ten consortia, each focused on a different cluster of at least three related diseases, and a central Data and Technology Coordinating Center (DTCC), tasked with developing computational means for coordinating rare diseases research. Another group of consortia was chosen for funding in 2009. At this time, the DTCC was re-configured and re-titled a Data Management Coordination Center (DMCC), with somewhat different responsibilities. There are currently a total of 19 consortia in the RDCRN. Of these, five of the original ten have received continued funding, fourteen new consortia have been funded, and five consortia no longer are part of the network.[2] Each consortium involves a number of research or clinical centers. NIH funds consortia for a five-year period, subject to renewal, with a maximum of $1.25 million per year.

This project will apply an Ostrom IAD framework, as modified by Madison, Frischmann, and Strandburg for commons arrangements in the cultural environment, to study (i) the RDCRN, (ii) consortia nested within the RDCRN, (iii) patient advocacy groups, which appear to be partially nested within consortia while at the same time maintaining independent existence outside the RDCRN/consortium environment, and (iv) various other groups participating in rare diseases research outside of the RDCRN, whether on one of the diseases included in the RDCRN or one of the thousands of diseases that the RDCRN does not address. Within the rare disease research environment there are many nested commons at different scales that interact with each other and with the external environment in very complex ways. The long term goal of the project is to understand whether and in what ways the RDCRN affects the larger social endeavor of combatting 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 funding approach such as this one, which aims to produce commons and collaboration, inevitably interacts with pre-existing collaborative arrangements, strengthening or undermining them. A cultural commons approach to studying the rare disease research environment will provide a window into these interactions.

In this preliminary report, we begin by focusing on the structure of the RDCRN itself

[2] https://rarediseasesnetwork.epi.usf.edu/about/rdcrn1.htm#bmfc

and on two consortia that have been part of the RDCRN since the beginning in 2003 – the Urea Cycle Disorders Consortium (UCDC) and Angelman, Rett & Prader-Willi Syndromes Consortium (ARPWSC). To date, we have conducted a literature review, used the cultural commons framework to structure our observations, which we present below. Based on what we have observed thus far, we have begun to identify potential hypotheses and questions to investigate as we continue our research into these initial cases by interviewing various participants.

II. The Background Contexts for the RDCRN and Member Consortia

The Rare Disease Research Network and its individual consortium constituents are not "grassroots" commons. They operate within many constraints dictated by their government origins, in addition to the context of biology, law, and social norms that affect any attempt to find treatments for rare diseases. They do, however, take advantage of certain grassroots relationships, such as those between research collaborators (which, though determined to some degree by grant funding are largely determined by researchers' common interests and approaches), between patients and families coping with the same disease, and between physicians and their patients, seeking to funnel those relationships in particular directions. One eventual goal of our case study approach is to investigate how the interactions between the NIH's imposed structure and goals and pre-existing relationships and tension have played out on the ground.

A. The Rare Disease Context

The most evident background contexts for these consortia are the diseases they are designed to attack. Unlike some types of "cultural commons," which seem limited in their activities primarily by the bounds of human creativity and cooperation, these consortia are in some sense like the natural environment commons for which the IAD framework was originally developed: they are severely constrained by physical and biological reality. Thus, the success of any particular consortium may be strongly dependent on the extent to which current scientific understanding permits progress to be made. Some approaches to the diseases themselves or to their clinical study simply will not work, however well they are governed or deployed.

1. Angelman, Rett & Prader-Willi Syndromes

Angelman Syndrome and Prader-Willi Syndrome each occurs in about one of every 10,000-15,0000 live births, while Rett Syndrome occurs at about the same frequency, but only among females.[3] Angelman and Prader-Willi syndromes are for the most part genetically based disorders, which have different symptoms, but are in most cases related to defects in the same chromosomal region. Angelman syndrome results primarily from the deletion of a maternally derived chromosomal segment, while Prader-Willi syndrome results primarily from the deletion of the same chromosomal segment inherited from the father. The situation in which the genetic contribution of one parents is dominant is known as "genomic imprinting." Study of these diseases is motivated in part by research suggesting that genomic imprinting of the same chromosomal segment plays a role in autism. The relationship between these syndromes and the genetic defects is complex and not yet understood. While most patients have observable genetic abnormalities, a sizable fraction

[3] http://main.uab.edu/Sites/uabmagazine-spring2008/articles/45167/

do not. Rett Syndrome is a rare disorder which involves autism-like symptoms. The genetic origins of Rett syndrome are under investigation. The three syndromes have somewhat overlapping symptoms, complicating diagnosis, which is always problematic for such rare disorders.[4]

2. Urea Cycle Disorders

Urea cycle disorders result from a group of rare inborn errors of metabolism due to accumulation of ammonia, a toxic product of protein metabolism. Because of enzyme deficiency, individuals with urea cycle disorders cannot metabolize the ammonia that accumulates in their body as a product of protein digestion. There are currently eight enzyme deficiencies that have been identified as linked to inborn errors of ureagenesis. Many of the UCDs produce similar symptoms because they affect the body in the same way. The symptoms may begin at birth, during childhood, or in adulthood (milder deficiencies).

Elevated ammonia in the blood is a strong indication of the presence of a UCD. Amino acid analysis can be used to diagnose a specific urea cycle disorder. The level of the amino acid arginine is ordinarily low in all urea cycle disorders, except arginase deficiency, in which it is elevated. A definitive diagnosis of enzyme deficiency requires a combination of family history, clinical presentation, and a battery of laboratory tests, including amino acid and orotic acid measurements, molecular genetic testing (lab tests), and measuring enzyme activity from a liver biopsy specimen or red blood cells (arginase). Research into improved diagnosis, and in particular, earlier diagnosis for newborns and children, is ongoing.

Treatment involves various methods for reducing the amount of ammonia in the blood. Diet, medication to assist in the excretion of ammonia, and treatments aimed at reducing the risk of brain damage are typical. Research into treatment options is ongoing.[5]

B. The Broader Cultural Context

The RDCRN consortia lie at the intersection of at least four systems of laws, norms, and regulations. First, all of these consortia necessarily involve the norms and practices of the medical environment, involving patients, physicians, and other care-givers. The norms of this environment are guided by physicians' ethical duties toward their individual patients and toward their fellow physicians. It also involves commitments of patients to one another through patient advocacy organizations. Patient advocacy groups have played an important role, particularly with respect to some rare diseases, in advocacy, education of physicians and patients, and promotion and funding of research. The medical environment also involves the context of health insurance and healthcare regulation, and, importantly, serious concerns with patient privacy. Many of the consortia are located at non-profit hospitals or medical centers, which are governed by a complex set of regulations and practices. Second, these consortia involve the norms and practices of academic research. The consortia are funded by the National Institutes of Health and the researchers involved are located at academic medical centers. Academic research is both cooperative and competitive by nature and various scientific disciplines have different practices regarding when and with whom to share data and results. Third, because these consortia seek to develop drugs and other medical treatments, they must interact with the commercial pharmaceutical industry, with its norms

[4] http://rarediseasesnetwork.epi.usf.edu/arpwsc/learnmore/index.htm#as
[5] http://rarediseasesnetwork.epi.usf.edu/ucdc/learnmore/index.htm

and practices of proprietary control of data and patenting of discoveries. Finally, the consortia deal with clinical research and thus must adapt to the regulatory regime of the Food and Drug Administration. In other words, the background environment in which these consortia "live" is extremely complex. These complexities inevitably constrain the degree to which and means by which "open" and "collaborative" approaches can succeed in producing the socially desirable result of improved medical treatment.

C. The National Institutes of Health Context

The RDCRN is a project of the National Institutes of Health, which funds a complex structure of initiatives related to rare diseases. Within the office of the directorate of NIH is the Office for Rare Diseases Research, which coordinates NIH efforts in this area. The NIH is comprised of more than 25 institutes and centers, each focusing on a particular field of disease research. Funding for the RDCRN comes from both the Office of Rare Disease and the individual institutes and centers. The institutes and centers also support rare disease research with grants to individual investigators. Many other NIH initiatives, such as the Human Biospecimen Database, the National Rare Disease Biospecimen Resource, the Office of Technology Transfer, the National Center for Research Resources (particularly its Division for Clinical Research Resources, which provides funding for research in clinical and translational science, a network of general clinical research centers, and support for clinical research informatics networks) contribute to rare disease research and to the work of the RDCRN.

D. The RDCRN Context

The RDCRN sits within a nested structure. Above the RDCRN sits the NIH, which selects and funds participating consortia and a Data Management Coordinating Center (DMCC) (renamed and moderately repurposed in 2009 from the Data and Technology Coordinating Center (DMCC)), which is intended to promote coordination and collaboration between consortia using information technology. Consortia were selected for funding based on research proposals responsive to an NIH "request for applications" (RFA).[6] The selection of consortia was based on a two-step process, beginning with peer review according to specific criteria, which include scientific merit and the capacity for coordinating the consortium's multidisciplinary efforts, followed by review by a "special emphasis panel" organized specifically for the RDCRN project.[7] The DMCC was funded in a similar manner. The DMCC is housed at the University of South Florida and has been since the initial funding round in 2003.[8]

Consortia must meet certain criteria in order to be funded. Each consortium must deal with at least three rare diseases. In addition:

An RDCRC must include the following:

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)

[6] 2003 RFA, 2008 RFA
[7] Pre-App meeting PowerPoint Slides
[8] See http://rarediseasesnetwork.epi.usf.edu/about/dmcc.htm

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 and

7. A description of Overall Clinical Research Program, Leadership & Resources[9]

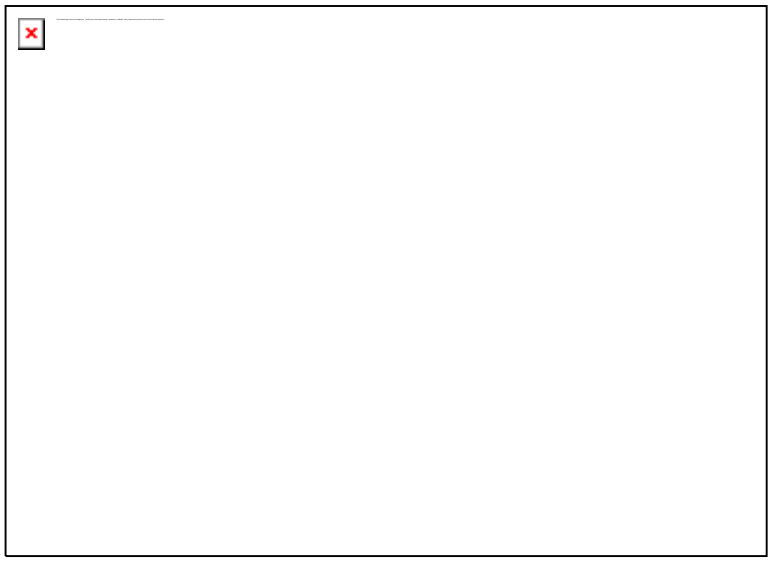
While these requirements impart a certain degree of homogeneity, each consortium was proposed by a principal investigator and a group of collaborators, presumably based at least to some degree on pre-existing research collaborations. Moreover, each consortium is nested within a pre-existing context for its particular disease cluster, which includes patient advocacy groups, with their particular histories and activities, other researchers worldwide who are not officially included in the consortium, and a particular degree of scientific understanding and existing capacity for treatment and patient care for its focus diseases.

The RDCRN consortia interact with one another in a variety of ways. All consortia have access to (and indeed are in some respects required to use) the DMCC for data collection and management, website management, maintaining a patient registry, and other functions. The Patient Advocacy Groups associated with each consortium join together in the Coalition of Patient Advocacy Groups (CPAG). Finally, the RDCRN is overseen by a Steering Committee composed of the Principal Investigators for the individual consortia and the DMCC, representatives from NIHs in-house scientific staff and the Office of Rare Diseases, and the chair of the Coalition of Patient Advocacy Groups (CPAG).

The nested structure of the RDCRN and its place within the broader NIH setting complicates our description of the basic characteristics of the commons because there is some overlap among communities, and resources and institutional features may be shared at different "levels" within the nested structure. Consider the following Figure, which appeared in Seminara et al. (2010)[10]:

[9] Taken from PowerPoint Slides presented to potential applicants in connection with the 2008 RFA. http://rarediseases.info.nih.gov/ASP/resources/extr_res_archived.asp

[10] Mol Genet Metab. 2010; 100(Suppl 1): S97–S105. Published online 2010 February 10. doi: 10.1016/j.ymgme.2010.01.0



This figure illustrates the network of relationships in which a given consortium (in this case the UCDC) is embedded. Here, NUCDF is the patient advocacy group for urea cycle disorders, PRC is an "NIH-led Protocol Review Committee [], which provides in depth scientific review of protocols developed by the consortia," and DSMB is "the Data and Safety Monitoring Board [], which monitors study protocols, ensures the safety of study participants and the integrity of studies."[11] ORD is the NIH Office of Rare Diseases, NCRR is the NIH National Center for Research Resources, and NICHD, NIAMS, NHLBI, NIDDK, and NINDS are particular NIH institutes relevant to urea cycle disorders. The figure would be essentially the same for other consortia, with appropriate substitutions for consortium name, patient advocacy group, and the particular NIH institutes involved.

While the Seminara et al figure usefully displays the networked relations among various actors/communities from the perspective of a particular consortium, it obscures hierarchy and the broader overlapping contexts within which the UCDC is situated. To assist in organizing our observations, it is helpful to identify four different levels within the nested commons structure: (1) NIH; (2) RDCRN; (3) individual consortia; (4) (i) individual research sites, (ii) patient advocacy groups, and (iii) professional health care communities. At the fourth level, we identify three different communities that interact with patients on the ground, interact with each other, and interact with and participate in the higher-level commons. As we will discuss, these levels overlap and interact in various ways.

Level 1 (L1) Interactions across the health system generally. For present purposes, this level is represented by the NIH.

Level 2 (L2) Interactions across rare diseases. At this level are the RDCRN, the CPAG, the DMCC, and, potentially, other fora for interaction across diseases, such as the National Organization for Rare Diseases (NORD), which was recognized in the Rare Disease Act of 2002 for its role in advocating for persons with rare diseases.

Level 3 (L3) Interactions involving a particular rare disease (or cohort of diseases). At this level are individual consortia, such as UCDC and ARPWSC, patient advocacy groups,

[11] Seminara.

and, potentially, other organizations of physicians or researchers focused on particular diseases.

Level 4 (L4) Interactions between sub-groups involved with a particular diseases. At this level are research sites, collaborations between individual researchers working on a particular disease, interactions between patients and their physicians, and so forth.

II. *Basic Characteristics of the Constructed Cultural Commons*

In this preliminary report, we focus on the RDCRN and two specific consortia: the Urea Cycle Disorders Consortium and the Angelman, Rett, and Prader-Willi Syndromes Consortium. Both of these consortia were funded during the initial round in 2003 and renewed during the 2009 funding cycle. The RDCRN and member consortia describe themselves as a research network and research consortia, respectively. These designations suggest that the relevant resources are research inputs and outputs and that the relevant community is comprised of researchers. In applying the framework, however, we take a broader view, looking for *any* intellectual-cultural-information resources and *any* community members (people or organizations) that appeared to be potentially relevant.[12] As we will discuss below, the broader inquiry highlights the important role of patients and patient advocacy groups as providers of resources as well as beneficiaries and users of research results. We have also included in this list of resources, where there was potential overlap with the work of the RDCRN and its consortia, some resources that are available from patient advocacy groups, independently of their role in the RDCRN. At least for the UCDC and APWRSC, the associated patient advocacy groups are well-established and very important actors in rare disease research and education.

A. Resources

The RDCRN and member consortia involve the generation and sharing of many different types of intellectual and related resources. Here we attempt to categorize and describe the resources based on our literature review and to characterize them according to the level at which they are shared or generated. It is likely, however, that the literature review method biases our description toward particular types of resources, which are relevant to the public presentation of the RDCRN. We anticipate that interviews will clarify these descriptions and may identify other important resources. It is also important to note that the fact that a particular resource is categorized as shared at a particular level does not mean that it is shared *openly* at that level. Funding, for example, is shared at the level of a particular disease or cohort of diseases, but is available only to researchers who are members of a consortium. Similarly, the DMCC and its resources are shared across diseases, but appear to be available only to researchers who are members of RDCRN consortia.

1. Resources at L1: Shared Across the Health System

At this level, there are many resources provided by the background environments of open science, physician norms and practices, hospitals and medical centers, and so forth. We do not discuss these resources in detail, but acknowledge their importance. The general structure of the NIH also provides norms and practices shared by medical researchers, which are reflected, for example in the DSMB and PRC. The NIH also provides the funding for the consortia, but, except as used to develop the DMCC or to support Steering Committee meetings or network-wide meetings and conferences, the funding is not a shared resource since it is assigned to particular consortia.

2. Resources at L2: Shared Across Rare Diseases.

[12] Not only do we think this is the most appropriate approach with our framework, but we believe a myopic focus on the research processes is too narrow and likely to lead to a rather shallow understanding of the interactions among different members of the community.

At this level, the DMCC plays an important role as a provider of information technology-based resources to RDCRN members. In particular, the DMCC provides the following types of shared resources:

Patient Registry. A major resource developed by and shared between consortia is the *Patient Registry*, which is managed by the DMCC. It is an online registry for patients, which collects name, address, date of birth, place of birth, email, and various medical data regarding disorders. The data are stored in a secure database, and personally identifiable information is not shared without informed consent. In fact, the data in the registry are not shared with investigators or researchers; rather, the DMCC uses the data to identify potential participants and to send those individuals information about studies and research protocols, including eligibility, study descriptions, open sites, and contact information. Thus, the DMCC serves as an intermediary connecting these two groups within the community (researchers and patients). The DMCC communications are automated, standardized, and data-driven. The DMCC provides periodic communications between researchers and patients, including updates on new studies, research findings, new protocols, and a bi-annual "Consortium Update."

Informatics protocols, standards and data management practices — The DMCC is the centralized data and technology coordinating center for the rare disease research consortia; among other things, it is tasked with managing "integration of various kinds of data—genetic, microarray, clinical, laboratory, and imaging;" "develop[ing] common data elements, data standards, and data structures;" and "data sharing and federated databases at distributed sites."

Secure web-based platforms for data collection—The DMCC has created an online platform with standardized Case Report Forms; it enables coding, data gathering, and search.

Communications platform – The DMCC maintains a platform for email communications within the network and a password-protected website for accessing network resources.

Besides the information technology resources which are the focus of the DMCC, the RDCRN, through its Steering Committee, and through conferences and research meetings,[13] is intended to foster the development of a shared body of knowledge and experience about the particular problems involved in clinical research on rare diseases and approaches to solving them.

Research protocols—research methods and protocols tailored to the acute problems of rare disease research. While specific research protocols must be tailored to individual research projects, one of the goals of the RDCRN is to develop approaches to clinical research that are appropriate for small patient cohorts.

3. Resources at L3: Shared At the Level of a Particular Disease

Most of the resources we have identified so far are shared at this level, rather than across diseases, though some are shared under the auspices of the DMCC, using its protocols, standards, and platforms. At this level, we can loosely distinguish (1) resources which are generated by others and used by the consortia, (2) resources created and used by the consortia (and perhaps by others), and (3) resources created by the consortia for use by others. As noted below, there is unavoidable overlap between these categories.

[13] See, e.g., 2009 Meeting, "Advancing Rare Diseases Research Through Networks and Collaboration"

Resources generated elsewhere and used by the consortia:

Research funding – As discussed, the NIH provides funding to particular consortia, which is shared by researchers within the consortium. It is also worth noting that, at least in the two cases we investigated, patient advocacy groups also provide significant research funding, though we do not yet know whether they fund the same researchers who are members of RDCRN consortia.

Research Subject Registries—e.g., pools of potential research subjects; administrative registries ("used to identify patients with particular conditions, usually for later epidemiological study"); genetic registries ("identify individuals with a given mutation or profile"); lists of affected individuals who express an interest in participating in clinical studies or trials. Because there are so few individuals affected by any given rare diseases, patients are a critical resource/input for research. Besides the Patient Registry maintained by the DMCC, the patient advocacy groups associated with both the UCDC and APWRSC consortia diseases also maintain patient registries. (This categorization is somewhat over-simplified since the consortia do play an important role, through their websites, in recruiting patients to participate in the DMCC *Patient Registry*.)

Research participants—patients play various roles with respect to RDCRN, but it is evident (for example, from perusing consortium websites) that one of their most important roles is as research participants. In this role, they function as resources for the research, and therefore we list them here. Clearly, there may be tensions between patients' and their family's roles as patients, as advocates, and as research subjects, which should be explored in our further study.

Research Methodology, including Tacit Knowledge (R9)—Because of their rarity, it can be difficult to recruit and training new researchers. The NIH requires that each consortium have a plan for training young investigators. Of course, some knowledge about research methodology will be generated by the consortia as they pursue their studies, but to a large degree researchers bring this resource with them into the consortium and the focus is on passing it along to new researchers

Resources generated by the consortia for use by consortium researchers:

Data and biological materials relevant to or produced by ongoing clinical research studies—e.g., patient-specific data; raw depersonalized data; tissue, cell, and DNA banks; population-based disease registries ("disease-related data (either from self-report or from medical records after patient consent) that is later used for data mining").[14] One of the purposes of an RDCRN consortium is to conduct clinical studies across geographically separated sites and over time. This approach is necessitated by the rarity of the diseases. To do this, data and perhaps even biological materials must be shared, but so must standards for collecting, storing, and analyzing data and materials. RDCRN consortia share data at least in part by using the DMCC and are they are required to use the DMCC's data standards. Moreover, each consortium must support a major longitudinal study that collects various patient-specific data, medical histories, blood samples, and dietary information.

[14] Richesson et al., at 56.

Information to support the design of future clinical trials—The Office of Rare Diseases asked applicants for funding to "approach a longitudinal study with the question: What knowledge/tools are needed regarding the rare disease in order to design efficient efficacy trials for this rare disease?"

Information about the results of completed clinical studies—e.g., research findings, suggestions for future research. This information can be relevant to researchers, funding agents, doctors and other health care professionals, government officials, and patients. Some findings are reported in scientific journals, and some findings are communicated to patients and patient advocacy groups through email updates and a bi-annual "consortium update."

Authorship credit – While one might not immediately think of authorship credit as a "resource," in fact a successful research enterprise produces publications, which, besides their informational content, also convey reputational credit to the scientists involved. To be successful at producing collaborative efforts, any research effort must find some way to handle authorship issues. In fact, the authorship issue has been the subject of presentations at RDCRN conferences[15] and is the subject, at least within the APWRSC consortium, of a written policy document, which will be discussed below in the context of governance.

Resources generated by the consortia for use by others:

Information about ongoing clinical studies and experimental treatments for potential participants—e.g., who is doing the research, what they are doing, when it takes place, how to participate. To increase participation rates in studies, it is important to communicate this information to researchers at different sites, doctors and other professionals capable of referring patients, patient advocacy groups, and patients and their families. Consortium websites provide information about RDCRN ongoing clinical studies. Of course this resource is not created entirely for the use of potential research participants – its purpose is to recruit participants for RDCRN studies. Indeed, at least in some cases patient advocacy group websites provide more complete information about ongoing studies, since they include studies that are not being performed under the auspices of the RDCRN, including studies by non-consortium researchers, including researchers in Canada, and trials sponsored by pharmaceutical companies.

Diagnostic tools (and facilities—A major research objective of the RDCRN is improving diagnostic tools through research. Diagnostic tools are intended for physicians, but will of course be valuable to clinical researchers as well.

Educational materials—e.g., materials explaining what rare diseases are, how they can be detected, how they can be treated, what to do and who to contact if you think you or a family member or a patient might have one of the disorders. This information can be relevant to patients and families as well as health care professionals because, as mentioned previously, the rare nature of the disorders means that many doctors, nurses, and other clinicians have never seen or heard of them. The NIH required each research consortium to develop a website, and those websites provide educational materials. At least in the cases of the UCDC and APWRSC, however, the education materials provided by patient advocacy groups are significantly more extensive than those provided by the consortia. Therefore, it is not clear from our literature review how much value the educational materials provided by

[15] Cite to presentation

the consortia add. One possibility is that having an authoritative source on the Internet, particularly with conspicuous NIH backing, helps patients and families feel more comfortable with the materials. Much of the medical "advice" found online is less trustworthy.

Information about support groups, coping, and experiences of others—This type of information is not a focus of the RDCRN consortia. Patient advocacy groups play a major role in providing this information.

B. Participants and Roles

Rare disease clinical research involves a diverse collection of participants, who may see themselves as belonging to different communities. In a sense, each consortium integrates an academic research community, a professional health care community, and a patient–family community. Industry actors, such as pharmaceutical and biotechnology companies, also participate in and fund activities within and among these communities.[16] And, as already mentioned, patient advocacy groups participate in ways which may or may not be entirely aligned with the interests and concerns of individual patients. [See Figure from Seminara et al, above, for an illustration] Here we attempt to map out the various types of participants in the RDCRN and its consortia, and the roles they play in the activities of the RDCRN.

1. *Rare Disease Researchers.* Researchers may participate in an RDCRN in two very different ways. Most obviously, researchers may participate as members of a particular consortium, whose work is funded by the consortium. Other researchers interested in a particular disease may be consumers of the research results which are produced by the consortium.

Researchers whose work is funded by the consortium may come from a variety of academic backgrounds. Some are PhD scientists, some are M.D.s, and some may have other relevant degrees. Some are graduate students or postdoctoral researchers, while others are established clinical researchers. They may be trained in a variety of disciplines. Researchers will also be working in different locations. To illustrate the diversity of researchers, we briefly describe the backgrounds of some of the researchers involved in the UCDC and APWRSC consortia.

The UCDC began in 2003 with 10 investigators with 8 different specialties[17] from 5 academic institutions.[18] By 2009, it had grown to "43 faculty investigators and 26 research

[16] There is some indication of successful collaboration with pharmaceutical and biotechnology companies. Specifically, Seminara et al (S104), suggests "the UCDC has engaged in a number of collaborations with the pharmaceutical industry that are developing orphan products and biotech firms that are developing diagnostic technology for UCD." But I have not found any details on these relationships.

[17] Genetics, Metabolism, Developmental Pediatrics, Clinical Pharmacology, Neurology, Psychology, Biostatistics, and Neuroimaging.

[18] Children's National Medical Center in Washington, DC (lead institution); Baylor College of Medicine in Houston, Texas; Children's Hospital of Philadelphia in Pennsylvania; University of California Los Angeles in California; and Vanderbilt University.

staff members."[19] There are 15 sites, including three outside of the United States (Toronto, Zurich, and Heidelberg).[20] "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."[21]

The Project Director for the UCDC at its inception and for the 2009 grant was Dr. Mark L. Batshaw, M.D., a graduate of University of Chicago medical school who currently holds the following appointments: Executive Vice President and Chief Academic Officer, Children's National Medical Center, Director, Children's Research Institute, Principal Investigator, Center for Clinical Community Research, "Fight for Children" Chair of Academic Medicine, and Professor and Chairman of the Pediatrics Department of the George Washington University, School of Medicine and Health Sciences.[22] Dr. Batshaw performs clinical and translational research on urea cycle disorders. Although not mentioned on the NIH grants website, Dr. Mendel Tuchman is also listed as a Principal Investigator on the NUCDF website.[23] Dr. Tuchman, a graduate of Sackler School of Medicine, Tel-Aviv University, is the Chief Research Officer, Vice Chairman for Research and Scientific Director of the Children's Research Institute at Children's National Medical Center, George Washington University. Dr. Tuchman, a pediatrician and geneticist, performs research on the molecular bases for inherited UCD and ureagenesis regulation. Both Batshaw and Tuchman have longstanding involvement with the NIH, have served on various scientific advisory committees and editorial boards, and are longstanding recipients of NIH research support.

The APWRSC also begin in 2003 and currently involves a number of institutions and

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[19] "The UCDC is working to activate its 15th site at University of Minnesota in Minneapolis in late 2009, completing geographical coverage of the contiguous United States plus Alaska, Ontario and Switzerland." Seminara et al. at S98.

[20] The sites and principal investigators are:

1. Children's National Medical Center, Washington, D.C. (Uta Lichter, M.D.)
2. Georgetown University (Andrea Gropman, M.D.)
3. Children's Hospital of Philadelphia, Philadelphia, PA (Marc Yudkoff, M.D)
4. Baylor College of Medicine (Brendan Lee, M.D.)
5. University of California at Los Angeles (UCLA), CA (Stephen Cederbaum, M.D.)
6. Yale University School of Medicine, New Haven, CT (Gretta Seashore, M.D.)
7. Mount Sinai School of Medicine, New York, NY (George Diaz, M.D.)
8. Rainbow and Babies Hospital, Cleveland, OH (Douglas Kerr, M.D.)
9. Children's Hospital of Boston/Harvard, Boston, MA (Harvey Levy, M.D.)
10. Oregon Health & Science University, Portland, OR (Cary Harding, M.D.)
11. Seattle Children's Hospital, Seattle, WA (J. Lawrence Merrit, M.D.)
12. Children's Hospital Denver, Colorado (Renata Gallagher, M.D.)
13. Hospital for Sick Children, Toronto, Canada (Annette Feigenbaum, FRCPC, FCCMG)
14. University Children's Hospital, Zurich, Switzerland (Tamar Stricker, M.D.)
15. Centre for Pediatric and Adolescent Medicine, Heidelberg, Germany (Georg F. Hoffmann)

[21] Id. ("The UCDC also employs several staff members at CNMC for programmatic, grant management, administrative and biostatistical support.")

[22] I happened upon a settlement agreement between the U.S, government and Dr. Batshaw. See http://www.circare.org/foia3/batshawsettlement.pdf; see also FDA letter, http://www.circare.org/fdawls3/batshaw_20001130.pdf.

[23] See http://www.nucdf.org/research_ucdc.html. Tuchman may have joined Batshaw as a Principal Investigator after the second round of grant funding.

research groups: Baylor College of Medicine (seven faculty members and three current clinical studies); Children's Hospital Boston (two principal investigators and three current clinical studies); Rady Children's Hospital, San Diego (one physician and two current clinical studies); Greenwood Genetic Center, South Carolina (one geneticist and one physician and three current clinical studies); Vanderbilt Children's Hospital, Vanderbilt University Medical Center (one psychology professor and two current clinical studies), University of Alabama at Birmingham (one physician and one current clinical study), UC Irvine Medical Center (one principal investigator and one current clinical study), University of Florida Health Science Center (two M.D. faculty members and one current clinical study), Kansas University Medical Center (one faculty member and one current clinical study). In total, the consortium is currently running five clinical studies (some of which involve several of the above institutions).[24] The researchers involved in these studies have varying backgrounds, reflecting the highly interdisciplinary nature of clinical medical research, particularly when the research involves complex syndromes such as those that are the focus of this consortium.

The Project Director for the ARPWSC at its inception was Dr. Arthur L Beaudet, M.D., a graduate of Yale medical school, who is currently chair of the Department of Molecular and Human Genetics at Baylor College of Medicine. Dr. Beaudet's research focuses on the genetic and epigenetic causes of autism and on the Prader-Willi and Angelman syndromes.[25] For the renewal application in 2008, the Project Director was Dr. Alan K. Percy, M.D., a graduate of Stanford medical school, currently on the faculty of the University of Alabama at Birmingham and director of the university's Civitan International Research Center. Dr. Percy's research focuses on Rett syndrome.[26] Both have longstanding involvement with the NIH, have served on various scientific advisory committees and editorial boards, and are longstanding recipients of NIH research support.

2. *Information Technology and Informatics Specialists and Researchers*

The Data Management and Coordinating Center is housed at the University of South Florida. Its website lists the following "key personnel":[27]

- Jeffrey P. Krischer, Ph.D. (Applied Math), Principal Investigator, Professor, Department of Pediatrics, Division of Bioinformatics and Biostatistics, University of South Florida
- Rachel L. Richesson, Ph.D. (Health Informatics), Co-Investigator, Associate Professor, Department of Pediatrics Division of Bioinformatics and Biostatistics, University of South Florida Area of expertise: Informatics, data standards, electronic case report forms, patient registries, patient advocacy groups liaison
- Kathleen J. Paulus, CIP, Director, Data Management and Regulatory Affairs
- Jennifer L. Harris, MSPH, Certified Clinical Research Professional (CCRP)
- Karalyn Grant, MBA, CCRP, Research Compliance Manager

[24] http://rarediseasesnetwork.epi.usf.edu/arpwsc/centers/index.htm
[25] http://www.bcm.edu/genetics/index.cfm?pmid=10579
[26] http://www.bcm.edu/genetics/index.cfm?pmid=10579
[27] http://rarediseasesnetwork.epi.usf.edu/about/dmcc.htm

- Kenneth G. Young II, BS, IASA, Applications Project Manager. Area of expertise: Application Architecture, IVR Speech Engine, Adverse Event System, Application Business Logic, Security, Contact Registry
- Heather Guillette, MS, Applications Project Manager, Area of expertise: Electronic case report form implementation, Adverse Event System, lab/specimen system, pharmacy system, IVR system
- Jennifer Schauble Lloyd, BFA, Coordinator, Marketing and Communications, Area of expertise: Direction and implementation of all public branding and communications for the RDCRN, including web site, logo, electronic mail, print publications, and general marketing

3. *Treating Physicians and other Health Care Personnel*

The professional health care community includes doctors, nurses, genetic counselors, and nutritionists/dieticians, among others. Clinical research inherently demands coordination with treating physicians and other health care professionals who are not directly participating in the research. In particular, patient participation in clinical studies and trials is heavily dependent on the support of treating clinicians. Health care professionals are important sources of referrals—informing patients about ongoing clinical studies—and consumers of research outputs (e.g., diagnostics, treatments). One of the goals of the consortia is to educate physicians to be able to diagnose and treat these rare diseases. Thus, for example, the consortium website provides disease definitions and other information for physicians, as well as physician-directed information about the Contact Registry. Translating research into clinical practice is also an important objective (see goals/objectives section below).

5. *Patients and Families*

Patients and their families (families are particularly important since many of those afflicted with rare diseases are children) are the intended beneficiaries of RDCRN research and, at the same time, an essential resource for research to progress.

6. *Patient Advocacy Groups*

Patient advocacy groups are both directly and indirectly involved in the RDCRN. Each consortium must involve "collaboration" with a patient advocacy group. Moreover, the Coalition of Patient Advocacy Groups is represented on the Steering Committee of the RDCRN. At least for the UCDC and ARPWSC consortia, the relevant patient advocacy groups are independent actors, which provide patient and physician education, fund research, and assist in connecting patients with clinical studies and have been doing so since long before the establishment of the RDCRN.

To illustrate, we describe the patient advocacy groups associated with the ARPWSC consortium in some detail. There are three patient advocacy groups associated with the ARPWSC consortium, one for each syndrome. The Angelman Syndrome Foundation undertakes a wide range of services, including an extensive website, newsletters, conferences, fundraising, research funding, and support groups for patients' families. The Foundation

has been in operation "for more than 20 years" and has been funding research since 1996.[28] It has awarded a total of $3.6 million and awarded $1 million in 2009. One of its fundraising events is an annual walk, which raised about $750,000 in 2010. The Board of Directors is a group consisting primarily of parents of children with Angelman Syndrome, along with the head of the Scientific Advisory Committee. It has a staff of five, including an executive director, development director, events coordinator, web manager, and "prospect researcher." The scientific advisory committee has seventeen members who are scientists or medical professionals, including Dr. Beaudet, former principal investigator of the ARPWSC consortium, and the president of the Foundation, Fred Pritzker, who is an attorney whose adult son has Angelman syndrome. The organization has regional representatives in many parts of the country[29] and maintains a list of doctors and other professionals with experience in treating AS patients. The list is compiled from recommendations from members.[30] The Angelman Syndrome Foundation also provides information about participation in clinical studies, including a list of available studies. While there is a link to the RDCRN Patient Contact Registry on the webpage devoted to clinical studies, there are a significantly larger number of studies listed by the Foundation than by the ARPWSC Consortium on its website. In general, there is little mention of RDCRN or the ARPWSC Consortium on the Foundation's website.

The Prader-Willi Syndrome Association was organized in 1975 and has as similarly extensive set of activities, including education and research funding. Its organization is similar to that of the Angelman Syndrome Foundation in that it is governed by a 15-member Board of Directors and has a Scientific Advisory Board. The PWSA also has a Clinical Advisory Board. Its staff is larger than that of ASF and it appears to have a more substantial regional presence. PWSA maintains a database of information about persons with Prader-Willi Syndrome and serves as an intermediary for contacts between those individuals and clinical researchers. The database included 1600 people as of 2007.[31] PWSA also maintains a list of studies for which participants are being solicited. Again the list is more extensive than the list maintained by ARPWSC. While the RDCRN is mentioned on the website, it does not have a prominent place.

The International Rett Syndrome Foundation has a similar program to that of the other two associated patient advocacy groups, though research seems to take a more prominent role.[32] The IRSF has awarded more than $24 million dollars in research grants.[33] Its research strategy currently focuses on "research programs that link basic, translational and clinical research. Part of [its] current strategy to treat and reverse Rett syndrome is to focus on funding clinical research to re-purpose promising treatments that are already available or are poised to enter the clinic for other indications."[34] The IRSF also appears to be more active in political advocacy than the other two organizations.[35] It was formed in 2007 by a merger of the International Rett Syndrome Association (formed in 1984) and the Rett

[28] http://www.angelman.org/media/files/ASF%20fact%20sheetFINAL.pdf
[29] http://www.angelman.org/about-us/regional-support/
[30] http://www.angelman.org/about-us/professional-references/
[31] http://www.pwsausa.org/population/index.htm
[32] http://www.rettsyndrome.org/index.php?option=com_content&task=view&id=253&Itemid=815
[33] http://www.rettsyndrome.org/content/blogsection/6/944/
[34] http://www.rettsyndrome.org/index.php?option=com_content&task=view&id=526&Itemid=944
[35] http://www.rettsyndromeadvocacy.com/ (though this is based only on website prominence so far).

Syndrome Research Fund (formed in 1999). The IRSF maintains databases of individuals with the syndrome and of physicians who treat it. Its governance is similar to that of the other two foundations, with a board of trustees, a staff of seven, and scientific and medical advisory boards (instituted in 2009). Dr. Percy serves on the Medical Advisory Board. The IRSF also has a Family Advisory Board and a group of Professional Advisors, who are available for advice and consultation. The IRSF also maintains a list of clinical studies seeking enrollment. As above, the list extends well beyond the ARPWSC list. Again, there is little mention of RDCRN or the ARPWSC on the IRSF's website. The National Urea Cycle Disorders Foundation (NUCDF) is a volunteer health organization that undertakes a wide range of activities, ranging from education, research, fund raising, and support groups. The NUCDF plays an important role in the UCDC. The executive director of the NUCDF is a voting member on the Steering Committee of the UCDC. According to one author, the NUCDF has played a role in developing the Patient Registry, designing the longitudinal study, developing protocols, and developing the UCDC website. The NUCDF also recruits patients for clinical research studies, disseminates educational materials, and hosts an annual conference for patients, families, health care professionals, and researchers.

The National Urea Cycle Disorders Foundation (NUCDF) similarly undertakes a wide range of activities, including education, research, fund raising, and support groups. The NUCDF also recruits patients for clinical research studies, disseminates educational materials, and hosts an annual conference for patients, families, health care professionals, and researchers. The NUCDF website not only lists ongoing research studies sponsored by the UCDC, but it also lists ongoing industry-sponsored clinical trials.

The NIH RFA did not specify the extent or type of "collaboration" that consortia are to have with patient advocacy groups. From the information available from our literature review, the NUCDF appears to play an important role in the UCDC. The executive director of the NUCDF is a voting member on the Steering Committee of the UCDC. According to one author, the NUCDF also has played a role in developing the Patient Registry, designing the longitudinal study, developing protocols, and developing the UCDC website.

C. Goals and Objectives of the RDCRN

The RDCRN mandate provides the overall purpose of the consortia:

The purpose of the 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
- 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)[36]

[36] (from presentation for 2008 RFA)

Rare disease research consortia coordinate research among distributed entities, bringing various research sites and groups of people together. The overarching goal is to alleviate research problems attributable to the rareness of the disorders: getting a sufficient number of study participants is a "big challenge," and thus the consortia help researchers connect with patients and those who may refer patients (health care professionals). Because there are so many rare diseases (more than 6,000) and the RDCRN funds only 19 consortia, the RDCRN also seeks to develop infrastructure and procedures that will be applicable across diseases. The establishment of the DMCC is the primary step toward that goal thus far.

Each individual consortium is concerned primarily with research into the particular cohort of diseases upon which it focuses. The goals of RDCRN consortia have been set out by the NIH:

"The unified goals for each consortium within the network are to: (1) perform collaborative clinical research in rare diseases, including observational longitudinal studies, clinical studies (including phase 1 and 2 trials), and pilot projects; (2) train clinical investigators in rare diseases research; and (3) establish a centralized data repository and data sharing for rare diseases."[37]

At least as reflected on the websites of the UCDC and APWRSC, it appears that a (if not the) primary concern is the recruitment of patients to participate in clinical studies.[38] Thus, the UCDC website describes the consortium's purpose as: "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." Its 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 Consortium has established centers of clinical and scientific excellence across the United States to work with patients and physicians to provide information and care with the latest information and technology. 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. "

Similarly, according to the APWRSC website: "The Angelman, Rett, and Prader-Willi Syndromes Consortium is a team of doctors, nurses, research coordinators, and research labs throughout the U.S., working together to improve the lives of people with Angelman, Rett, and Prader-Willi Syndromes through research. Since Angelman, Rett, and Prader-Willi

[37] From Tuchman et al (398):
[38] Of course, websites are aimed at the public – and specifically at patients and their families – so this source of information may over-emphasize the importance of patient recruitment.

Syndromes are rare, there are low numbers of research volunteers and this adds a greater level of difficulty for researchers struggling to learn more about these disorders. 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 these disorders. This important first step is necessary if we are ever to find newer treatments."

D. Degree of "openness"

In some respects the RDCRN and research consortia are entirely closed. To be a part of the RDCRN, a research consortium must be selected by the NIH, and the only researchers who have access to the funding, the DMCC resources, and so forth, are those who are members of a consortium. Funding of consortia is determined by a presumably rigorous NIH peer review process. There are only 19 consortia, while there are thousands of rare diseases. Our research uncovered on instance in which the denial of an application for a consortium grant, led a patient advocacy group to generate an online petition urging the NIH to reconsider. The petition garnered nearly 900 signatures.[39]

Access to the infrastructure developed by the DMCC also appears, at least at this point, to be confined to consortium members and there is little description of the DMCC's activities on its publicly accessible website. It is not clear how or when the DMCC infrastructure will be made more widely available, though presumably the goals of the RDCRN project are to develop infrastructure and methodology to be used more broadly in the study of rare diseases.

The openness of access to the data garnered during the clinical studies is less clear. Of course, results of the studies are made publicly available through publications and given the need to justify renewed funding and the usual incentives of academic research, presumably as many results eventually are published as possible. However, a "Publication Policy" for the APWRSC Consortium suggests that the timing and fora for publication and presentation of results are closely governed so as to protect and allocate publication rights and credit. A 2006 press release about the RDCRN generally indicated that "data will be made publicly available" consistent with privacy protections. We have seen no indication, however, that raw data has actually been made publicly available or available to researchers who are not within a consortium. The UCDC and APRWSC have a "RDCRN Research Members Login," which presumably leads to information about the studies, perhaps including study data. Moreover, the privacy issues involved in sharing data may well be severe.

Given the great need for research participants, clinical studies are presumably open for patient participation as long as the patients meet the specific criteria of the study (and presumably must be vetted by the researchers in order to participate).

III. Activities and Governance

The governance of the RDCRN occurs on all of the levels we have discussed above. Thus, funding decisions are made at the NIH level through a peer review process that

[39] http://www.petitiononline.com/mod_perl/signed.cgi?BHVMNIH

includes a specially convened panel, which is charged with making final funding decisions. The RDCRN as a whole is governed by a Steering Committee which, as described above, includes representatives from all consortia, from NIH, and from the Coalition of Patient Advocacy Groups. The UCDC and APWRSC are also governed by Steering Committees.[40] The steering committee of the UCDC "is composed of the UCDC directors, the principal investigator from each site, 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." The publication policy of the APWRSC (discussed below) describes "steering committee consisting of the PI and the lead investigators for each disorder." There is also at least some overlap in governance between the consortia and the associated patient advocacy groups. Thus, the UCDC's steering committee includes the executive director of the NUCDF and at least some researchers from the APWRSC sit on the boards of the various PAGs.

Beyond this bare bones information, however, the publicly accessible documentation provides little information about the governance of the RDCRN and its consortia in practice. The most detailed window into consortium governance that we have at this point is the APWRSC Publication Policy.[41] The policy is a 4-page written document that sets out specific policies for authorship of articles resulting from consortium research, for dealing with the media, for scientific presentations, and for subsequent data use. This aspect of governance is obviously very important to the researchers in the consortium. The publication policy deals with 1) responsibility for submitting primary results for publication; 2) authorship of articles concerning primary results, which must have a representative from each participating site; 3) dispute resolution concerning order of authorship, which is handled by the steering committee; 4) a one-year window during which the "investigator who conceptualizes the specific study" must submit the results for publication or lose lead author position; 5) similar policies for secondary publications; 6) lead author and co-author responsibilities. The Media Policy requires that 1) press releases and interviews contain only materials approved by the consortium steering committee; 2) approval of abstracts for presentation at scientific meetings by PI or study leaders; 3) use of data that has been presented but not yet published.

The very existence of this policy is of interest because it highlights the importance to members of the consortium of assigning publication credit and controlling publication timing. In our further research into the RDCRN we will attempt to identify further action arenas that are likely to raise issues of conflict requiring governance solutions. We plan to focus on those activities that distinguish the RDCRN and its consortia from grants to individual researchers or smaller collaborations since the ability of the consortia to govern these particular activities will help to determine whether they succeed.

Based on what we have learned so far, likely areas of potential difficulty, other than dividing authorship credit among a large and diverse group of researchers, include:

- Allocation of funding between research centers within a consortium
- Setting research priorities so as to allocate funding between projects within a

[40] Seminara (for UCDC); Publication Policy (for APWRSC)
[41] We did not find such a policy for the UCDC.

consortium

- Setting priorities for the DMCC
- Disputes between individual consortia and the DMCC about such things as data format standards and the need for the DMCC to enforce its standards[42]
- Tensions between time and effort devoted to developing and supporting infrastructure for the RDCRN as a whole and time and effort devoted to consortium research[43]
- Control over access to data and other materials collected by the consortia by other researchers
- Relations with Patient Advocacy Groups, with respect to issues such as research priorities and recruitment of patients for clinical studies

We will use these potential areas of conflict to frame our further research into consortium governance.

IV. Outcomes

There are several metrics that one might employ in evaluating the outcomes of the RDCRN and the individual consortia:

- Development of new treatments
- Accelerated research results
- Improved recruitment of patients for clinical studies
- Improved infrastructure and methodology for rare disease research

Since recruitment of patients for clinical studies began only about five years ago, it is probably too soon to expect new treatments to have emerged. The website of the UCDC lists no trials of new treatments among available studies. The APWRSC website does list one study "designed to evaluate the possible therapeutic benefits of L-5-methyltetrahydrofolate (Metafolin), vitamin B12, creatine and betaine in children with Angelman Syndrome (AS). Though numerous publications are listed on the websites of the UCDC and APWRSC consortia, it is difficult to know whether research is progressing any faster than it was under previous individually-funded NIH grants, though it may be possible to gain insight into the acceleration of research results by looking at publication records.

One metric which has been the subject of some study is the recruitment of patients for clinical studies. Richesson (2009) studied the effectiveness of the DMCC Patient Registry and found enrollment figures "impressive" as the RDCRN network is young and at that time

[42] See DMCC Pre-App PowerPoint's, listing one role of the DMCC as "Monitor Network protocol adherence, data collection and data submission, and reporting violations to the Steering Committee"
[43] Such tensions are possibly reflected in changes in the responsibilities of the DMCC over time. See DMCC Pre-App PowerPoint's. (DMCC will stop providing "Statistical support during protocol development," which will now "be the responsibility of the consortium." Consortia will now "have the option of developing their own [data collection] forms" and the "DMCC will work with consortia to integrate forms into Network")

had not been the subject of "formal marketing." The participation rate of enrolled patients in clinical studies relatively near their homes averaged about 20%, similar to that for patient registries in other disease contexts. However, the study did not compare enrollment through the RDCRN with enrollment in registries maintained by patient advocacy groups. Interestingly, the report did report that registry enrollment was higher where particular patient advocacy groups had actively encouraged registry enrollment, a connection that suggests that, at least in 2009, patient advocacy groups might still have had an advantage in enrolling patients for clinical studies.

Besides assessing the potentially positive outcomes of the RDCRN, we plan to consider the possibility of negative externalities, particularly with respect to funding for research on other rare diseases. To gain insight into this issue we hope to explore why some consortia were dropped from the network during the second round of funding and what has happened to projects whose proposals were rejected, such as the one which generated the patient advocacy petition discussed above, were rejected. We also are interested in finding out whether the consortium structure has had any negative implications for relationships and collaborations between researchers on a particular disease who are in or out of a funded consortium.