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An Automated Communication System in a Contact Registry for Persons with Rare Diseases: Scalable Tools for Identifying and Recruiting Clinical Research Participants

R. L. Richesson, PhD, MPH^{*}, H.S Lee, PhD, D. Cuthbertson, MS, J. Lloyd, K. Young, and J.P. Krischer, PhD

Department of Pediatrics, University of South Florida College of Medicine, Tampa, FL

Abstract

Objectives—Strategies for study recruitment are useful in clinical research network settings. We describe a registry of individuals who have self-identified with one of a multiplicity of rare diseases, and who express a willingness to be contacted regarding possible enrollment in clinical research studies. We evaluate this registry and supporting tools in terms of registry enrollment and impact on participation rates in advertised clinical research studies.

Methods—A web-based automated system generates periodic and customized communications to notify registrants of relevant studies in the NIH Rare Diseases Clinical Research Network (RDCRN). The majority of these communications are sent by email. We compare the characteristics of those enrolled in the registry to the characteristics of participants enrolled in sampled RDCRN studies in order to estimate the impact of the registry on study participation in the network.

Results—The registry currently contains over 4,000 registrants, representing 40 rare diseases. Estimates of study participation range from 6–27% for all enrollees. Study participation rates for some disease areas are over 40% when considering only contact registry enrollees who live within 100 miles of a clinical research study site.

Conclusions—Automated notifications can facilitate consistent, customized, and timely communication of relevant protocol information to potential research subjects. Our registry and supporting communication tools demonstrate a significant positive impact on study participation rates in our network. The use of the internet and automated notifications make the system scalable to support many protocols and registrants.

Keywords

Registries; Patient Selection; Rare Diseases

^{*}Corresponding author: Rachel Richesson, PhD, MPH, Assistant Professor, USF College of Medicine, Department of Pediatrics, 3650 Spectrum Blvd., Suite 100, Tampa, FL 33612, Office: (813) 396-9522, Fax: (813) 396-9601 or (813) 910-5922, Email: richesrl@epi.usf.edu.

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INTRODUCTION

Clinical Research Participation and Rare Diseases

Obtaining sufficient numbers of participants to meet study objectives has always been a challenge for clinical research and is a particular problem for rare diseases. [1,2] Diseases or conditions that affect < 200,000 persons in the United States are considered rare diseases under the Rare Diseases Act of 2002.[3] Because of the low prevalence of these conditions, the identification of sufficient numbers of research subjects is also a big challenge. The Rare Diseases Clinical Research Network (RDCRN) coordinates research studies on over 50 rare diseases. [1,4] The network consists of ten clinical research consortia, each focused on a group of related rare diseases. A centralized Data and Technology Coordinating Center (DTCC), located at the University of South Florida (USF) College of Medicine, has developed and maintains an administrative disease registry to help identify potential research subjects for the RDCRN network studies. Our registry system collects only contact information, self-reported diagnosis, and demographic information. A web-based system supports the electronic collection of contact information and provides automated communications with individuals who self-identify with a rare disease and express interest in clinical research participation. The automated Contact Registry we describe is scalable to support many studies, thereby sustaining a pool of possibly eligible participants for clinical protocols on a spectrum of rare diseases. Here we describe the system and present early evaluation using study participation rates as an outcome measure.

Disease Registries

Disease registries - controlled lists of persons with a specified clinical condition, and their associated data - are used to support public health and clinical research activities. Such registries have been used in cancer research since the 1940s as tools to estimate cancer incidence and support etiological exploration by recording cases reported within a defined time or place. [5] Disease registries can be characterized by their purpose. *Administrative registries* are used to identify patients with particular conditions, usually for later epidemiological study. *Population-based registries* collect disease-related data (either from self-report or from medical records after patient consent) that is later used for data-mining, hypothesis generation, and secondary research questions. More recently, *genetic registries* (those that identify individuals with a given genetic mutation or profile) are becoming more frequent for recruiting and follow-up of relatives of affected individuals.[6,7] Registries of all types have been used to support research of rare diseases such as Mucopolysaccharidosis Type I (MPS I) [6,7], Fabry Disease [8], Lymphangioleiomyomatosis [9], and Parkinson's disease. [10] For more prevalent conditions, such as diabetes, multiple registries might exist for a single disease. [11-17] In addition to identifying persons afflicted with diseases or conditions, registries can be used to ascertain recipients of procedures and devices. For example, the New Approaches to Coronary Intervention (NACI) registry is funded by the National Heart, Lung, and Blood Institute (NHLBI) to track outcomes of new coronary interventional devices [18], and INTERMACS is a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. [19]

Disease registries have long been used to assist the clinical research process. Registries have been used to estimate achievable sample size for prospective clinical trials [20] and to explore research questions on incidence [21,22], screening [23,24], growth rates [23,25], co-morbidities [26-29], and mortality [23,30-32] in hundreds of diseases, including heart disease [33] and Cystic Fibrosis (in multiple countries). [26,30,32,34-36]

A major challenge in clinical trials is identifying potential research subjects. The notion of maintaining lists of affected individuals who express interest in participating in clinical

research trials as a “pool” of potential research subjects is an appealing prospect for researchers, who often are forced to advertise for research participation. Cultivated and managed lists of possibly eligible and interested research subjects simplify study recruitment and perhaps increase the likelihood of complete trial accruals. Registries have been used in this way to identify and recruit patients for clinical research studies. [37–40] The National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members collects information from affected individuals (and their unaffected family members who elect to join) and matches them with scientists who are looking for subjects to participate in research trials.[41] Affected individuals join the registry to receive personal notification of research projects they may be eligible to participate in, and researchers can approach the registry for assistance recruiting people to participate in their studies.[39]

Informed Consent and Notification Issues

The protection of confidentiality and assurance of meaningful informed consent are important issues when recruiting patients for clinical research from disease registries [42], although several studies imply that potential research subjects appreciate direct communication of clinical research information. A survey of policies for research contact with patients registered in cancer registries revealed that the strategy used most frequently (among those registries that allowed patient contact) was for investigators to contact patients after notification of their physician, rather than more restrictive policies requiring registry staff to obtain physician permission to contact patients. [43] A comparison of these two strategies for study recruitment (direct contact by research staff and contact by research staff after physicians alert potential participants) from a cancer registry found no difference in study participation rates. [42] Authors concluded that although there are confidentiality concerns when recruiting research participants from disease registries, the notification of physician might create pressure for participation. A separate survey of 100 registrants in another cancer registry found that the majority of patients said they preferred that researchers contact them directly about their interest in research participation, rather than checking with their physician first. [44] Among those respondents who wanted their physician involved, most preferred a physician notification rather than a physician permission approach. [44] Each of these studies emphasized the need for registry enrollees to be clearly informed about how the registry will be used for research.

Internet as an Outreach Medium

The internet has created virtual communities for affected individuals and opportunities for education for disease management, treatment and research information, advocacy, and social support. The use of the internet to support recruitment of participants has been successful in other research contexts. [45,46] In addition, the use of the internet to support the enrollment and communication with individuals enrolled in administrative registries, such as the RDCRN Contact Registry, show potential to link with the increasing number of on-line and electronic clinical trial registries. [47–52]

SYSTEM DESCRIPTION

Overview

The information collected by the RDCRN Contact Registry is used by the DTCC to identify potential study participants (by diagnosis, age, gender, and/or geography) and to send customized information regarding open or planned clinical studies on behalf of RDCRN investigators. The DTCC does not share any identifying information from contact registrants with RDCRN investigators. Rather, RDCRN investigators use the DTCC to send consortium and protocol-specific information to potential research subjects enrolled in the Contact Registry. This information typically includes titles of open protocols, eligibility criteria,

protocol descriptions, open sites, and contact information. If individuals are interested in participating in RDCRN studies, they must contact study personnel on their own behalf.

Enrollment

The RDCRN Contact Registry is designed for access by the general public, [<http://www.rarediseasesnetwork.org>]. Users access an enrollment form for the Contact Registry via one of ten consortium-specific web pages. Each of these consortium specific web pages describes the collaborators and research activities of the clinical research consortium, information about the diseases under study in that consortium, current and planned research protocols for that consortium, and links to support resources. The consortium-specific public web pages act as portals to the registry. The RDCRN consortia web-pages and associated links to the Contact Registry are accessible from disease-specific searches on a variety of internet browsers.

When a new patient enrolls in the contact registry, their contact information and self-reported diagnosis are stored in a central database at the DTCC. The new registrant then receives a confirmation of his/her registration via email, including a user name and password to update contact information or to withdraw from the registry at any time. The RDCRN Contact Registry is compliant with the U.S. Health Insurance Portability and Accountability Act (HIPAA). All registrants must read and acknowledge a privacy statement before they can submit their information to the registry. This privacy statement and authorization states that the registrant is voluntarily sharing their personal information for purposes of receiving communications related to potentially relevant clinical studies, and that their information will not be used for other purposes without their explicit consent. The authorization also states that data may be used by USF personnel to understand, analyze and conduct research. Additionally, the registrant is informed that they must contact a research site directly in order to discuss eligibility and enrollment in any advertised research study.

Communication

Communications from the Contact Registry include automated messages for new registrants, and announcements of new protocols and new clinical site openings for active protocols. A “New Registrant email” is sent to every individual upon Contact Registry enrollment (i.e., completion of the online initial enrollment form). This email contains a welcome statement, and instructions for the recipient on how to keep their information updated. The system extracts descriptive information from all relevant studies (based on disease and age exclusion criteria) and displays it in the email template. When a new protocol opens, a “New Study email” is sent to registrants who are potentially eligible for that protocol (based on criteria such as disease, age, gender, or geography, as determined by study investigators). Whenever a new clinical site opens for an active protocol, a “New Site email” is automatically generated and sent to relevant Contact Registrants. This email includes the recent update (i.e., addition of new clinical research site), in addition to all previous descriptions and site information on that protocol. Standard template features are included, such as disclaimer and sponsor information, consortium information, and the update information links.

In addition to communications regarding new studies and site openings, periodic communications are sent to all registrants. Every 6 months, a “Consortium Update” communication is sent to all registrants of that consortium. This bi-annual email gives them an opportunity to keep their contact information current, keep them informed of the most up-to-date information, or encourage them to return to the Consortium-specific RDCRN web site to check for updates. Additional communications and content can be sent at the request of RDCRN consortium investigators.

The automated communication system is data-driven. The protocol information (e.g., study description, eligibility criteria, etc.) that is sent to registrants is automatically extracted from the DTCC protocol management database and inserted into standardized email or letter templates. The system monitors the addition of new protocols or changes in information (e.g., study sites opening or closing) from internal DTCC databases and automatically notifies the contact registrants of such changes as they occur. The type and frequency of automated communications are defined for each of the ten RDCRN consortia.

Monitoring

The system is configured and monitored by staff at the DTCC using a set of interfaces called the Campaign Manager. A campaign is defined as a group of automations or mailings that is sent to one or more registrants via an automation trigger. Triggers include events, such as protocol activation or a new IRB-approved institution, and scheduled dates. A schedule date can be recurring (e.g., every 6 months) or a set execution date (e.g., March 15). Each campaign (i.e., each email or postal batch mailing) can be customized by consortium, disease, protocol, or event. The Campaign Manager interfaces allow DTCC staff to monitor the system and customize campaign automations. Other interfaces let a registry administrator view all past and scheduled campaigns related to a given disease, protocol, or RDCRN clinical research consortium.

Troubleshooting and Tracking

When a patient joins the registry, they are asked for several different forms of contact information: email, phone, fax, and mailing address. In the event that an email fails, or a printed mailing returns to the DTCC, a DTCC representative will utilize other contact information provided by the registrant in order to resolve the error. Periodic internal reports and an on-demand interface allow the DTCC to determine the number of registrants that receive each email, the number of bad addresses, the number that we attempted to track and update information, and the number lost to follow-up. The interface allows an administrator to update contact information manually as needed.

Alternate Media

While the system is designed for web-based access and communications, the DTCC does support alternative access. The DTCC maintains a toll-free number for the public to enroll or update contact information, and standard postal mailings can be used instead of emails for the Contact Registry enrollees who prefer. (The Contact Registry enrollment form asks for the preferred method of contact: email, standard mail, facsimile, or telephone.) The same information that is displayed in the email templates is extracted from the database and placed by the system into a similar (MS Word) template. A registry administrator receives an email alerting them that paper mailings have been printed and are ready to be distributed.

System Reports

The DTCC's automated system posts weekly reports of the numbers of individuals enrolled in the contact registry, by diagnosis and consortium, to a private RDCRN members' site, for researchers and administrators to view. These reports detail the number of new enrollees per disease, preferred method of contact, referral method (i.e., "How did you find out about us?"); demographic information (e.g., age, gender, race-ethnicity and residence) per disease, and maps illustrating numbers of contact registrants relative to active clinical sites.

EVALUATION

Utilization

The RDCRN consists of ten clinical research consortia categorized by disease types. As of November 2007, over 4,000 individuals representing over 40 different rare diseases from 61 different countries were enrolled in the RDCRN Contact Registry: Angelman, Rett, & Prader-Willi (ARP: n=623); Bone Marrow Failure (BMF: n=326); Cholestatic Liver Disease (CLIC: n=230); Neurologic Channelopathies (CINCH: n=108); Genetic Diseases of Mucociliary Clearance (MCC: n=233); Genetic Steroid Disorders (GSD: n=42); Rare Lung Disease (RLD: n=232); Rare Thrombotic (RTD: n=334); Urea Cycle Disorders (UCD: n=235); and Vasculitis Clinical Research (VCR: n=1597). Of those, 64% were female, and the majority of those enrolled in the registry reported their race as Caucasian (91%) and ethnicity as non-Hispanic (81%).

The numbers of enrollees vary across consortia in part due to differences in disease prevalence and also to the active endorsement and advertisement of the RDCRN Contact Registry by certain patient advocacy and support groups representing diseases under study by different research consortia. Overall, most of the registry enrollees to date reported that they first heard of the RDCRN Contact Registry via the internet (43%) or support groups (41%) and overwhelmingly prefer to be contacted via email (71%). However, the referral by support group was significantly more frequent than by internet in five consortia, including ARP($p<0.0001$), CLIC($p=0.0001$), MCC($p=0.0003$), RLD($p<0.0001$) and UCD($p<0.0001$), where p -values were obtained to test whether or not the proportion of support group referral is equal to that of internet referral. Multiple testing was not adjusted, but the correlation between two proportions was adjusted since two referral methods were chosen within each consortium.

While the RDCRN Contact Registry has been enrolling potential subjects since 2004, the Campaign Manager system began sending automated communications in Spring 2007. To date, over 5,600 automated email messages have been mailed out with close to 100% delivery rate. The few delivery errors that have occurred have been resolved either by correcting the entered email address (example: person enters jdoe@yaho.com instead of jdoe@yahoo.com) or, more rarely, by contacting the registrant by phone or mail.

Impact on Study Enrollment - Methods

Based upon the reported diagnosis in the registry, 87% of those enrolled are potentially eligible for at least one open RDCRN study. To evaluate the Contact Registry as a resource for RDCRN studies, we aimed to investigate what portion of contact registrants had actually enrolled in one of network-sponsored clinical studies.

A limitation to this analysis is that since the DTCC does not collect identifying information on subjects enrolled in RDCRN studies, it is not possible to directly figure out whether or not an enrollee participates in one of the RDCRN studies. Moreover, some RDCRN studies require eligibility data that can not be found from the information reported in the Contact Registry. Hence, we selected 12 open studies from five clinical research consortia (Angelman, Rett, Prader-Willi Syndromes, Bone Marrow Failures, MCC (genetic disorders of Mucociliary Clearance), Urea Cycle Disorders and Vasculitis clinical research consortia) where the eligibility of a Contact Registry enrollee can be determined from the reported information. For each of the twelve studies, we compared the disease, birth date and gender data recorded for all subjects enrolled on study with the same data as reported in the Contact Registry.

Because registration on RDCRN Contact Registry is accessible to virtually anyone in the world, it is understandable that there will be contact registry enrollees that are logistically unable to participate due to factors such as geography and national citizenship, regardless of whether or

not they are clinically eligible for a particular RDCRN study. Hence, a more accurate measure of study participation rates would include only “eligible and accessible” contact registrants in the denominator of study participation rates. Therefore, we also examined the participation rates by restricting our contact registrants eligible for a particular study to be those who live within 100 and 200 miles (measured from the center of the patient-reported zip code in the Contact Registry) of a participating clinical site.

Impact on Study Enrollment - Results

Table 1 shows the participation rates for studies in 5 RDCRN research consortia overall and by restricting the eligible contact registrants who live within 100 and 200 miles of a study site. The overall study participation rate without limiting distance from enrolling study sites was 12% (ranging by consortium from 6% to 27%). However, when we restricted the definition of eligible contact registrants to those who live within 200 miles from a closest eligible study site, the overall rate was 16% (ranging by consortium from 8% to 42%). When study eligibility was restricted those within 100 miles, the overall rate increased to 21% (ranging by consortium from 12% to 43%). Closer distance showed higher participation rates for all consortia but MCC consortium. The MCC showed a lower participation rate for 100 miles than for 200 miles due to a significant reduction in the number of contact registrants who live within 100 miles of an open study site.

Additionally, we examined how study participation rates differ by referral methods to the RDCRN Contact registry. Table 2 shows the results for the contact registrants who live within 100 miles from a closest eligible study site by source of referral to the RDCRN contact registry. Although most contact registrants were referred via internet or support groups, the registrants referred by medical professionals had the highest study participation rates. The participation rates between internet and support group referral methods were compared and not significantly different in each consortium [Angelman, Rett, & Prader-Willi ($p=0.2801$), Genetic Diseases of Mucociliary Clearance ($p=0.3778$), Bone Marrow Failures ($p=0.4645$) and Vasculitis ($p=0.0689$)], except for the Urea Cycle Disorders consortium ($p=0.0013$). P-values were obtained without multiple testing adjustment.

DISCUSSION

Limitations

Without a direct link between individuals on study (for which the DTCC has only de-identified information) and those in the Contact Registry, it is impossible to know for sure whether we have matched individuals correctly. However, since the sampled RDCRN studies target rare diseases, the likelihood that two individuals on a given study happen to have the same birth date is presumably very low. In fact, we did not find the same birth date between any two individuals among the subjects whose birth date matches to the contact registrants we identified as enrolled in the selected RDCRN studies. Our assumption is that the combination of birth date, gender and affected status is sufficiently precise to match individuals across data sources (contact registry enrollees and RDCRN study participants). While this matching approach might be less valid in other more common diseases, it seems to be valid in our RDCRN samples.

There is also no way to determine whether the individuals in the Contact Registry actually have the diseases that they claim, and consequently, our denominator of “eligible” patients is undoubtedly inflated. In this case, the proportions of clinically eligible individuals in the Contact Registry that actually enroll in RDCRN studies are likely to be higher. Many rare diseases are difficult to diagnose, and sometimes individuals mistakenly identify with a rare disease when indeed they don’t meet the clinical criteria. It is only after a further evaluation and screening that the patients we classified as “eligible” (based on self-reported disease and

demographics only) for studies can be truly classified as eligible. Additionally, enrollment in a clinical study requires meeting other eligibility criteria, and accepting the demands for study procedures and follow-up, or in the case of intervention studies, the risk-benefit ratio.

Impact

The enrollment of the Rare Diseases Clinical Research Network Contact Registry is impressive as the network is relatively young (3 years) and has undergone no formal marketing at the network level. Variation in the numbers of registrants per consortium is due not only to prevalence differences among the various diseases under study in the network, but also due to activities of the disease-specific Patient Advocacy Groups, some of which have advertised the RDCRN Contact Registry heavily within their membership. Anecdotally, we see higher numbers of enrollees in RDCRN clinical research consortia that represent diseases whose Patient Advocacy Groups have promoted and actively encouraged registry enrollment. Other researchers have shown that personal contact with potential participants can be effective in achieving increased registry enrollment. [53]

The majority of those enrolled in the Contact Registry are Caucasian, which might reflect the demographics of those having these diseases, or simply represent the likelihood that they have better access to rare disease specialists for disease diagnosis and care. It is possible that the high rates of Caucasians enrolled in the RDCRN Contact Registry, which is heavily reliant upon computer access, reflect a population of affected individuals with access to the internet. Examination of over 700 individuals enrolled in a registry for stroke or traumatic brain injury found no difference in registry enrollment by race, and found that higher education and younger age were associated with consenting to enroll in their registry. [54] The same study found that, for all demographic groups, lower (reported) concern over privacy was associated with willingness to enroll in the registry. [54] Further exploration of expected demographics by disease would give insight as to whether the RDCRN Contact Registry enrollment is generalizable to the greater population of individuals affected by the rare diseases or if there are access or other obstacles to enrollment. It also should be noted that subjects that enroll in voluntary administrative registries such as ours - because of their willingness to enter a trial - could lead to biased groups of patients being entered into clinical research studies and may not be representative of the real patient population. Of course, this is a problem for all clinical trials, but it is possible that a registry may create more of this type of bias, since subjects are volunteering to be considered for trials with little or no knowledge of the nature of the studies forthcoming.

Overall, the study participation rates for enrollees of the RDCRN Contact Registry are comparable to other registries. In a registry of 708 patients who underwent surgery for a malignant glioma, the frequency of clinical trial participation of 21.3% was lower than participation estimates we saw in areas of urea cycle disorders (27%), and diseases of mucociliary clearance (27%), but higher than overall participation in RDCRN studies in Rett and Angelman Syndromes (15%), bone marrow failures (7%), and vasculitis (6%). [37] The aforementioned study collected more clinical information in the registry, and presumably had patients that were more eligible for the study participation than members of our registry, which does not require documentation of clinical diagnosis. When we limit eligibility for study participation to those contact registrants who live within 100 miles of a clinical site, we see a study participation rates 28% or higher in all disease areas but bone marrow failures and vasculitis. In general, we saw the lowest study participation rates in studies of the Vasculitis Clinical Research Consortium (6% participation overall, and 8% and 12% when restricted to individuals living within 200 and 100 miles of clinical site respectively), but this consortium has the highest enrollment in the contact registry overall (n=1597) and also the highest number of contact registrants potentially eligible for studies based upon disease and demographic

criteria (n=1325). It is possible that the low proportion of contact registrants that actually enrolled in RDCRN studies is due to a limited enrollment capacity (~900 for the 5 sampled studies) for studies in this consortium.

Another study that recruited women from a cancer registry found that of 179 identified eligible women, 60 (34%) were recruited and enrolled in the trial, and suggest that registry-based recruitment efforts may be useful for expanding recruitment to the larger community. [38]

Maintenance Requirements

The DTCC ensures that each registrant receives current and timely updates on all protocol information. An automated system of communication to registrants reduces this burden on the DTCC, and can accommodate indefinite growth in registry enrollment without expending additional resources. We found that the majority of individuals enrolled in the RDCRN Contact Registry (70%) prefer to use the internet to send and receive communications related to the RDCRN. Web-based information and enrollment tools that facilitate self-referral and enrollment in the RDCRN Contact Registry serve to make the registry universally accessible, more utilized, and scalable to support multiple studies or diseases.

This automated system has proven to be scalable – the resources of the DTCC are independent of the volume of the registry. Increased communication volumes impact on cost only marginally. The number of registrants preferring standard mail has been small enough that this has not been a substantial burden for the DTCC. Currently, a registry administrator spends approximately 5 hours/month to monitor the RDCRN Contact Registry, which includes reviewing and correcting bad email addresses and contact information, handling technical support requests from the public, review and quality control of mail-outs, and customizing the system for changing consortium needs.

Implications

Currently, there are over 25 active protocols enrolling over 2,000 subjects at 42 different sites in the RDCRN. In a research network addressing various rare diseases, methods for mass dissemination of targeted information to increase the pool of informed and potentially eligible research subjects is much needed. Methods for disseminating relevant information to targeted individuals offer possibilities for potential research subjects to understand study eligibility requirements, protocol logistics, geographic location, and availability of enrollment capacity before speaking with research staff. Automated methods, such as our contact registry system, offer an inexpensive approach to communicating with potential study participants, and are scalable to communicate with ever-growing numbers of individuals without a corresponding increase in resources. The costs associated with identifying and recruiting participants in any clinical study are non-trivial, and strategies that identify populations of potentially eligible individuals can allow those resources to be used more effectively than approaches that target the general public or mainstream media. In addition to cultivating a pool of potential research subjects for RDCRN protocols, the RDCRN Contact Registry represents a community of affected individuals that rare disease researchers can communicate with regarding treatment advancements and planned research activities. The information provided to this community is of high importance as expanding the public's understanding of the benefits and risks of clinical research participation, and the awareness of available clinical studies can be crucial to study recruitment.

We observed higher study participation rates, regardless of location to clinical sites, for those referred to the RDCRN Contact Registry by a medical professional, which is consistent with other studies.[55–57] We would like to look more closely at the differences between eligible individuals referred to the Contact Registry by other means who did not participate in clinical

studies, to guide future interventions to increase study participation in our network. We believe that exploration in this area could increase our understanding of barriers and attitudes toward clinical research participation – and be applicable in domains outside of rare diseases.

CONCLUSION

The RDCRN Contact Registry offers a means to accumulate potential study participants for network studies. The automated communication system provides rapid, economical, and scalable methods for Contact Registry maintenance. The registry can be a resource of potentially eligible and interested subjects and can increase efficiency of clinical trial recruitment. In the diseases under study in the RDCRN, the Contact Registry has contributed a proportion of participants to clinical research protocols. These results imply that an automated online patient contact registry can be an important tool for clinical research.

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References

1. Hampton T. Rare Disease Research Gets Boost. *JAMA* 2006;295:2836–2838. [PubMed: 16804140]
2. Aitken L, Gallagher R, Madronio C. Principles of recruitment and retention in clinical trials. *Int J Nurs Pract* 2003;9(6):338–46. [PubMed: 14984070]
3. Rare Diseases Act of 2002. [Page 116 STAT. 1988] Public Law 107–280. 107th Congress, http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_cong_public_laws&docid=f:publ280.107
4. PEC. Rare Disease Clinical Research Network Public Website. Pediatrics Epidemiology Center. 2006. <http://www.rarediseasesnetwork.org>
5. Parkin DM. The evolution of the population-based cancer registry. *Nature Reviews* 2006;6:603–612.
6. Pastores GM, et al. The MPS I registry: design, methodology, and early findings of a global disease registry for monitoring patients with Mucopolysaccharidosis Type I. *Mol Genet Metab* 2007;91(1):37–47. [PubMed: 17336562]
7. Montano AM, et al. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit Metab Dis* 2007;30(2):165–74. [PubMed: 17347914]
8. Eng CM, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inherit Metab Dis* 2007;30(2):184–92. [PubMed: 17347915]
9. Tattersfield AE, Glassberg MK. Lymphangiomyomatosis: a national registry for a rare disease. *Am J Respir Crit Care Med* 2006;173(1):2–4. [PubMed: 16368790]
10. Hampton T. Parkinson disease registry launched. *JAMA* 2005;293(2):149. [PubMed: 15644526]
11. Berger B, et al. The prevalence of diabetes in a Swedish population of 280,411 inhabitants. A report from the Skaraborg Diabetes Registry. *Diabetes Care* 1998;21(4):546–8. [PubMed: 9571340]
12. Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. *Diabetes Care* 1999;22(5):773–8. [PubMed: 10332680]
13. Brown J, Glauber H, Nichols G. Impact on a population-based registry of changing diagnostic thresholds for diabetes. *Diabetes Care* 1998;21(8):1374–5. [PubMed: 9702458]
14. Bruno G, et al. Incidence of type 1 and type 2 diabetes in adults aged 30–49 years: the population-based registry in the province of Turin, Italy. *Diabetes Care* 2005;28(11):2613–9. [PubMed: 16249528]

15. Nielsen GL, et al. Analyses of data quality in registries concerning diabetes mellitus--a comparison between a population based hospital discharge and an insulin prescription registry. *J Med Syst* 1996;20(1):1–10. [PubMed: 8708487]
16. Palta M, et al. Longitudinal patterns of glycemic control and diabetes care from diagnosis in a population-based cohort with type 1 diabetes. The Wisconsin Diabetes Registry. *Am J Epidemiol* 1996;144(10):954–61. [PubMed: 8916506]
17. Tenconi MT, et al. [The incidence of insulin-dependent diabetes mellitus: preliminary data from an organized population registry in Pavia Province]. *Epidemiol Prev* 1991;13(48–49):149–50. [PubMed: 1843296]
18. Fishman NW, et al. New Approaches to Coronary Intervention (NACI) registry: history and methods. *Am J Cardiol* 1997;80(10A):10K–18K.
19. Deng MC, et al. Mechanical Circulatory Support Device Database of the International Society for Heart and Lung Transplantation: Third Annual Report—2005. *J Heart Lung Transplant* 2005;24:1182–1187. [PubMed: 16143231]
20. Peelen L, et al. The use of a registry database in clinical trial design: assessing the influence of entry criteria on statistical power and number of eligible patients. *Int J Med Inform* 2007;76(2–3):176–83. [PubMed: 16829179]
21. Bossi A, et al. What is the incidence of cystic fibrosis in Italy? Data from the National Registry (1988–2001). *Hum Biol* 2004;76(3):455–67. [PubMed: 15481678]
22. Viviani L, et al. [The Italian registry for cystic fibrosis: what has changed in the last decade]. *Epidemiol Prev* 2003;27(2):91–6. [PubMed: 12848021]
23. Lai HJ, Cheng Y, Farrell PM. The survival advantage of patients with cystic fibrosis diagnosed through neonatal screening: evidence from the United States Cystic Fibrosis Foundation registry data. *J Pediatr* 2005;147(3 Suppl):S57–63. [PubMed: 16202784]
24. Wang SS, et al. Early diagnosis of cystic fibrosis in the newborn period and risk of *Pseudomonas aeruginosa* acquisition in the first 10 years of life: A registry-based longitudinal study. *Pediatrics* 2001;107(2):274–9. [PubMed: 11158458]
25. Lai HC, et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. *J Pediatr* 1998;132(3 Pt 1):478–85. [PubMed: 9544905]
26. Koch C, et al. International practice patterns by age and severity of lung disease in cystic fibrosis: data from the Epidemiologic Registry of Cystic Fibrosis (ERCF). *Pediatr Pulmonol* 1997;24(2):147–54. [PubMed: 9292912]discussion 159–61.
27. Koch C, et al. Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: data from the European Epidemiologic Registry of Cystic Fibrosis. *Pediatr Pulmonol* 2001;32(5):343–50. [PubMed: 11596158]
28. Mastella G, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis. A European epidemiological study. *Epidemiologic Registry of Cystic Fibrosis. Eur Respir J* 2000;16(3):464–71. [PubMed: 11028661]
29. Melzi ML, et al. Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. *Transpl Int* 2006;19(9):726–31. [PubMed: 16918533]
30. Koch C, et al. European Epidemiologic Registry of Cystic Fibrosis (ERCF): comparison of major disease manifestations between patients with different classes of mutations. *Pediatr Pulmonol* 2001;31(1):1–12. [PubMed: 11180668]
31. McCormick J, et al. Comparative analysis of Cystic Fibrosis Registry data from the UK with USA, France and Australasia. *J Cyst Fibros* 2005;4(2):115–22. [PubMed: 15978536]
32. Singer RB. Cystic fibrosis mortality: registry data of cystic fibrosis. *J Insur Med* 1997;29(4):233–9. [PubMed: 10181162]
33. Masson S, et al. Clinical correlates of elevated plasma natriuretic peptides and Big endothelin-1 in a population of ambulatory patients with heart failure. A substudy of the Italian Network on Congestive Heart Failure (IN-CHF) registry. *IN-CHF Investigators. Ital Heart J* 2000;1(4):282–8. [PubMed: 10824729]
34. Bossi A, et al. [Italian Cystic Fibrosis Registry: 10 years of activity]. *Epidemiol Prev* 1999;23(1):5–16. [PubMed: 10356860]

35. Guilloud-Bataille M, et al. Cystic fibrosis mutations: report from the French Registry. The Clinical Centers of the CF. *Hum Hered* 2000;50(2):142–5. [PubMed: 10799974]
36. Schoni-Affolter F, et al. [Swiss registry for patients with cystic fibrosis: design, programming, implementation and first examples of use]. *Schweiz Med Wochenschr* 2000;130(39):1373–81. [PubMed: 11059028]
37. Chang SM, et al. Clinical trial participation among patients enrolled in the Glioma Outcomes Project. *Cancer* 2002;94(10):2681–7. [PubMed: 12173337]
38. Andersen MR, et al. Using a population-based cancer registry for recruitment of newly diagnosed patients with ovarian cancer. *Am J Clin Oncol* 2005;28(1):17–20. [PubMed: 15685029]
39. Martens, W., et al. Resources of NIH Registry of Myotonic Dystrophy (DM) and FSHD Patients and Family Members. 5th International Myotonic Dystrophy Consortium; 2005; Quebec City, Quebec.
40. Moon TE, et al. Design and recruitment for retinoid skin cancer prevention (SKICAP) trials. The Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomarkers Prev* 1995;4(6):661–9. [PubMed: 8547834]
41. University of Rochester Medical Center; 2007. Electronic Newsletter. National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members. <http://www.urmc.rochester.edu/nihregistry/pubs/pubs.cfm>
42. Sugarman J, et al. Ethical ramifications of alternative means of recruiting research participants from cancer registries. *Cancer* 1999;86(4):647–51. [PubMed: 10440692]
43. Beskow LM, Sandler RS, Weinberger M. Research recruitment through US central cancer registries: balancing privacy and scientific issues. *Am J Public Health* 2006;96(11):1920–6. [PubMed: 16571700]
44. Beskow LM, et al. Patient perspectives on research recruitment through cancer registries. *Cancer Causes Control* 2005;16(10):1171–5. [PubMed: 16215867]
45. Paul J, Seib R, Prescott T. The Internet and Clinical Trials: Background, Online Resources, Examples and Issues. *Journal of Medical Internet Research* 2005;7(1):e5. [PubMed: 15829477]
46. Marks RBH, Conlon M, Pepine CJ. Enhancing clinical trials on the internet: lessons from INVEST. *Clin Cardiol* 2001;24(11 Suppl):V17–V23. [PubMed: 11712772]
47. Zarin DA, et al. Issues in the Registration of Clinical Trials. *JAMA* 2007;297(19):2112–20. [PubMed: 17507347]
48. Hirsch LJ. Clinical trial registry initiative. *Bull World Health Organ* 2006;84(4):336. [PubMed: 16628313]
49. Sipkoff M. Support grows for establishing national clinical trial registry. *Manag Care* 2005;14(7):24–26.
50. Van Der Weyden MB, Ghersi D. The Australian Clinical Trial Registry. *Med J Aust* 2005;183(1):7. [PubMed: 15992328]
51. Scroccaro G, et al. Registering clinical trials. Italian clinical trial registry is kept by pharmacists on local ethical committees. *BMJ* 2000;320(7245):1340. [PubMed: 10885922]
52. Zarin DA, Keselman A. Registering a clinical trial in ClinicalTrials.gov. *Chest* 2007;131(3):909–12. [PubMed: 17303677]
53. Friebe TM, et al. Active recruitment increased enrollment in a hereditary cancer registry. *J Clin Epidemiol* 2004;57(11):1172–6. [PubMed: 15567634]
54. Phipps E, et al. Investigation of ethnic differences in willingness to enroll in a rehabilitation research registry: a study of the Northeast Cognitive Rehabilitation Research Network. *Am J Phys Med Rehabil* 2004;83(12):875–83. [PubMed: 15624565]
55. Ellington L, et al. Decision-making issues for randomized clinical trial participation among Hispanics. *Cancer Control* 2003;10(5 Suppl):84–6. [PubMed: 14581909]
56. Brown RF, et al. Promoting patient participation and shortening cancer consultations: a randomised trial. *Br J Cancer* 2001;85(9):1273–9. [PubMed: 11720460]
57. Jeffe DB, et al. Frail older women's participation in a trial of hormone replacement therapy: perceived benefits and concerns. *Menopause* 2001;8(2):127–34. [PubMed: 11256873]

Table 1
Number of Eligible[†] Contact Registrants & Study Participation Rates (%) for Selected^{††} RDCRN Studies.

Clinical Research Consortium Conducting Studies (# of studies selected, the earliest activation date among the selected studies)	Total # of Contact Registrants Eligible for Studies (% enrolled in selected studies)	Within 200 miles of a clinical site		Within 100 miles of a clinical site	
		Total # of Contact Registrants Eligible for Studies (% enrolled in selected studies)		Total # of Contact Registrants Eligible for Studies (% enrolled in selected studies)	
Angelman, Rett, & Prader-Willi (3, 2/23/2006)	648 (15%)	213 (20%)		98 (29%)	
Bone Marrow Failures (1, 4/3/2006)	282 (7%)	96 (13%)		46 (17%)	
Genetic Diseases of Mucociliary Clearance (2, 5/5/2006)	315 (27%)	52 (42%)		32 (28%)	
Urea Cycle Disorders (1, 2/24/2006)	207 (27%)	97 (37%)		68 (43%)	
Vasculitis (5, 4/17/2006)	1325 (6%)	482 (8%)		229 (12%)	
All sampled studies (12, 2/23/2006)	2777 (12%)	940 (16%)		473 (21%)	

[†] Eligibility for study was determined by matching reported disease and demographics (age and gender) reported in Contact Registry to relevant protocol eligibility requirements.

^{††} Study was selected when the eligibility can be determined from the information reported in Contact Registry.

Table 2
Number of Eligible[†] Contact Registrants & Study Participation Rates (%) for Contact Registrants Who Live Within 100 miles of a Study Site – By Source of Referral to Contact Registry.

Clinical Research Consortium Conducting Studies (# of studies selected, the earliest activation date among the selected studies)	Total # of Eligible Contact Registrants within 100 miles of study site (% enrolled in selected studies)	Referral Source		
		Internet	Support Group or Foundation	Medical Professional Other
Angelman, Rett, & Prader-Willi (3, 2/23/2006)	98(29%)	37(24%)	37(30%)	16(44%) 8(13%)
Bone Marrow Failures (1, 4/3/2006)	46(17%)	23(9%)	10(10%)	11(46%) 2(0%)
Genetic Diseases of Mucociliary Clearance (2, 5/5/2006)	32(28%)	6(17%)	13(23%)	10(50%) 3(0%)
Urea Cycle Disorders (1, 2/24/2006)	68(43%)	6(0%)	17(41%)	38(55%) 7(14%)
Vasculitis (5, 4/17/2006)	229(12%)	79(3%)	96(8%)	31(48%) 23(9%)
All sampled studies (12, 2/23/2006)	473(21%)	151(9%)	173(17%)	106(50%) 43(9%)

[†] Eligibility for study was determined by matching reported disease and demographics (age and gender) reported in Contact Registry to relevant protocol eligibility requirements.