CYSTIC FIBROSIS FOUNDATION THERAPEUTICS

The TDN Times

A Publication for Members and Associates of the Cystic Fibrosis Therapeutics Development Network

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A Note from the Editor

Dr. George Retsch-Bogart

Happy New Year to everyone…

The beginning of the year is traditionally a time of high expectations, resolutions, starting over, and hoping to do better. Our sense of success or disappointment depends on the expectations we set for ourselves in the year to come. The issue of expectations confronts us once again as we prepare to receive the results of the two large phase 3 corrector and potentiator trials combining lumacaftor and ivacaftor. Expectations and enthusiasm are high on the part of the CF community, as reflected by the rapid enrollment for both studies. However, given the stunning results of the ivacaftor (Kalydeco) trials in patients with the G551D mutation two years ago, expectations for subsequent CFTR modulator studies may be unrealistically high. The recent report on results of ivacaftor for patients with R117H mutation showed promising results, but did not reach its primary endpoint. How do we go about putting these results into perspective for our patients, their families, our clinical care teams (and frankly, for ourselves) as we anticipate the next wave of outcomes from CFTR modulator trials?

One strategy would be to step back and appreciate the larger context of these individual trials, something difficult to do while we are immersed in the minute details of clinical research or clinical care. The phase 3 trials of combined ivacaftor and VX-809 treatment, TRAFFIC and TRANSPORT, are part of a larger plan. If the results are positive, that would be wonderful, but it is still just one step along the way of a longer-term plan to develop a regimen with even greater effectiveness. If the results are intermediate or not successful, we need to remember that other corrector drugs, such as VX 661 and second generation agents, are also being tested. At the last two North American CF Conferences, we heard in the plenary sessions just how complex the problem of effective correction was going to be for F508del mutation. We all know that a fair percentage of trials and drug development programs do not progress to new approved medications. However, it is much more difficult to accept this when it occurs with drugs that we hope could benefit the vast majority of our patients. For that reason, developing reasonable expectations will be more difficult but all the more important.

In this Issue

TDN Expands for 2014

The TDN welcomes Memphis, TN, Worcester, MA, and Portland, OR as new Therapeutics Development Centers (TDCs) for the 2014 award year (Jan 1, 2014 to Dec 31, 2014). The CFFT funded these three additional sites to meet the increasing need for research participants within the network, bringing us back to a total of 77 centers.

CFFT invited TDC applications from accredited CF care centers that were not funded in the last award cycle. Site awards were determined based on the same criteria used for existing TDN sites, with the major factors being center size, enrollment in CFFT sanctioned studies over the last two years, and research program leadership.

- Amy Hoffman

Integrating clinical research into clinical care is efficient and enhances a culture of research, but must be done carefully. Patients and families may get confused about what is being done for clinical care versus what is part of the research. A research study visit could be considered a clinic visit by them or inadvertently delay their return for a regular CF clinic visit. The RC Perspective in this issue (page 9), written by Thomas Matthews from Lurie Children's Hospital of Chicago, explores the ways clinical research and clinical care can be integrated without detracting from the vital importance that each plays to patients with CF and care centers.

Clinical care drives many of the questions addressed in the clinical research we undertake, regardless of whether these are observational studies designed to understand modifiable risks, interventional studies structured to test the effectiveness of new drugs or combinations

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Note from the Editor, cont.

of approved therapies, or the assessment of biomarkers or novel outcome measures. As clinicians we are constantly assessing how our patients perceive their own health, symptoms and well-being. Patient-reported outcomes or PROs have recently become part of many clinical trials and reflect the patient's experience of health and symptoms. Chris Goss, Margaret Rosenfeld, Donald Patrick and Todd Edwards provide a review and perspective on the development and role of PROs in CF for us in this issue (page 4). They highlight the development of different tools and the process of validating these unique measures, while demystifying some of the language which is often used in this process.

We have many examples of how a mature culture of research can be a critical component of successful TDCs. The creative ways that a site can develop awareness and focus on the importance that research plays for their patient population can be enhanced by a variety of tools. Many "I am the Key" materials, which are very effective and have been widely used and distributed, are now available in Spanish (see page 10). A book written and developed specifically to explain participation in clinical research to children is also now available. Emma Green (see page 11) was written by this year's Judy Williams Award winner, (see page 8) Zoe Davies. This story can help engage young patients who have never participated in clinical research and reflect Zoe's creativity and experience with children in the research setting.

I highly recommend reading the site spotlight by the team from Grand Rapids (page 12). In addition to their obvious enthusiasm for research, this group describes an effective model for research coordinator support and the integration of clinical research activities within a well-organized institutional program. It's a model that is efficient in adjusting to increases and decreases in study activity and demands on research coordinator time, something we have struggled with as a network over the past few years as our number of studies and demand for enrollment has fluctuated.

Despite the excitement about breakthrough therapies, one of the problems we may confront is the unintentional failure to adequately enroll some key studies given the high workload of TDN sites and the apparent preference of potential study subjects to select CFTR modulator studies over other trials. This situation may have multiple adverse effects. The availability of important new antimicrobial formulations may be eliminated, because studies essential to drug development may end before reaching target enrollment. The option of using continuous alternating inhaled antibiotic therapy with FDA approved agents may not be reimbursed by insurance companies due to lack of efficacy data from controlled trials. Biotech companies may think twice about drug development work in CF if key phase 2 or phase 3 studies cannot be completed. To prevent such serious adverse effects on CF clinical research, we must find ways to address these issues. It is important for all of us to be aware of the forces which influence our choice of studies as participating TDC sites, and the factors which guide our patients and families in deciding which studies to participate in. These topics are being actively discussed by the TDN Steering and Clinical Research Executive Committees. We will be soliciting ideas from all sites as we search for solutions together in this new year.

-George Retsch-Bogart, MD

CYSTIC FIBROSIS FOUNDATION

Foundation Focus: Identifying Strategies for a Bright Future

Preston Campbell, MD; Cindy George, FNP, MSN; and Bruce Marshall, MD

Last year the CF Foundation completed the most comprehensive strategic planning initiative in its history. Under the guidance of an outside consultant, a representative group from the Foundation and the CF community met to extensively examine the current state of the organization and envision a future in which the Foundation will further advance science and tackle new challenges stemming from a dynamic health care environment. The result is a new five-year Strategic Plan.

One of five specific strategies identified through this intensive effort is to continue to support and grow our pipeline of innovative therapies that modulate CFTR and treat various manifestations of CF. Based on input from a team including Garry Cutting, MD (Johns Hopkins University), Philip Thomas, PhD (University of Texas Southwestern Medical School), and CFF scientific leadership, this aspect of the new plan centers on enriching the therapeutics pipeline with a special focus upon identifying means of restoring CFTR function in those patients with rare CFTR mutations.

Our future research focus will not be limited to CFTR-directed therapies, however. We will also continue to support the development of exciting therapies to target disease manifestations of CF. The team's recommendations were far-reaching -- from understanding how different CFTR mutations are affected by existing CFTR modulators to exploring the potential of innovative new technologies that can alter a cell's genomic DNA. We expect to convene several workshops and issue requests for applications over the next several years that will seek to solve practical issues related to therapeutics development. Likewise we anticipate that tools developed to understand individual CFTR mutations will be beneficial to many labs.

We are excited about these new drug discovery opportunities which will take us into the future and lead to 100% of people with CF being treated with CFTR modulation therapy. Other initiatives identified through the strategic planning process include advocacy, quality of care, fundraising, communication and adherence, all of which will get underway in the coming months.

We thank those of you who participated in this planning initiative and look forward to working with more of you as these programs develop. Our collective and collaborative work as a community has resulted in better therapies for people with cystic fibrosis. This will continue to be the cornerstone by which further progress will be made in the future.

Annual Site Calls to Start Soon

Site calls for 2014 will begin in March.

These annual 30-minute calls are an important means of communication between the TDN Coordinating Center-CF Foundation team and each TDN site. They provide an opportunity for sites to meet new TDNCC and CFF staff, share information, review available resources, and discuss concerns. This dialogue permits a richer understanding of each site's successes and challenges, and continues to be an excellent way for the operations team to identify issues occurring across the network.

It typically takes 2-3 months to complete all the site calls, and Leila Atry will be in touch with the primary research coordinator at each site about scheduling. Please respond promptly to her email to help us complete all site calls in a timely fashion.

Participating on the calls this year will be Cindy George and Christina Román (see page 10) from CFF and Jean Kirihara, Leila Atry and Amy Hoffman (see page 15) from the TDNCC. Site calls are an opportunity for this group to get to know your team better, so please ensure that all TDN research coordinators are present on the call. We encourage PIs and all interested clinical research team members at your site to participate as well.

Last year we made the calls more interactive by asking your team to prepare a few questions for discussion in advance. Thanks to all of you who submitted questions; it helped us to prepare and hopefully address your concerns more effectively.

We look forward to catching up with you soon!

-Jean Kirihara

In the Works: Upcoming Studies

Several new industry studies were reviewed by the PRC in the last quarter of 2013.

First, Novartis submitted two protocols for Phase 4 studies of tobramycin inhalation powder (TIP): 1) the "human factors study," designed to confirm that the instructions associated with use of the TOBI® Podhaler® are adequate; and 2) a 6-month study comparing once daily continuous use of TIP vs. TIP administered twice daily over three cycles of 28-days on/28-days off.

Second, Pharmaxis submitted another six month, double-blind, placebo-controlled Phase 3 study of dry powder mannitol for inhalation.

Third, Vertex submitted a protocol for a Phase 2 study of VX-661 given in combination with ivacaftor to CF patients homozygous for F508-del CFTR mutation.

As always, we appreciate all of your hard work to meet the demands of multiple sponsors!

- Jill Van Dalfsen

Strategies to Improve Network Relationship with Sponsors

During the TDN Meeting (see pg 15) and several of the RC sessions at NACFC (see pg 14), we heard about some of the recent challenges sites are facing, many of them related to our relationships with study sponsors. In order to alleviate some of the burden, the Steering Committee has prioritized the concerns and requested that the TDNCC implement the plan described below.

Challenge	TDN Strategy
Some sponsors are not providing source document templates.	The TDNCC has developed guidance for sponsors related to providing source document templates. When new studies are reviewed by the Protocol Review Committee, sponsors will be notified of our recommendation to provide source document templates. If the sponsor chooses not to provide these templates, the TDNCC will coordinate their development with help from a few lead sites. Site representatives will be compensated for their time by the sponsor.
Budget negotiations have been difficult and often there is no reimbursement for development of source document templates and/or monitoring visits.	Specific line items have been added to the Site Budget Tool for costs associated with source document template development and monitoring visits. Sponsors will be encouraged to use the TDNCC budget template for future studies.
Communications with some sponsors has been difficult; for example, identifying the appropriate contact person, timelines of responses to inquiries, and redundancy of email communications.	The TDNCC is developing guidance for sponsors on providing streamlined communications to TDN sites. Sponsors will be encouraged to identify the person(s) who have decision-making authority whether at the CRO or the sponsor organization itself.
Study monitors hired by sponsors and CROs could use some additional training in cystic fibrosis.	The TDNCC is developing a training program for monitors with CF-specific information relevant to clinical research. This will be offered to sponsors/CROs within the next year.
Sites would be able to plan ahead better if they knew what studies were going to start up in the next 6-12 month time frame.	The TDNCC will communicate more regularly with sponsors to determine pipeline plans and distribute that information to sites as available. Information about upcoming studies will continue to be available on the Studies page of CF ClinicalResearchNet, in the TDN Times, and on bi-annual TDN PI calls.

- Amy Hoffman

Continued Advancements in Patient- and Observer-Reported Outcomes for Cystic Fibrosis

Christopher H. Goss, MD, MSc; Donald L. Patrick PhD, MSPH; Todd C. Edwards, PhD; and Margaret Rosenfeld, MD MPH; University of Washington

Dr. Chris Goss

Over the past 20 years, tremendous progress has been made in defining and measuring patient-reported outcomes (PROs), with growing recognition of their importance in health outcomes research[1]. The Food and Drug Administration (FDA) defines a PRO as a "report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"[2]. Such reports may include observable events, behaviors or feelings (e.g., walking slowly; lack of appetite; expressions of anger) or unobservable outcomes that are known only to the patient (e.g., sensations of pain; feelings of depression).

PROs are useful for measuring treatment benefit or risk in clinical trials because they are the chief method for assessing how the *patient* perceives his or her feelings and functional status. PROs can provide additional key data in conjunction with more commonly employed physiologic endpoints such as FEV_1 or pulmonary exacerbation.

In order to utilize a PRO as a primary or secondary endpoint in a clinical trial, it must first meet rigorous psychometric criteria for reliability and validity. Efforts to develop PROs that meet these criteria have been very successful, resulting in the availability of numerous well-validated instruments and a growing base of evidence supporting the use of PROs. The FDA formally recognized the importance and clinical utility of PROs in 2009 with publication of its Guidance for Industry on PROs 2, which describes considerations for their development and usage.

The CF community anticipated this innovation and has been working on PROs for many years, beginning with an initiative by the Cystic Fibrosis Foundation in the late 1990's. At that time, CFF began supporting the work of Dr. Alexandra Quittner to develop an English translation of a CF-specific quality of life instrument originally developed in France (the Cystic Fibrosis Questionnaire), renamed the Cystic Fibrosis Questionnaire - Revised (CFQ-R).

Given the major role that the CF community has played in testing PROs in several large clinical trials over the last two decades, a review of these concepts and what new developments are underway seems appropriate.

FDA Guidelines for PROs

The FDA accepts adequately developed PRO measures as primary or secondary endpoints in clinical trials if they are appropriate for the disease, product and indication. The FDA Guidance outlines a number of criteria that should be considered in evaluating and validating a PRO instrument for use as a clinical efficacy endpoint in a clinical trial. These criteria include:

- The **characteristics** of the instrument, including selection of relevant symptoms ("concepts of interest") that should be assessed for the particular disease and product being tested
- The **conceptual framework** – the relationship between the questionnaire or items in the PRO instrument and the concepts being measured, including how they are grouped into domains or categories
- The **content validity** – whether it measures what it purports to measure

Establishing content validity for a PRO instrument includes assessment of not only what items are included, but also the data collection method (e.g., paper vs. electronic), mode of administration (interview vs. self-administered), instructions, document formatting, type and structure of response options, recall period required, patient understanding, respondent and administrator burden, and scoring methodology. Typically numerical scores are assigned to each answer category based on the most appropriate scale of measurement for the item.

The initial content validation of an instrument is followed by further tests of its reliability, construct validity, ability to detect change following an intervention or change in the condition, and finally, guidelines for interpretability. These concepts are further described in Table 1 and the text below. The FDA expects all aspects of testing the instrument to be completed using well-established psychometric methods.

Property	Test	What is Assessed
Reliability	Internal Consistency	Whether the questions grouped together in a domain statistically measure a similar symptom (e.g., coefficient alpha)
	Test-retest	Responses to questions don't change over short time intervals when no change occurred in the patient
	Inter-rater Reliability	Agreement between two or more different raters or interviewers
Construct Validity	Content or Face Validity	Extent to which items and response options are relevant and measure the emotions or symptoms of interest
	Convergent and Divergent Validity	Responses to a new questionnaire are similar to those from other related questionnaires or measures
	Discriminant Validity	Questionnaire results differentiate patients who differ by disease severity, age, gender, race, ethnicity, etc.
	Predictive Validity	Questionnaire results predict changes in health status or other relevant variables
Ability to Detect Change	Calculations of effects size and standard error of measurement, among others	Ability of a questionnaire to detect a change in predicted direction when the patient's condition changes or no change when patient is stable.
Interpretability	Minimal Clinically Important Difference (MCID) or the Minimum Important Difference (MID)	Smallest difference that can be reliably detected by patients and has clinical meaning.

Table 1: Evaluating psychometric properties of PRO instruments[3]

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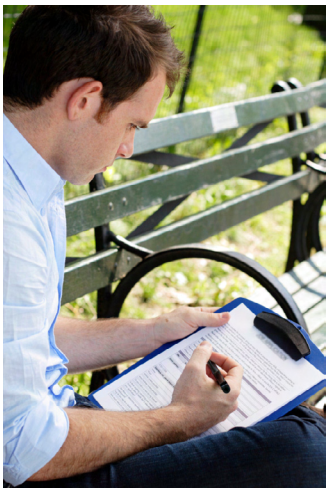
Patient- and Observer-Reported Outcomes, cont.

Interpretation of PROs

Beyond confirming an instrument's ability to detect change, it is also important to quantify how much change in a numeric score is clinically meaningful. This facilitates interpretation of the scores. This change has been referred to as the "minimal clinically important difference" (MCID) or "minimally important difference" (MID) score. For example, the CFQ-R has an estimated MID for acute pulmonary exacerbation of 8 points and for the treatment of chronic airways infection of 4 points (both on a 100 point scale)[4].

While MCID and MID are important concepts in interpreting PROs, the FDA has focused on another concept, the a priori development of a responder definition[1] – determining at the onset of a clinical trial what PRO score change for an individual patient over a pre-determined time period should be interpreted as a treatment benefit. For example, a 50% reduction in the number of incontinence events noted in a diary might be used to define a responder on a PRO instrument that assesses annoyance of incontinence. Responder definitions can also be based on the patient's overall assessment of health state (global ratings of change), as was done for the CFQ-R, or how much change in a score one might see naturally without a change in treatment. The responder definition continues to be one of the most challenging aspects of interpretation of a PRO.



HRQOL Instruments for CF

The most validated PRO instruments in CF research are those that measure health-related quality of life (HRQOL). The body of literature regarding HRQOL has increased dramatically in the last 20 years in CF research. To date, two different disease-specific HRQOL instruments have been developed specifically for CF, the CFQ-R developed by Dr. Quittner and the Cystic Fibrosis Quality of Life (CFQoL) questionnaire developed by Dr. Gee in the U.K. Both of these are considered valid instruments with demonstrated reliability, internal validity, and sensitivity; however, the CFQ-R has become the most widely employed PRO in CF. The CFQ-R (specifically the respiratory domain) is the only PRO to date that has been used as a co-primary and a key secondary endpoint in a phase 3 therapeutic trial program in CF. Studies employing the CFQ-R include randomized placebo controlled studies of hypertonic saline, macrolides, growth hormone, inhaled antibiotics, and novel therapies which correct the basic defect.

Symptom-Specific Measurement

To date, PRO instruments for CF that focus on specific sets of symptoms have had a more limited development. Symptom measurement has been confined to disease-specific quality of life instruments that have symptom domains — a subset of questions that can be used to derive a symptom sub-score. For example, in addition to nine quality of life domains and an overall health perception scale, the CFQ-R includes three symptom scales, one of which focuses on respiratory symptoms.[5] This symptom scale, however, was not developed to assess acute change in respiratory symptoms, but rather changes in symptoms over the past 2 weeks. Also, it is not employed in isolation — the subject has to complete the whole instrument (which includes 50 questions for the CFQ-R) because all of the validation data is based on use of the whole instrument.

More recently, an additional PRO, the CF Respiratory Symptom Diary (CFRSD), has been developed by a team at the University of Washington in order to provide a symptom measure for CF patients that has limited questions and can be used daily if needed[6]. The CFRSD is a multi-module diary that includes questions about respiratory symptoms and their impact. It is designed to be completed at the same time every day.

A study by Quon and colleagues showed that symptoms captured in the CFRSD had the expected correlation with activity levels measured by the daily use of pedometers[6]. Field testing of the CFRSD by Bennett and colleagues demonstrated that the mean score for CF respiratory symptoms captured through daily recall differed only slightly from scores for those same symptoms captured with weekly recall[7]. However, it is clear that daily recall is more likely to capture acute changes in clinical status.

Nested within the CFRSD is the CFRSD Chronic Respiratory Infection Symptom Score (CFRSD-CRISS). While this is similar to the respiratory domain score in the CFQ-R, the overall CFRSD can be completed in less than five minutes, much more quickly than the CFQ-R. The CFRSD-CRISS contains eight items: difficulty breathing, cough, cough up mucus, chest tightness, wheeze, feeling feverish, tired, and chills/sweats. Total scores provide a one-dimensional measure that quantifies symptom severity for the previous 24 hours across these eight symptoms. Total score ranges from 0 to 100, with a higher score indicating greater severity in symptoms. The CFRSD-CRISS can capture the magnitude of respiratory symptoms in patients with stable CF, during medically treated CF exacerbations, and during recovery from an exacerbation.

Data supporting validation of the CFRSD-CRISS instrument are now available from a pooled sample of five CF clinical trials that employed the instrument[9]. This instrument, because of its ease of use, may have increasing applications both in clinical trials and clinical care.

ObsROs in CF

Another category of increasing importance is the observer-reported outcome (ObsRO). In these instruments, an observer (commonly a parent of a child in pediatric conditions) reports on observable events and behaviors that the patient experiences. Thus, although PROs and ObsROs may overlap, there are differences in who reports and in the composition, design, purpose and age groups that are targeted by the instrument.

Currently, clinical trial endpoints in infants and young children with CF are largely surrogate endpoints such as growth, lung function, and respiratory microbiology. Many children in this age range are too young to report for themselves in a valid and reliable manner on a range of outcomes, so an observer-reported outcome (ObsRO) may be an appropriate alternative to a PRO. Acknowledging that young children may not reliably report their own symptoms, the FDA recommends that parent report of signs may substitute for and/or augment child report of symptoms in this young age range [2]. Signs are patient phenomena that can be observed by another individual such as a caregiver (parent) or health care provider (e.g., infant behavior thought to be caused by pain), whereas symptoms are those patient-reported phenomena that can not necessarily observed by anyone other than the patient (e.g., actual infant pain intensity).

Few ObsROs have been developed and published in any chronic disease in early childhood[10] and, to our knowledge, no validated ObsRO specific to CF exists. Such measures are essential for clinical outcome assessment and trial endpoints

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PROs and ObsROs, cont.

that assess direct treatment benefit to the child as observed by their parents.

A team at Seattle Children's Hospital has recently developed two draft CF-specific ObsROs, one for ages 0-6 ($CFRSD_{0-6}$) and one for ages 7-11 ($CFRSD_{7-11}$), and are currently conducting field testing in order to evaluate their measurement properties. Each instrument contains 15 items reflecting signs of a pulmonary exacerbation and takes less than two minutes to complete. This team's overarching goal is to ensure that a series of seamless CF-specific, age-appropriate, parent-reported and patient-reported outcome measures is available for CF clinical trials across the entire age spectrum.

Conclusions

The use of PROs in clinical trials has increased dramatically over the past decade, and with the publication of the FDA Guidelines on Patient-Reported Outcomes, this trend is likely to continue. If adequately developed and validated, PROs can be used as either primary or secondary outcomes in clinical trials to evaluate the benefits of new treatments or compare the efficacy of existing treatments from the patient's perspective. CF-specific PROs are now well-accepted end-points for clinical trials in CF patients and we look forward to a time when there are age-appropriate instruments available across the life span.

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MARK YOUR CALENDARS
for the bi-annual TDN PI Calls

Friday, March 7,
1-2 pm EST / 10-11 am PST

Monday, March 10
3-4 pm EST / 12-1 pm PST

All TDN PIs should plan to attend one of these two identical calls. Dial-in information will be emailed and posted on CF ClinicalResearchNet.

Have You Worked on Your Assignment?

At last October's TDN meeting (see article page 15), Wayne Pines, crisis management consultant, spoke about the importance of being prepared for an unanticipated crisis in a clinical trial. He emphasized that above all else, preparation is critical to managing negative situations well. Prominent real-world news stories regarding past deaths in clinical trials served as reminders of the impact these unfortunate events can have on principal investigators clinical research programs, institutions and the public trust.

The audience was charged with an assignment upon returning home from the October meeting: Meet with people in your institution and create a clinical trial crisis communication plan. Have YOU set aside time as a team to work on this action item? The start of a new year is a great time to begin new projects or resolve to complete ones that may have been in the "to do" stack.

"The public forgives a mistake…but does not forgive how that mistake is handled."

Partnering with your institution's IRB and Communications/Media Relations departments is essential in the development and implementation of a comprehensive crisis management strategy. Preparation includes knowing whom to call and when, developing template materials, and receiving training on how to respond to the media. At the TDN Meeting, PIs Karen McCoy and Ron Rubenstein attested to the value of having established relationships with other key institutional departments based on their experiences with research-related crises. While speaking with reporters may not be foremost in our minds when devising a plan, PIs may be called upon to do just that. J.P. Clancy and Jim Chmiel illustrated this point in the October presentation as Mr. Pines stepped us through the do's and don'ts when speaking with the media. Equally important in times of crisis are comments made by other site investigators, who should remember to avoid criticizing others when speaking about the situation as their statements could add further harm.

While a majority of the audience agreed that being prepared for a potential crisis is important, few sites acknowledged actually being prepared. Colleen Dunn, RC at Stanford, highlighted the process that their CF team went through to create and implement their plan, the Stanford Unanticipated Problem Communication Strategy. Documents from the Stanford plan, as well as the CFFT Crisis Communication Plan and related templates, were reviewed by Chris Goss during the meeting and are posted in the Crisis Communications library, located in the Clinical Research Toolbox on CF ClinicalResearchNet. These materials can be customized to suit your center's needs and institutional requirements.

Please take the time to learn the basics and to put into place the processes you and your institution need. Information about a life-threatening event or death related to a CF clinical trial study drug or procedure could spiral out of control if not managed well, potentially jeopardizing current and future research endeavors. Mr. Pines advised us that "The public forgives a mistake…but does not forgive how that mistake is handled." We only have one chance to do it right.

- Cindy George

CFCRNet Upgraded; Alert Reset Required

Have you noticed anything different about CF ClinicalResearchNet lately? In mid-January, the TDN upgraded its version of Microsoft SharePoint, the platform being used to run CFCRNet. This change will improve our ability to maintain and develop CFCRNet in the future.

At this point, most users should only see minor differences, if any, between the old website and the new one. Additional updates planned for the coming months, however, may include more obvious changes to the website's visual style and user interface. For example, you may see some new colors, a new logo, and the addition of a tool "ribbon" at the top of the page like that used in newer versions of Microsoft Office applications. More information on these changes and instruction for users will be provided in the future as needed.

One unfortunate consequence of the upgrade process was the loss of previous alert settings. Alerts allow you to receive an email notification when there are changes to a specific section of CFCRNet (e.g., the Site Tools library, Announcements, etc.), and can be very useful for keeping up with all the new information and tools being posted to the website. CFCRNet users will need to sign up again for any alerts they would like to receive. See instructions at right.

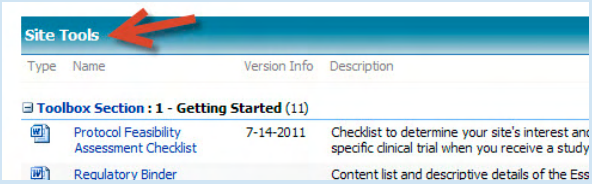
Access to CF ClinicalResearchNet has not changed, but if you experience any difficulties logging on or using the website please contact Leila Atry at Leila.atry@seattlechildrens.org.

Feedback on content or usability of CFCRNet is always welcome, and should be sent to natalie.beauchene@seattlechildrens.org.

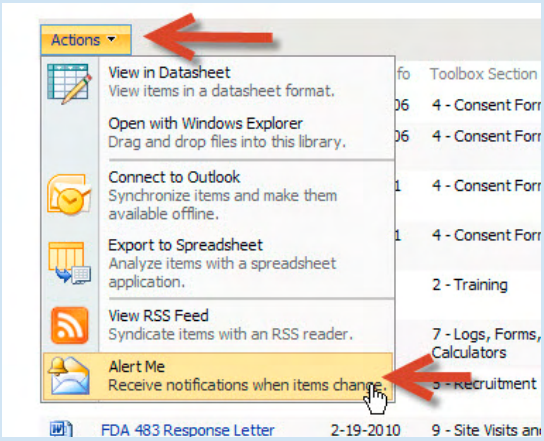
- Natalie Beauchene

How to Sign Up for Alerts on CF ClinicalResearchNet

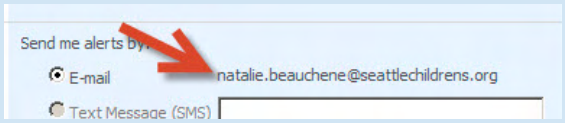
1) Click the name in the blue header for a library or list you want to receive alerts on.



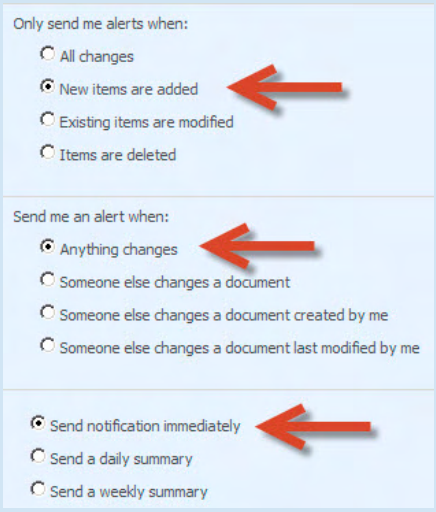
2) Click the arrow next to Actions and choose "Alert Me" from the dropdown menu.



3) On the setup page, first verify that your email address is correct (and please notify Leila Atry if it is not).



4) Choose your desired configuration options, then click OK. Settings shown at right are recommended for most users.



5) You should receive a confirmation email that you have successfully set up an alert for the selected section of CFCRNet.

6) Repeat the above steps for additional libraries or lists as desired.

Reminder: ABP Certification Credit Available for QI Projects

Need some extra incentive for embarking on a research quality improvement project with eQUIP-CR? How about Maintenance of Certification (MOC) Part 4 credit for pediatricians from the American Board of Pediatrics?

All projects requesting MOC credits for 2014 will need to obtain approval through CFF **before** beginning the project. First create a plan for a specific improvement project as shown in the sample table on page 2 of the eQUIP-CR document, "Engaging the Team in Goal Setting." Your project plan should include a specific goal, proposed actions to achieve the goal, a timeline, and a measurement plan. Email your completed plan to Christina Roman at croman@cff.org for initial approval.

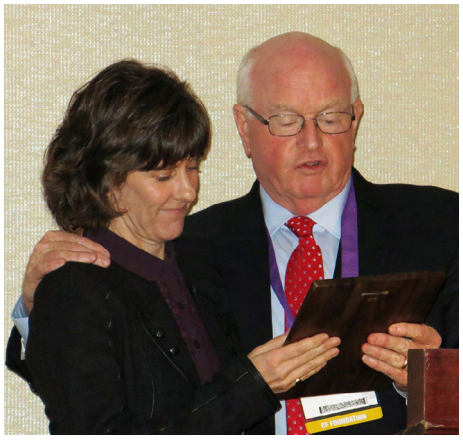
To qualify, the pediatrician requesting MOC credit must have an active role in the project over an appropriate period of time. For more information, see the recently updated document, Maintenance of Certification Process for eQUIP-CR, available on the Learn page of the eQUIP-CR section on CF ClinicalResearchNet.

- Christina Román

Davies Honored with Judy Williams Award

The CF Foundation is proud to congratulate Zoe Davies, recipient of the 7th annual Judy Williams Award for Research Coordination Excellence. Davies' passion, creativity, and dedication to all aspects of cystic fibrosis research have made her an invaluable asset to her patients, her institution, and the CF research community. She was presented with the award by Dr. Bob Beall in October at the RC Reception at the 2013 North American CF Conference.

Davies works at the Lucile Packard Children's Hospital at Stanford, where she has served as a CF research coordinator for 18 years. Her site was among the first TDN centers, and Davies has played an integral role in its success. She was one of the first NPD operators during early gene therapy trials and has become an expert in developing nasal potential difference capabilties at her center.



Davies had contributed greatly to the cystic fibrosis community by sharing her knowledge, experience, and creativity. She has contributed to a national clinical research best practice document, written articles in professional journals, presented at U.S. and international scientific meetings, and served for five years as a mentor in the CF Foundation's RC mentoring program.

Lower left: CF Foundation CEO Dr. Bob Beall presents the Judy Williams Award to Zoe Davies. Above: Davies (seated, holding plaque) with colleagues from the Stanford CF team.

Davies is described by her colleagues as passionate about CF clinical research. "She is wonderful with patients and uses the research visit as an opportunity to enhance a patient's knowledge of CF," says Colleen Dunn. "She is forever pulling a piece of paper towel and drawing a cartoon of an airway cell to help patients understand complex mechanisms of action of the drug we're studying."

Davies' creativity in reaching patients was shown most recently through her authorship of the story, "Emma Green: Science Superstar." (See related article, page 11).

Read more about Davies in her profile on the Judy Williams award page on CF ClinicalResearchNet.

- Christina Román

Welcome New TDN Committee Members and Steering Committee Chair

As we bring in the New Year, we have some important committee changes to announce! You probably recall that committee membership undergoes a partial rotation every January (affecting approximately one-third of the membership), while committee chairs rotate every two years.

In August 2013, a call for nominations was sent out to TDN members for the planned committee rotation. Over 20 nominations were received for the TDN Publications and Presentations and Protocol Review Committees. Most of the nominees were accepted and the new members (listed below) were invited to attend their respective committee meetings at NACFC 2013.

This month is also the time for a transition in leadership of the TDN Steering Committee. Dr. Joseph Pilewski (Pittsburgh) has served as the chair of the TDN Steering Committee since 2011 and has been instrumental in guiding network operations over the last two years. While we are sad to see him step down, we are also excited to welcome the new chair, Dr. Mike Boyle (Baltimore), who has served as vice chair for the last year.

Dr. Mike Boyle

Please join us in saying thank you to our outgoing committee members and leaders for all their hard work and in welcoming the incoming teams. We're looking forward to another great and productive year from the TDN committees!

New Publications and Presentations Committee Members

Daniel Dorgan – Philadelphia, PA
Steve Strausbaugh – Cleveland, OH

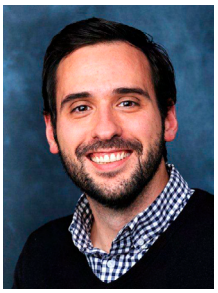
New Protocol Review Committee Members

Dawn Baker – Gainesville, FL
Tara Barto – Houston, TX
Ariel Berlinski – Little Rock, AR
Isolde Brazil – Austin, TX
Catherine Correia – Boston, MA
John Columbo – Omaha, NE
Daniel Dorgan – Philadelphia, PA
Bob Fink – Dayton, OH
Susie Millard – Grand Rapids, MI
Isabel Neuringer – Boston, MA
Kim Spoonhower – Cleveland, OH
Denis Stacklie – Minneapolis, MI
Steve Strausbaugh – Cleveland, OH
Mary Teresi – Iowa City, IA
Seth Walker – Atlanta, GA
Dave Weaver – Cleveland, OH

- Lisya Van Housen

RC Perspective: Effective Integration of Clinical Care and Clinical Research Benefits Everyone

Thomas Matthews, MPH, RRT, Lurie Children's Hospital, Chicago, IL



Thomas Matthews

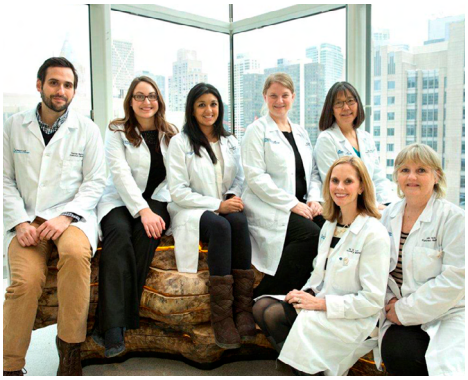
At Ann & Robert H. Lurie Children's Hospital of Chicago, our seven-member cystic fibrosis clinical research team is an integral component of the multidisciplinary care team. The research team comes from various backgrounds, both clinical and non-clinical, some with experience in CF and some without. Although our main responsibility is to facilitate safe and effective research for our patients, we understand that superior clinical care comes first, so we attempt to integrate research in a way that is both accessible and convenient for our patients.

Whether our research studies are clinic-embedded observational studies or interventional clinical trials, we do our best to blend them seamlessly within the greater clinical program. For example, understanding that clinical procedures such as blood draws can be traumatic for the pediatric population, we attempt to combine any routine clinical blood work with research blood draws whenever possible. This decreases the number of pokes our patients endure while saving them time travelling to and from our center.

Communication and Scheduling Coordination are Key

Continual communication between the research team, nurses, nurse practitioners, and physicians helps us plan in advance and is key to our current process. Every Monday or Tuesday, our center coordinator, Eileen Potter, emails our research staff the next week's schedule for both upcoming clinic visits and research appointments that have been made separately in our Clinical Research Center. This allows us to screen the charts and identify any patients coming in for clinic who may be eligible for upcoming studies. It also gives us ample time to plan any research activities that need to take place within the clinical visit, and to look for ways to streamline on both sides. For example, if a blood draw is involved in an upcoming research visit, the RCs can reach out to the nurse and physician to see if the patient needs any clinical labs that could be done at the same time.

On Thursday mornings, our entire multidisciplinary team (providers, nurses, research coordinators, social workers, dieticians, respiratory therapists, PFT technicians, chaplains, and child life specialists) meets to review the current inpatients, upcoming clinics, and research appointments. This gives us an opportunity to make sure all clinical needs are being met and further streamline where we can. For example, if a patient who is usually seen at a satellite location is coming to the main hospital for a study visit, we review their record to see if can take advantage of that visit to complete annual CF-related health maintenance procedures like glucose tolerance tests or exercise tests.



Members of the Lurie Children's pulmonary research team. Top row, L-R: Thomas Matthews, Ashley Covell, Noopur Singh, Eriika Etshokin, Eileen Potter. Bottom row: Amy Lobner, Julie Nufer. (Photo by Jan Terry).

This model works well for us on many levels. Having our research team work in conjunction with the clinical team promotes a culture of research and allows the research program to have a "face" within the CF center. Ensuring that the clinical team knows which research procedures need to take place within a visit not only helps us facilitate those activities, it also creates a greater level of respect for everyone's specific role on the team. Families also appreciate this integration because it allows them to participate in important research activities in a way that best utilizes their time during appointments.

Interventional Trial Participation May Impact Attitude Toward Clinical Care

Although our process works well for clinic-embedded, post-marketing, and other types of observational studies, some aspects of balancing clinical trial visits with clinical care are still a work in progress. For example, several of our patients are involved in interventional clinical trials which require them to come to campus much more often than they usually do for their regular CF care. This translates to more days away from work or school, as well as sometimes longer and more stressful commutes to our center for many patients. These patients and families are actually seeing a physician more often and having more frequent clinical and laboratory assessments, which is a good thing in many ways. However, we find that because of this, many clinical trial participants downplay or forget the importance of regular quarterly CF clinical visits during the time they are participating in a study.

This has several implications, including a decrease in the frequency these patients see other key members of our multidisciplinary team such as those in nutrition, respiratory therapy, and social work. Additionally, although some laboratory tests from clinical trials overlap with annual CF labs, this may not always be the case, and things like vitamin levels and sputum cultures may be put off for several months or even missed altogether. Missed quarterly visits, incomplete clinical testing, and lack of ancillary team contact may also have a negative impact on the center's quality improvement outcomes and completeness of data in the CF Patient Registry.

cont. on page 10

CFF Welcomes New Clinical Research Team Member

The CF Foundation welcomes Christina Román to the Medical Team as clinical research resources senior program coordinator. Román will be working in conjunction with Cindy George and staff at the TDNCC to coordinate and manage the Foundation's national clinical research resources and programs.

Christina Román

Román has a Master of Public Health, Health Systems, Management and Policy degree from the University of Colorado and worked as a Health Policy Intern at the AIDS Institute/AIDS Alliance before joining the Foundation in October 2013.

While pursuing her Master's degree, Román became familiar with cystic fibrosis research through her part–time work at the Children's Hospital Colorado CF Care Center. Working closely with the research coordinators, she entered data for various studies and assisted with the distribution and analysis of their eQUIP-CR surveys.

"I am very excited to be working at the Cystic Fibrosis Foundation" says Román. "It is an honor to be able to support the CF research community and play a small role in the path towards a cure to CF."

- Cindy George

But Wait, There's More...

Be sure to read the upcoming Winter 2014 issue of CFF Network News for introductions to several other new CFF team members, including:

- New Grants and Contracts staff: Sean Marz, Edwin Gregorian, and Justin Masters
- Alyssa Maher, executive assistant to Bruce Marshall

Network News is emailed to all CF Care Centers and posted on the home page of CF ClinicalResearchNet.

RC Perspective, cont.

How Research Team Can Help

Although the importance of routine CF care is explicitly outlined in clinical trial consent forms and explained to patients during the process of obtaining informed consent, we continue to see this problem come up from time to time with some clinical trial participants. This presents a unique challenge for the research coordinator. Although our role is to facilitate research participation for our patient population, we also understand that we have an opportunity to encourage our patients to keep up with their regular clinical care while they participate in a clinical trial. One way we can do this is by scheduling clinical and research visits and tests in a way that is as convenient as possible for patients and families . For example, when scheduling clinical trial visits weeks and months in advance, we can try to offer patients the opportunity to conduct their clinical trial visit in the morning and their CF clinic visit in the afternoon.

Working effectively with the clinical care team on areas like scheduling demonstrates to patients and families that their time is valuable and their participation in ongoing CF research is appreciated. It also shows the larger clinical team that research can be integrated within clinical care and may even be mutually beneficial (such as when safety lab work is shared). As research coordinators, we can help set the tone by demonstrating the kind of flexibility and teamwork that will help our whole team reach its common goals.

Integration: An Ongoing Project

Here in Chicago, effective integration of clinical care and research at our center continues to be a work in progress, as I said. We've started looking more closely at what we're doing right and what we could be doing better, and are just beginning to work on the problem of maintaining adherence to quality clinical care in an active research environment.

In the future, we hope to utilize the eQUIP-CR process and present our experience in a more detailed and data-orientated way. For now, we're happy to report that we have all the "tools" in our tool box to successfully implement meaningful improvements and make sure we are offering the best research experiences for our patients and families!

Editor's Note: This edition of RC Perspective is the result of a proposal submitted to the TDN Times. If you are interested in writing an article for this column, we'd love to hear from you! Please submit a brief outline of your idea to TDNTimes@seattlechildrens.org.

New Spanish Materials are "Key"

Updated Spanish translations of even more "I Am the Key" materials are now available!

Printed Spanish-language versions of the "I Am the Key" brochure, note card, and posters (one of which is pictured at right) can now be ordered through resources@cff.org. In your email please include in which items you want to order, the quantity, your name, address, and phone number.

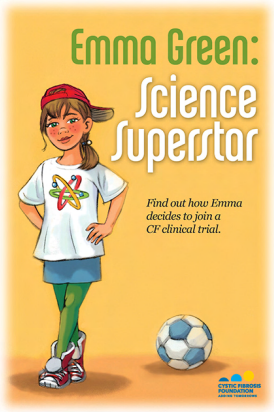
Digital copies of these materials — as well as the Spanish-language versions of the" Informed Consent Fact Sheet" and "About Clinical Trials" brochure — can be found in the CFF Clinical Research Awareness Program folder on CF ClinicalResearchNet. An updated order form for printed materials is also available there.

- Christina Román

Tool Time: Emma Green

Have you had a chance to meet Emma Green yet? Emma is the main character in a new illustrated children's book, "Emma Green: Science Superstar," about a young girl with CF who is offered an opportunity to participate in a clinical trial. The story describes Emma's personal struggle with the decision about whether to become a study subject, as well as what happens once she does make up her mind to participate.

Emma Green is based on an original story by Zoe Davies (see related article, page 8), a research coordinator at Stanford who is known for her creative approach in educating children about cystic fibrosis and research. Asked by the CF Foundation to write a piece that could be used to help explain clinical trials in an engaging way to school age children, Davies had the idea to write a story that would take kids through the experience of someone like themselves learning about clinical trials.



In the story, Emma finds out that she is eligible for an interventional trial, but isn't sure about participating. The evening before her screening visit, Emma shares feelings of apprehension and nervousness with her mom and a friend. When she goes into the clinic, Emma and her mother are able to talk with both the PI and the RC about what it means to enroll in a clinical trial. They discuss what a clinical trial is and how it will affect Emma's usual CF care. Emma leaves feeling excited about the prospect of joining a clinical trial and being a part of getting new CF medications approved to help people like her.

This story is intended to be a resource to help educate school-age kids (ages 8-12) and their parents about the research process and what to expect when participating in a clinical trial. It provides definitions of words that are commonly used in research and describes the various research roles. Davies says that at Stanford, they have been handing out copies of the story to all kids with CF who are — or are thinking about — participating in a research study.

Emma Green is now available electronically on CF ClinicalResearchNet, in the CFF Clinical Research Awareness Program Folder on the Toolbox page. To order printed copies of the Emma Green book for your clinic, email resources@cff.org and include how many copies you would like, along with your email and phone number. There is a limit of 20 books per order.

- Christina Román

Upcoming RC Mentoring Opportunities

We are excited to announce that the next call for applications for the CFF Research Coordinator Mentoring Program is coming in February.

The RC Mentoring Program is designed to help RCs who are new to the position or new to CF navigate the world of CF clinical research by pairing them with an experienced RC. Helpful tips and information, new ideas and interaction with a national network of your colleagues are all things you can experience as part of the program.

This year we are seeking both new RC apprentices and experienced RCs to serve as mentors. The call for applications will go out the week of February 10, 2014 via an email to PIs and RCs, as well as a posting on the RC listserv and an announcement on CF ClinicalResearchNet.

The tentative dates for this year's program are as follows:

- February 10-14: Call for applications
- February 28: Match announcements
- April through June: Match site visits

For more details on the program, see the CF RC Mentoring Program Info Sheet on CF ClinicalResearchNet.

TDN Site Spotlight: Grand Rapids

Responses provided to the TDN Times by Mary Flanagan, Cindy Gile, Susan Millard, MD, and Sarah Nota

Tell us a little about your center...

Located in Grand Rapids, Michigan, our TDN site consists of the Spectrum Health Adult CF Care Center and the Helen DeVos Children's Hospital Pediatric CF Care Center. The center was separated into the individual pediatric and adult programs in the early 2000's, and we were approved as a TDN site in 2009. Our programs currently follow about 100 adult patients and 165 pediatric patients with CF.

We are affiliated with Michigan State University, but our physicians and staff are employed either by the Spectrum Health Medical Group or Spectrum Health Hospitals. Thus, we are a hospital-based practice, but have teaching responsibilities for medical students, residents, advanced practice provider students and pharmacy students. This organizational structure works well because it increases the range of resources we can tap into.

Members of the Grand Rapids research team, L-R: Tom Symington, Brian Postema, Cynthia M. Gile, Susan Millard, Stephen Fitch, Sarah Nota and Mary Flanagan.

Our core clinical research team is shared between the adult and pediatric centers, as is our TDN grant. Our inpatient CF admissions and the pediatric outpatient CF clinic are on the same campus downtown, while our adult clinic is about eight miles away.

Who is on your clinical research team?

- Susan Millard, MD, Director of Research (15 years) & Associate Director of the Pediatric CF Center (5 years)
- Steven Fitch, MD, Adult Program CF Center Director (10 years)
- John Schuen, MD, Pediatric Program CF Center Director (17 years)
- Catherine Keezel, RN, MSN, Adult Program CF Coordinator (3 years)
- Brian Postema, RN, AE-C, Pediatric Program CF Coordinator (6 years)
- Tom Symington, RN, Clinical Research Nurse (9 years)
- Sarah Nota, BS, Clinical Research Coordinator (2 years)
- Cindy Gile, BS, CRCC, Clinical Research Coordinator (7 years)
- Mary Flanagan, RMA, AE-C, Clinical Research Associate (8 years)

What is unique about your center?

More than 90 percent of Grand Rapids-area clinical research studies are connected to Spectrum Health, West Michigan's largest health system-based research program and largest employer. Our CF clinical research team members work as part of Spectrum's Office of Clinical Research Operations, a centralized research department that includes over 50 research nurses, clinical research coordinators, and research assistants. This team facilitates hundreds of studies across numerous clinical specialties, including cardiovascular, oncology, pediatrics, neurology/neurosurgery, women's health and emergency medicine, as well as pulmonology.

The staff members we consider to be part of the CF research team spend the majority of their time on CF studies, but most of them work in other specialties as well. Our CF team is also unique in that our research staff is shared between the adult and pediatric clinics, with team members working on both adult and pediatric studies. For both the CF program and the institution, having a "pool" of research staff that are cross-trained in many specialty areas gives us a lot of flexibility and ultimately improves study selection, reimbursement and patient satisfaction.

The Office of Clinical Research Operations is housed together with Spectrum Health's other key research administration and operations groups — the Office of Sponsored Programs, the Human Research Protections Program and Research Finance. This close physical proximity is vital to developing close working relationships, facilitating communications and making our research department more efficient. This is a benefit that disease-specific research teams working in a decentralized model might not have. Our finance, grants and IRB teams offer regular updates and trainings that directly pertain to our job responsibilities, and if we have a question, we can just walk over and ask the experts.

What makes you proud of your clinical research team?

Our research group has great communication and works well as a team. We are always willing to step up and help one another when needed. We share a common passion for our patients and the work we do. We have an excellent relationship with the primary and sub-investigators, clinic coordinators and the rest of the care teams.

cont. on page 13

Site Spotlight: Grand Rapids, cont.

Have you benefitted from any clinical research QI activities?

Our adult and pediatric CF centers get truly jazzed about quality improvement. We are very flexible, creative and willing to make changes. Our pediatric CF center participated in a previous Learning and Leadership Collaboration (LLC) for clinical care and the adult center is presently participating. Our pediatric CF care center and the research department are also currently involved in institution-wide "rapid improvement/lean" programs. Through this program, we decreased the wait time in pediatric pulmonary for a first appointment from months to a few weeks.

We are also currently participating in the eQUIP-CR coaching program. With the help of our coaches, Kate Hilliard (Cleveland) and Dr. George Retsch-Bogart (Chapel Hill), we identified specific areas to focus on. Our first goal is to improve our institutional leadership's understanding of the TDN and the eQUIP-CR program. We want them to appreciate how the metrics are calculated and how our scores affect our CFFT grant. Our coaches helped us make good progress on this initiative when they came to our site and met with leadership to explain how the program works. This laid the foundation for us to involve leadership in future discussions about our specific metrics.

Before the coaching program started, we bought and started using a white board as recommended in the eQUIP-CR seminars, and we surveyed our research and clinical team about job satisfaction. Following some staff turnover, we learned that we need to do more training and are now using the tools in the TDN toolbox for that.

Next, we are focusing on improving research-related communication between the adult and pediatric CF care centers. Given that the clinics are eight miles apart, it is a challenge for staff to get together. To improve this issue we added a weekly research-specific conference call with both centers. This was a small change, but has had a significant impact toward keeping everyone up to date and talking "in person."

What key advice would you give to less experienced clinical researchers?

Introduce yourself to patients and families as part of the CF care team, and incorporate research as an integral part of the patient visits. Do not wait until there is a research study available to establish a relationship with the patients. This will allow you to develop trust and make communication easier with potential participants when a study becomes available for them.

What does the future hold for clinical research at your site?

We are very excited for the future of CF clinical research here in Grand Rapids. By 2020, Spectrum Health will be a national leader for healthcare, and clinical research is a vital part of that plan. We have proudly participated in many complex industry-sponsored studies and are looking forward to seeing what the future holds for CF research. We are planning to grow our local investigator-initiated portfolio over the next few years as well. By using eQUIP-CR tools, we hope to improve efficiencies in our study start-up process and build a community that is knowledgeable about research and eager to participate. Both factors will be key in improving our metrics and achieving our institutional goals.

Welcome!

Greetings to the following new TDN personnel:

- **Atlanta, GA** - Derrick Carter, RC
- **Boise, ID** - Leah Witham, Regulatory
- **Chapel Hill, NC** - Jianmin Han, RA
- **Chicago, IL (Lurie)** - Eriika Etshokin, RC
- **Cincinnati, OH** - Ann Williams, RC
- **Denver, CO** - Caroline Jones, RC and Sarah Ellington, RC
- **Durham, NC** - Miranda West, RC
- **Grand Rapids, MI** - Charles McCaslin, investigator & Emily Gleason, RN
- **Lebanon, NH** - Jenny Helm, RC
- **Los Angeles, CA** - Gonzalo Marquez, Admin & Nicole Vajda, RC
- **Milwaukee, WI** - Patricia Hastings, RC
- **TDNCC** - Burl Bagley-Bright, accountant; David Rapp, database admin; Lauren Markle, CRA; and Shannon Kirby, CRA

- Leila Atry

MARK YOUR CALENDARS

eQUIP-CR Webinar Series

Monday, April 14
Invoicing and Payment Tracking
Kate Hilliard

Monday, June 9
Coverage Analysis & Research Billing
Kathy Hammerhofer,
Director of Finance,
University Hospitals Health System

Monday, September 8
Best Practices for Clinical Trial Financial Management
Kate Hilliard

A Wealth of RC Offerings at NACFC 2013

This was another great year at the North American Cystic Fibrosis Conference (NACFC) for research coordinators. A variety of topics were covered and hopefully there was something for everyone, from the new RC to the more experienced.

We would like to thank everyone who presented this year and all who attended the sessions. We'd also like to recognize the RC Advisory Committee that helped us with the organization of this year's sessions, including Cindy George, Jill Van Dalfsen, Emma Kennedy, Zoe Davies, Ingrid Gherson, Jim Cahill, Chris Kubrak and Jean Kirihara.

Below are some of the highlights. Links are provided where content is available in an electronic archive, either on the NACFC Content Library (fees may apply for non-attendees) or CF ClinicalResearchNet.

Short Course

The first RC session this year was the Short Course, "Nuts and Bolts for the Research Coordinator," moderated by Karen Callahan and Sharon McNamara. This course was designed for new RCs and for experienced RCs transitioning to CF. Several veteran RCs presented information on regulatory issues; recruitment strategies and tools; organization and management of study visits; documentation and data capture; study procedures unique to CF such as induced sputum, sweat chloride testing and nasal potential difference measurement; and preparation for monitoring visits. Additionally, Dr. Elliott Dasenbrook presented on the topic of CF microbiology and treatments.

TDN Metrics Lab

Last year's popular "Interpreting and Applying Your TDN Metrics in Clinical Research" session with Jill VanDalfsen and Colleen Dunn was repeated this year in the computer lab, and was once again well-attended. Participants reported that the information provided them a better understanding of how to use their metrics to improve their site.

Workshop

The workshop "Applying eQUIP-CR at Your Center: Methodologies for Success" was moderated by Ginger Reeves and Colleen Dunn. This inspiring session included representatives of six different centers sharing their strategies and results related to clinical research quality improvement. Although organized by RCs, this session was applicable to all clinical research team members interested in quality improvement.

Ingrid Gherson (in pink) and Christina Kubrak (in black) share a laugh with other RCs during one of the breakouts at the Caregiver Session.

Caregiver Sessions

Our attendance at the two Caregiver Sessions, which are open to everyone, has increased every year, and these sessions provide a great opportunity for networking with other RCs at a national level. The first session, "Effective Presentation Skills," was moderated by Jill Van Dalfsen, Colleen Dunn and Zoe Davies. Dunn and Davies presented scenarios on proper and improper presentation techniques. Break-out sessions provided RCs an opportunity to network and give VanDalfsen feedback on how the TDN can best support the research sites. (See related article, page 3).

The second Caregiver Session, "RC Updates and Networking Communications," was held Friday afternoon prior to the RC Reception. First, representatives of the NACFC Committee, CFF, the TDNCC, the TDN Times Editorial Board and the RC Mentoring program gave updates on activities, resources and opportunities available to RCs.

Next, Adrienne DeRicco and Ingrid Gherson moderated the networking portion of the session, which included breakout groups for discussions regarding monitoring, recruitment/retention, difficult co-workers, and electronic records and EDC. Each of the breakout groups shared the key points from their discussion with the larger group. This was a very interactive session in a relaxed environment that provided an opportunity for new RCs to network with more experienced RCs and exchange ideas and experiences from their centers.

Brown Bag

This year's RC Brown Bag session was "Maximizing Your Role as an Accomplished Research Coordinator," moderated by Heather Hathorne and Elizabeth Hartigan. The discussion focused on sharing tools and tips from experienced research coordinators, troubleshooting, and generating ideas for improving the culture of research, increasing RC visibility in the CF Center and managing difficult monitors.

Roundtables

Lastly, there were five roundtables for RCs this year: Study Start up: Budgeting (Emma Kennedy), Processing of Research Specimens (Theresa Kump), Preparing for ACRP/SoCRA Exams (Brenda Bourne), Recruitment/Retention in Clinical Research (Kelly Stephenson and Deanna Thomas) and Organizing the Regulatory Chaos in Clinical Research (Cindy Williams).

Looking Toward 2014

We encourage you to submit any suggestions for the NACFC 2014 sessions to Heather Hathorne hhathorne@peds.uab.edu, the incoming NACFC RC Representative. Your feedback each year is integral to planning the following year's events.

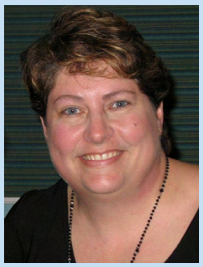
- Sandy Hurban & Heather Hathorne

Seattle's Alan Genatossio and Sharon McNamara

TDNCC Spotlight: Amy Hoffman

Amy Hoffman, MPH, new senior program manager for the TDN Coordinating Center's Network Development Unit, works to support TDN sites and network sponsors in a variety of ways. She collaborates with the CF Foundation and network leadership on initiatives such as planning the annual TDN Meeting, developing strategies for working with sponsors, and identifying educational opportunities.

Hoffman will have a leadership role in developing and maintaining resources to help the TDN centers maintain high standards of clinical research practice, including eQUIP-CR, the Clinical Research Toolbox and the upcoming Investigator-Initiated Study Toolbox on CF ClinicalResearchNet. Another major area of responsibility for Hoffman is overseeing development and utilization of the Contacts, Capabilities, and Study Metrics (CCSM) database.



Amy Hoffman

Hoffman actually worked for the TDNCC before, but as a Clinical Research Associate. She re-joined the TDNCC team in June 2013 after a four-year hiatus. During her time away, Hoffman was in the Washington, D.C. area helping develop the Newborn Screening Translational Research Network (NBSTRN), which provides infrastructure and resources to facilitate research aimed at improving the health outcomes of newborns with genetic or congenital disorders.

In her free time, Hoffman is a Girl Scout volunteer and loves to scrapbook, read, and spend time with her family. If you have any questions about network activities (or would like to chat about newborn screening) please feel free to contact her at amy.hoffman@seattlechildrens.org or 206-884-7540.

- Quynh Luong

Interactivity Makes TDN Meeting 2013 a Standout

This year's TDN Meeting was especially engaging and interactive, and we hope you enjoyed it as much as we did! The meeting was held on Wednesday, October 16th from 8:00 am to noon in Salt Lake City, Utah, the day prior to the main NACF Conference. Over 200 investigators and research coordinators from 64 TDN centers attended.

To kick off the meeting, Dr. Joe Pilewski, the current chair of the TDN Steering Committee, gave an overview of the "State of the Network" which included the following highlights of TDN activities and accomplishments:

- The Protocol Review Committee (PRC) reviewed 13 studies over the last year, including a review of the European CF Society Clinical Trials Network's MRSA eradication protocol (METRIC). Patient representatives were included in four PRC reviews.
- Projected enrollment in TDN studies almost doubled from 2012 to 2013. However, actual enrollment was only about half the number of subjects needed, due to study delays or holds and slow accrual in several studies. Enrollment rates were high in the Vertex studies due to the efforts of the study sites, while other studies had rates well below those planned.
- Overall enrollment projections will continue to increase in the next year, which will be a challenge. Best practices have been identified, and the key now is to sustain efforts to educate patients and families, expand the culture of research, provide enjoyable research experiences, and use patients as ambassadors for their peers.
- Several new clinical trial education materials are now available on CFF.org and CF ClinicalResearchNet. (See related articles, pages 10 and 11).
- The eQUIP-CR coaching program completed a successful pilot at five centers. Also in conjunction with eQUIP-CR, the TDN launched a financial webinar series and a Financial Management Toolbox on CFCRNet, both developed in collaboration with Kate Hilliard from Cleveland. (See page 13 for details on upcoming webinars in this series).

Dr. Carolyn Cannon of University of Texas Southwestern in Dallas enjoying the TDN Meeting.

- Several new web pages describing TDN expertise, practices and services have been added to CFF.org.
- The Translational Advisory Group (TAG) used a multi-step process to identify knowledge gaps, generate study ideas, and make recommendations to the CREC about priorities for clinical and translational research topics.
- Priorities previously determined by the CREC are: 1) identification of CFTR modulator therapy for all patients with CF; and 2) improvements in the treatment of pulmonary exacerbations through comparative effectiveness research. Several ongoing or upcoming studies have been designed to address these areas.
- The TDN continues to collaborate in several ways with the European CF Society Clinical Trials Network (ECFS CTN). Nico Derichs of Berlin, our new CTN liaison, attended the TDN meeting.

Dr. Jane Burns presented an overview of the TDN National Resource Centers, reminding attendees about the expertise offered by this third arm of the network and how to access it. She highlighted the personnel, services, and work accomplished by each of the seven centers.

cont. on page 16

2013 TDN Meeting, cont.

Interactive Poll Results

In a first for the TDN Meeting, an interactive polling system was used to gauge the status and priorities of TDN sites. Here are top answers to a few of the key questions:

Q: Now that enrollment in the Phase 3 Vertex studies has completed, what is your sense about enrollment in other studies at your center?

A: The other studies will enroll, but more slowly than planned rates. (50% of respondents)

Q: If you believe that enrollment in other studies will not proceed according to planned rate, which of the following do you think is the primary limiting factor at your center?

A: Lack of eligible patients. (45%)

Q: Which is the second most limiting factor?

A: Lack of eligible patients (47%)

Q: Estimate when your site can take on new studies.

A: (48% responded "We can take on new studies in the next 3-6 months)

Q: Which therapeutic interventions (beyond CFTR modulators) would you prioritize as most important to your patients?

A: Anti-infectives (52%)

Q: Which therapeutic interventions (beyond CFTR modulators) would you prioritize as second most important to your patients?

A: (32% responded "Anti-inflammatories")

Q: Consider how you use the CREC Strategic Fit score.

A: It doesn't matter if it is modified or not as we select our studies based on the local research priorities (80%)

Graphs showing complete question and answer data have been added to the Facing Challenges and Moving Forward presentation slides, available on CF ClincialResearchNet.

The educational focus of the meeting was on crisis communication. Dr. Benjamin Wilfond presented on the controversy surrounding the SUPPORT trial and its implications for clinical research. Wayne Pines and Dr. Chris Goss presented on crisis preparedness. (See related article, page 6.)

To end what was later described as "one of the best TDN meetings in recent years," Drs Bonnie Ramsey and Preston Campbell talked about enrollment challenges in the network and polled the meeting attendees for their views. Using mobile phone text messaging, the attendees were asked to respond to several questions. Live updates of the responses were shown to the audience. (See sidebar at left for more on the polling results.)

Matthias Salathe, University of Miami

The meeting wrapped up with a lively brainstorming forum on ideas for moving forward. The CF Foundation and TDNCC greatly appreciate everyone's feedback. The TDNCC will be developing and implementing several strategies over the next year based on input received at the TDN Meeting and other NACFC sessions (see page 14). Keep those ideas coming!

Amy Cooper, Vikki Kociela, and Dr. Jamie Wooldridge of Cardinal Glennon Children's Medical Center, St. Louis at the TDN Meeting

All presentation slides are now available on the Resources Page of CF ClinicalResearchNet. Look for the 2013-10 TDN Meeting folder under Meeting and Conference Materials.

- Amy Hoffman

Publications Watch

George Retsch-Bogart

BIIL 284 reduces neutrophil numbers but increases P. aeruginosa bacteremia and inflammation in mouse lungs. Döring G, Bragonzi A, Paroni M, Aktürk FF, Cigana C, Schmidt A, Gilpin D, Heyder S, Born T, Smaczny C, Kohlhäufl M, Wagner TO, Loebinger MR, Bilton D, Tunney MM, Elborn JS, Pier GB, Konstan MW, Ulrich M. J Cyst Fibros. 2013 Oct 31. pii: S1569-1993(13)00164-1. doi: 10.1016/j.jcf.2013.10.007. [Epub ahead of print] PMID: 24183915.

Ten years ago the TDN undertook a series of clinical trials designed to test a new, potent anti-inflammatory agent active against neutrophils which were known to play a central role in airway inflammation, both responding to infection and damaging conducting airways. A phase 2 placebo-controlled study testing the safety and efficacy of BIIL 284 was stopped early because a higher rate of pulmonary exacerbations was seen in the group receiving active treatment. To understand potential mechanisms for this outcome, the investigators used a well-defined agar bead mouse model of lung infection that mimics chronic *Pseudomonas* lung infection in CF. The mice receiving BIIL 284 had reduced lung neutrophils and increased bacterial counts, with significantly higher rates of bacteremia and lung inflammation. This suggests that modulation of the inflammatory response beyond a specific point during bacterial infection may place patients at risk for worse clinical outcomes.

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Publications Watch, cont.

Systematic review of blood biomarkers in cystic fibrosis pulmonary exacerbations. Shoki AH, Mayer-Hamblett N, Wilcox PG, Sin DD, Quon BS. Chest. 2013 Nov 1;144(5):1659-70. doi: 10.1378/chest.13-0693. PMID: 23868694.

One priority for the CF clinical research community (and the focus of the TDN Biomarker Consortium) is identification of biomarkers that could be used to define clinical conditions in CF, such as the presence of a pulmonary exacerbation, which to date have been difficult to define using the subjective judgment of clinicians or predetermined clinical features such as symptoms, change in pulmonary function or chest radiographs. The authors present an exhaustive systematic review of the medical literature for blood-based biomarkers that could be used to define a pulmonary exacerbation in CF, predict outcomes of an exacerbation or monitor change during treatment of an exacerbation. They reviewed 5500 papers published over a 17 year period and identified 50 for qualitative synthesis. This provides a useful summary of the work done in this area. The biomarker with the greatest potential for correlation with disease activity or change in response to therapy was C-reactive protein. Other biomarkers with potential utility include neutrophil elastase antiprotease complex, IL-6, myeloperoxidase, lactoferrin and calprotectin.

Air trapping and airflow obstruction in newborn cystic fibrosis piglets. Adam RJ, Michalski AS, Bauer C, Abou Alaiwa MH, Gross TJ, Awadalla MS, Bouzek DC, Gansemer ND, Taft PJ, Hoegger MJ, Diwakar A, Ochs M, Reinhardt JM, Hoffman EA, Beichel RR, Meyerholz DK, Stoltz DA. Am J Respir Crit Care Med. 2013 Oct 29. [Epub ahead of print] PMID: 24168209

Most clinicians and investigators in the field of CF are taught that the lungs of newborns with CF are normal structurally at birth and alterations in lung function occur after impairment of mucociliary clearance related to abnormal epithelial ion transport and exposure to environmental pathogens delivered through inspired air and secretions. The development of pigs with disrupted CFTR genes produced a phenotype with typical features of CF seen in humans. Examination of lung structure and function on the first day of life in CF piglets identified air trapping and airflow obstruction, which were associated with reduced airway lumen diameter in the proximal airways (mainstem to subsegmental bronchi), but not in the more distal airways. These findings raise a question as to whether congenital airway abnormalities occur in all human newborns with CF, in a subset of them, or not at all because CFTR dysfunction in the pig is fundamentally different than it is in humans, prenatally or postnatally. Also, if structural differences exist early in life in humans with CF, these may be heterogeneously distributed and help explain the predisposition to disease progression in the upper lobes.

A semiparametric approach to estimate rapid lung function decline in cystic fibrosis. Szczesniak RD, McPhail GL, Duan LL, Macaluso M, Amin RS, Clancy JP. Ann Epidemiol. 2013 Dec;23(12):771-7. doi: 10.1016/j.annepidem.2013.08.009. Epub 2013 Oct 5. PMID: 24103586

Tracking lung function for people with CF is important clinically. In clinical studies collecting longitudinal data on lung function, analysis of the fluctuations seen can be challenging and requires complex statistical techniques. In particular, knowing whether a decline is related to a pulmonary exacerbation or a more worrisome downward trend reflecting more rapid disease progression is important for clinical care and in the context of research. This paper describes use of a new technique, longitudinal semi-parametric mixed modeling, to evaluate lung function values over time to demonstrate rapid decline in lung function. The investigators used CFF Patient Registry data from a 50-year period including over 30,000 patients. They found that the decline in FEV_1 does not occur at a steady rate but changes with age. Other influences on rate of decline could not be assessed given the variation in clinical information collected in different eras of the patient registry. The most striking finding was the variation in rate of decline within the 10-to-20-year-old age group. This method may be useful in future research studies or in evaluating lung function changes in clinical care.

Increased rate of lung function decline in Australian adolescents with cystic fibrosis. Welsh L, Robertson CF, Ranganathan SC. Pediatr Pulmonol. 2013 Oct 31. doi: 10.1002/ppul.22946. [Epub ahead of print] PMID: 24178906.

The period of adolescence for patients with CF is particularly difficult for a number of reasons, and the rate of lung function decline is the most vivid marker of this vulnerability. The authors report the results of a retrospective analysis of clinical and lung function data collected on 98 patients over the five-year period before transfer of their care to the adult CF program (providing just over 1100 observations). They used the best annual lung function within a calendar year in their mixed model analysis, adjusted for individually repeated measures of FEV_1, to test the influence of age, sex, genotype, newborn screening, pancreatic insufficiency, CF-related diabetes (CFRD), Pseudomonas infection status, body mass index, hospitalization, and socioeconomic status. The rate of lung function decline almost doubled during adolescence. Increasing age, CFRD, mucoid Pseudomonas infection, pancreatic insufficiency, increased number of hospitalizations and homozygous F508del genotype were associated with an increased rate of lung function decline. This magnitude of decline is similar to that reported in other studies and similar to the maximum rate in the paper above (Szczesniak, et al).