



MASSACHUSETTS
GENERAL HOSPITAL

Clinical Research Program Program Review 2011



Clinical Research @ MGH: CRP Program Review 2011

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Director's Overview of the CRP: Year 15

*William F. Crowley, Jr., M.D.,
Director of Clinical Research, MGH*

As 2011 draws to a close, MGH concludes a spectacularly successful bicentennial celebration. At each of the year long festivities, a consistent theme was the introduction of innovative solutions to alleviate human suffering over 200 years. It was equally clear that the MGH has an abiding desire to continue this innovative tradition, which is a permanent feature of its leadership. Moreover, the scientific advances to achieve this goal are more promising than ever. The MGH commitment to basic research has expanded to capture these opportunities through the establishment of the Simches Centers Program. It is equally clear, however, that if we are to sustain this current level of innovation and keep pace with the new scientific discovery platforms on which translation into patient benefit ultimately depend, our methods, technologies, and infrastructure must be equally fluid.

In that regard, attached is the 15th annual report of the Clinical Research Program (CRP). In it, each of the CRP's Units defines its goals, reviews its annual progress, extracts the lessons learned, and outlines plans for the coming year. Each report is defined as quantitatively as possible. The CRP represents a substantial institutional commitment to a dynamic infrastructure that transfers advances in basic science into improved care of our patients. This translational goal is unique to Academic Medical Centers (AMCs) in general and a vital mission for institutions like the MGH in particular. Given MGH's remarkable record of innovation over its first 200 years it is clear that this particular mission is deeply embedded here and still responsive to changing structural needs.

The CRP has accepted the challenge of building an adaptable translational infrastructure. Since our first progress report in 1996, the CRP has made several important changes to meet its translational mission. Units like the Genetics and Genomics and the Translational Medicine did not exist in 1996. Now, these new Units spearhead new institutional challenges and opportunities to improve translation. Each is led by a senior scientist (Drs. Smoller, Slaugenhaupt, and Freeman respectively). The Clinical Effectiveness Unit has changed its focus, added mentorship in new disciplines, and services new institutional constituencies. Such changes were essential if we are to become an Accountable Care Organization over the shorter term and ultimately a self-learning organization.

The growth of the MGH's clinical research, both industrial (Fig. 1) and NIH (Fig. 2) continues to be robust. These figures show an excellent return on the MGH's investment in the CRP as well as the rest of the institution's clinical research infrastructure.

The MGH remains an exciting place where the dynamic tensions between basic and clinical research are balanced with the mandate to improve the efficiency and lower the cost of medical care. Such a creative balance is necessary to improve our future opportunities to translate scientific advances into better and more efficient patient care. We are at an exciting but anxious moment in our institution's history as several growing threats to institutional support appear. Nonetheless, our faculty, our leadership, and especially our patients depend upon the vigor of this franchise mission of translation to continue the innovations that have characterized the past two centuries of the MGH.

Figure 1: Clinical Trials Expenditures at MGH, FY 92-11

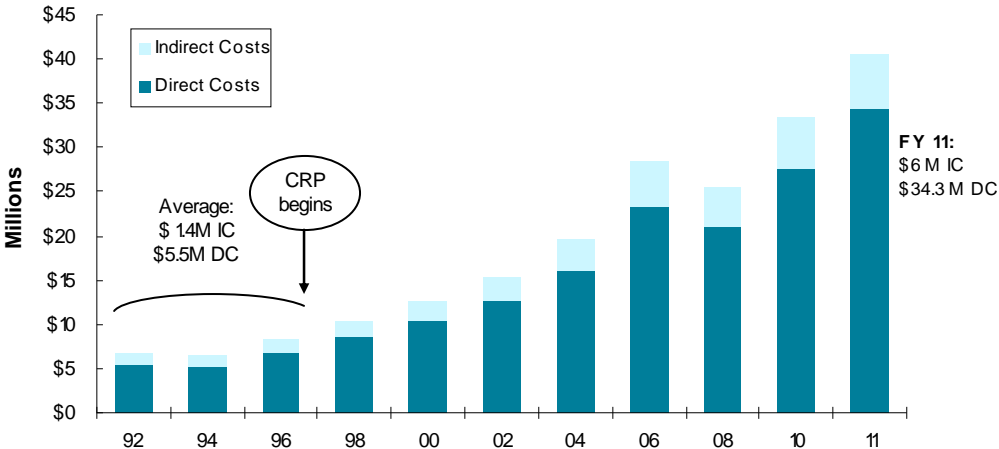
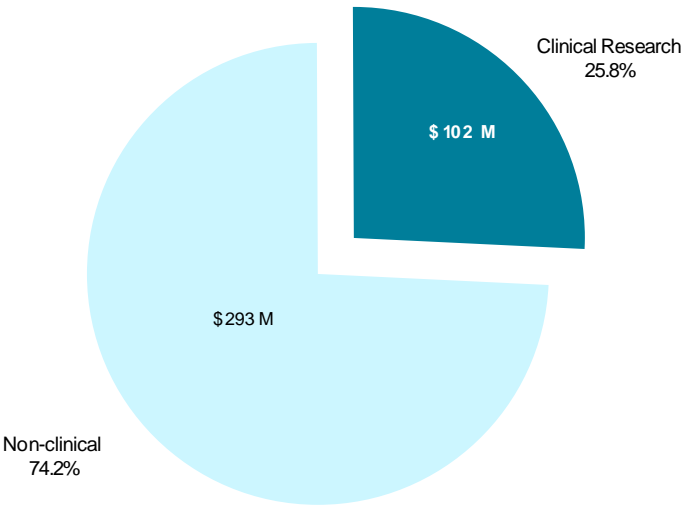


Figure 2: NIH and ARRA \$ for Clinical Research in FY 11 - Estimated @ \$102M



Clinical Research Support Office (CRSO)

Andrew A. Nierenberg, M.D., Director

GOALS

The mission of the CRP's Clinical Research Support Office (CRSO) is to provide a stable resource of infrastructure support for clinical research faculty at the MGH, particularly for younger clinical investigators seeking training and transitional support in clinical research as well as established investigators in clinical research in need of logistical support for continuing human research.

Our goals are to:

- improve the quality, quantity, and safety of clinical research;
- recruit our best and brightest young scientists to rewarding careers in clinical research;
- provide a nurturing environment to assure their long term career development and;
- by so doing, improve the quality of patient care via prompt implementation of clinical research into practice.

After 3 years as Director of the CRSO, Dr. Alexa B. Kimball stepped down to assume a Senior Vice Presidency in the MGH Physicians Organization. Andrew Nierenberg, MD was appointed Director of the CRSO in October 2011. Dr. Nierenberg is Professor of Psychiatry; Director, Bipolar Clinic and Research Program; and Associate Director of the Depression Clinical and Research Program. Dr. Nierenberg leads the national Bipolar Trials Network (BTN) that is supported by a \$10 million ARRA grant from the NIH for the Bipolar CHOICE study (Clinical Health Outcomes Initiative in Comparative Effectiveness).

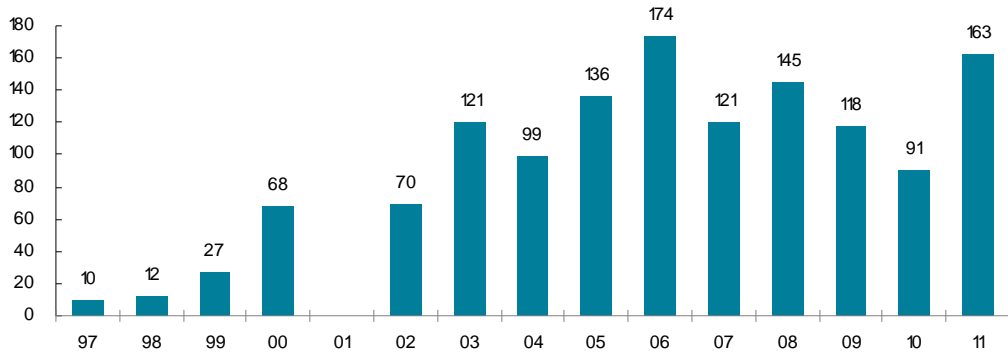
ACCOMPLISHMENTS

Mentoring

Mentoring faculty, especially junior faculty, continues to be a major focus of CRSO activities. This service is provided not exclusively by CRSO faculty but rather by all CRP faculty members. Thus, the CRP Faculty functionally serves as the institution's global mentors to junior and mid-rank faculty throughout the MGH clinical research community.

More than 163 faculty and research fellows reached out to the CRSO in 2011 (Fig. 1). This represents a 79% increase over the 91 investigators who sought CRSO consultations 2010. Dr. Nierenberg, has staffed consultations ranging from junior faculty preparing new Career Development (K) grant applications, working with current K award recipients in applying for independent funding, consulting on resubmissions of federal grants, and assisting with study design issues for new clinical studies and research networks. He also reviewed abstracts for Clinical Research Day, and presented at CRP-sponsored seminars on grant writing, how to give a presentation, developing careers in clinical investigation, and developed workshops for junior faculty who are intending to apply for NIH Career Development (K) awards.

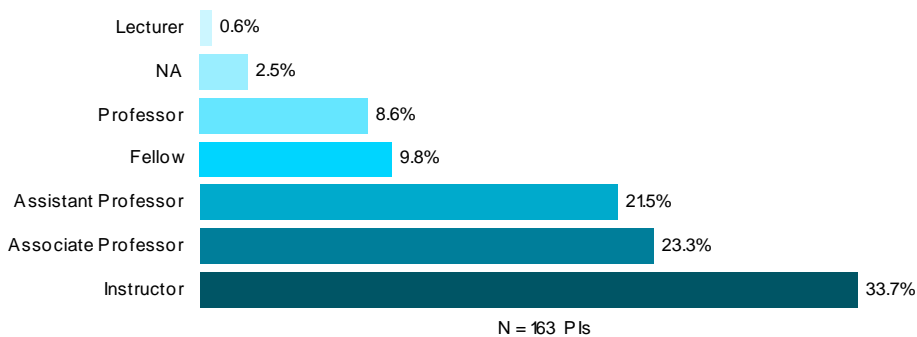
Figure 1: CRSO: PIs Served per Year, 1997 - 2011



Eleven percent (11%) of 163 investigators used more than one CRSO service including consulting with faculty, utilizing CRSO Project Manager (PM) support to identify potential grant support and prepare administrative sections of grant applications, and developing budgets for clinical studies and training staff to use Budget Builder. PMs participate in the CRP's Study Coordinator Orientation Program for MGH's newly hired study staff; offer guidance and training on IRB submissions; assist departments in training newly hired staff in tracking achievement of study milestones, invoicing sponsors and tracking payments, correcting errant charges and other practical interfaces with the Research Management and Financial Departments.

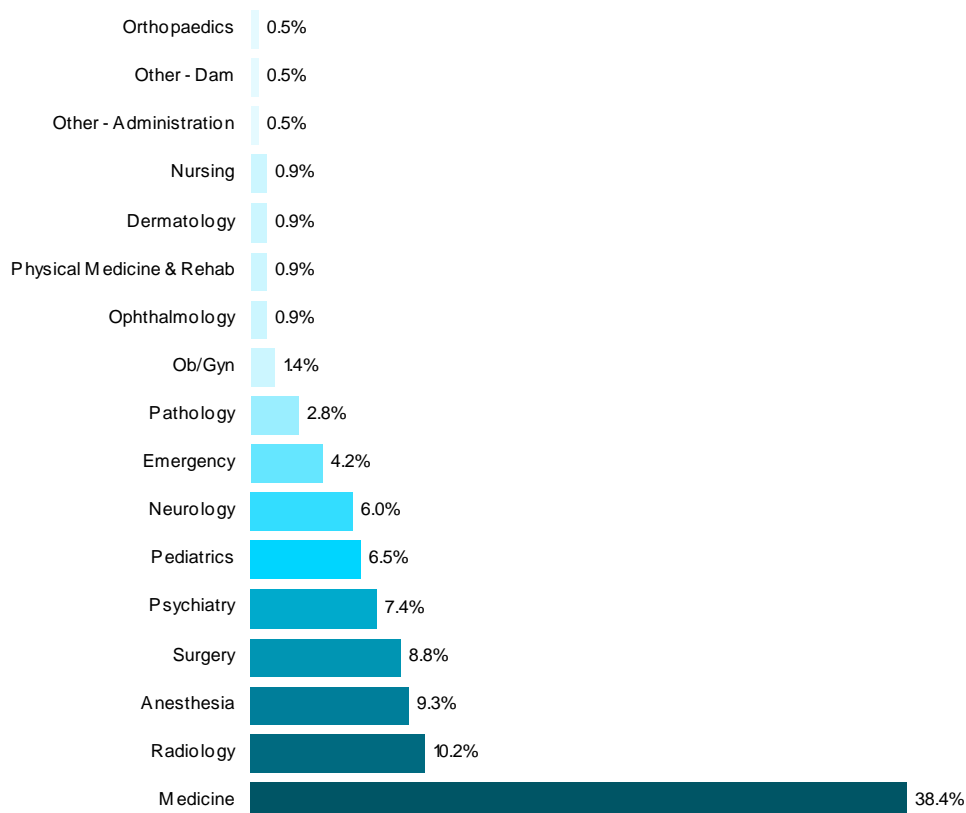
Of the 163 investigators assisted by CRSO faculty, project managers and coordinators, 55 % were junior faculty members (instructors and assistant professors), 32% were senior faculty (associate professors and professors); and 13% were residents, fellows, and others (Fig. 2).

Figure 2: CRSO: PIs Served by Faculty Rank in 2011



These 163 investigators came from 17 departments. Collectively Medicine, Radiology, and Anesthesiology accounted for 58% of all investigators served (Fig. 3).

Figure 3: CRSO: Projects by Department, 2011



Career Development Tool Kit

In the past 15 years, the CRSO has developed an impressive range of support services to meet clinical investigator needs for consultation on career development, as well as guidance on all phases of study implementation. We have also developed actively curated email lists of MGH junior clinical research faculty, applicants and recipients of K awards, research fellows, and graduates of the Harvard School of Public Health's Clinical Effectiveness course. These lists allow us to keep them up-to-date about CRP education, funding, and educational programs of particular interest to junior investigators. The CRSO and the CRP's Educational Unit also developed a new educational series specific for MGH applicants and junior faculty focusing on NIH Career Development Award applications (K08 and K23 awards). These new and highly practical services were well received because of their interactive features.

In 2009 and 2010, the CRP designed and launched an interactive intranet web resource (HUB) which allows MGH clinical investigators and their support staff to share their questions and study implementation problems with the wider clinical research community. Through HUB, investigators and staff can also access Key Clinical Research Resources provided by MGH, Harvard Medical School's Catalyst, and Partners for inclusion in their grant application's Resources and Environment sections.

The CRSO also offered a new interactive workshop specifically for Clinical Investigators applying for an NIH K Award. This workshop focused on practical approaches including timelines and grant structure, with an emphasis on the unique requirements of these grants. The workshop also gives senior investigators who already have a K24 an opportunity to mentor the larger MGH community beyond their departments. To further assist faculty applying for these K awards, the CRSO began assembling a library of K08 and K23 applications recently awarded to MGH junior faculty.

Study Coordinator Pool

The CRSO’s study coordinator pool is yet another important institutional resource established by the CRP for MGH clinical investigators. CRSO study coordinators have been accredited by the Norman Knight Nursing Center for Clinical and Professional Development to train MGH non-nurse study coordinators in basic phlebotomy, acquiring vital signs, and performing ECGs thus leveraging the CRP’s programs into the clinical operations. Over 150 MGH coordinators participated in these training programs in 2011. This service fills an important training need for our clinical investigative community’s staff.

Five fully funded CRP study coordinators support a wide variety of clinical research projects directed by MGH clinical investigators. This CRSO study coordinator pool assists with all aspects of a clinical study for a flat hourly rate of \$41 and *represents the only charged service of the CRP*. This staff can manage all day-to-day clinical study activities collection and entry, and study close out. In 2011, CRP study coordinators supported 46 individual clinical investigators from 10 departments on 92 individual studies (Fig. 4a & 4b).

Figure 4a: Study Coordinators: Projects by Department, 2011

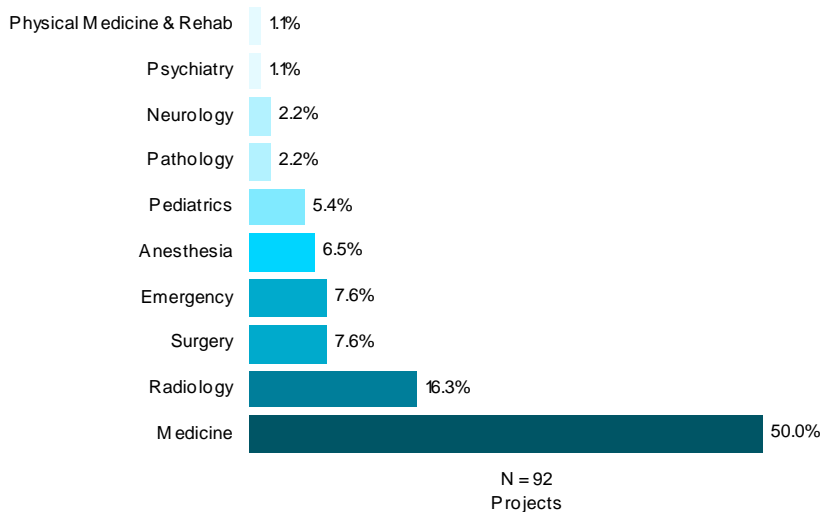
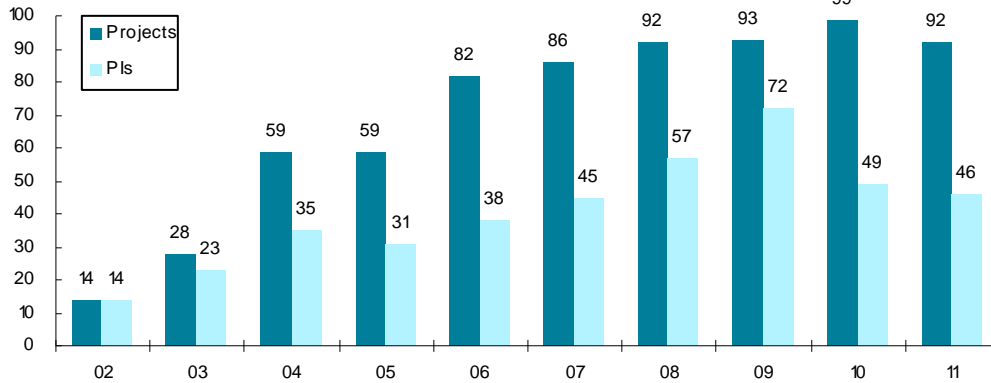


Figure 4b: Study Coordinators: Projects & PIs per Year, 2002 - 2011



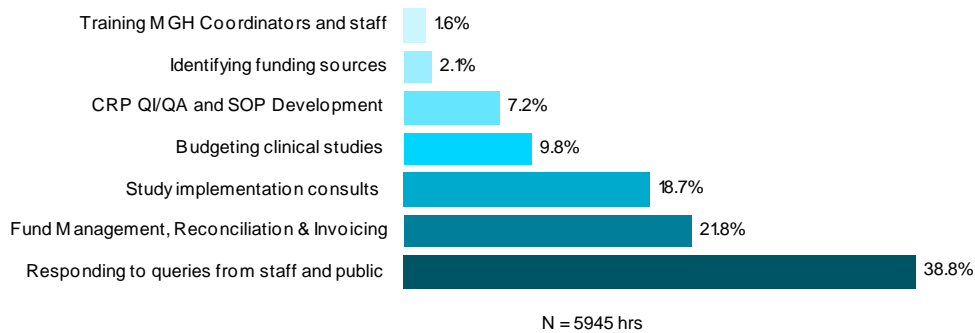
CRSO coordinators prepare and track approval of IRB submissions as well as gather and submit various regulatory documents for sponsors as part of study start up. Once a study is underway, CRSO coordinators assist in recruiting study subjects, attending clinic visits, collecting and entering study data, and meeting with sponsor’s study monitors.

Medicine accounted for 46.5% of clinical investigators served by the Coordinator Pool with Radiology accounting for 18.2%, Surgery for 10.1 % and Anesthesiology for 7.1%.

Project Management Support

The forty-six (46) Investigators who used a CRP CRSO study coordinator also benefited from CRSO project management (PM) support at no additional cost. PMs provide investigators with monthly reports detailing the precise status of their project’s subject recruitment. They also verify fund expenditures, follow up to identify and remove errant grant charges, provide a realistic assessment of projected fund balances, and review sponsor amendments which may affect study budgets. The PMs also invoice sponsors based on achievement of study milestones, and manage final fund reconciliation and grant close outs (Fig. 5). This service allows investigators to close out study funds quickly and avoid deficits caused by untimely accounting practices. Perhaps more importantly, these PMs reduce the broader institutional problem of fund deficits resulting from poor tracking of crucial clinical research financial details.

Figure 5: CRSO: Consulting Hours by Service Type in 2011



In 2011, CRSO study coordinators and PMs supported the Partners Biorepository for Medical Discovery (PBMD) project in selected MGH clinics. PMs facilitated start-up activity and rapid implementation of this PHS-wide resource. CRSO study coordinators obtain patient consent, perform phlebotomy, and collect and enter data into the PBMD consent tracking system. With 20% coordinator support, 315 patients provided consent and specimens for the biorepository. A full time coordinator will be able to generate 1575 consented samples. In addition, our PM for this project developed monthly reports which will inform the continued expansion of the PBMD throughout the MGH. These management reports detailed on a day-by-day and clinic-specific basis hours involved in interacting with clinic patients, number of patients who consented and refused consent, and administrative support including time associated with IRB interactions and with PBMD IT staff related to consent tracking software. We anticipate continued expansion of PBMD at MGH in 2012.

Monitor Online Record Access (MORA) Tool

Based on a 2008 survey, the CRSO conducted a survey of MGH research nurses and study coordinators that highlighted the excessive amount of staff time and effort required to support study monitor visits from outside commercial sponsors. In response to this need, the CRP's IT Unit, the Laboratory of Computer Sciences, and PHS's Enterprise Research Information Services programs have collaborated at the CRSO's initiation to develop a prototype of an electronic subject record access system for use by outside monitors/auditors. The CRSO study coordinators piloted this monitor direct access system and provided valuable feedback to enable the system to be launched at MGH and DFCI in late 2011.

Subject recruitment using the RSVP for Health database

The *Research Study Volunteer Program* (RSVP for Health) is a CRP-initiated study volunteer registry where pre-registered individuals receive information about clinical research studies that are active at the MGH. Both MGH and BWH research staff now use this program to recruit study subjects, and it has been very successful.

RSVP for Health saw its first full year of operation in 2005 and has had another year of steady growth in the number of registrants and in the number of MGH and BWH users. By the end of 2011, RSVP for Health contained over 20,500 registrants, up from 18,892 registered in 2010 (Fig. 6).

Of the 20,500 registrants, 13,003 (63%) are women and 15,543 have indicated an interest in participating in studies as healthy volunteers, thus serving as a critical resource for translational and physiologic/path physiologic studies.

The registrants' therapeutic interests reflect common disorders such as diabetes, obesity, mental health, cardiovascular disease, etc. In 2011, MGH investigators used the RSVP tool to recruit subjects for 60 individual MGH protocols. The heaviest users are investigators in the departments of Medicine, Psychiatry, and Radiology.

Figure 6: RSVP for Health: Registrants' Demographics

Category	Registrants	
	Count	%
Gender		
Female	13,003	63%
Male	6,494	32%
Not Recorded	1,003	5%
Total	20,500	100%
Race		
American Indian/Alaskan Native	85	0.4%
Asian	933	4.6%
Black or African American	2,552	12.4%
Native Hawaiian/Pacific Islander	67	0.3%
White	13,641	66.5%
Other	847	4.1%
Not Recorded	2,375	11.6%
Total	20,500	100.0%
Ethnicity		
Hispanic or Latino	1,278	6.2%
Not Hispanic or Latino	13,248	64.6%
Not Recorded	5,974	29.1%
Total	20,500	100.0%
Age		
<35	9,916	48.4%
36-45	2,890	14.1%
46-65	5,746	28.0%
66+	1,671	8.2%
Not recorded	277	1.4%
Total	20,500	100.0%
Contact Method		
Email	15,983	78.0%
Post	4,517	22.0%
Total:	20,500	100.0%

LESSONS LEARNED

The CRSO served a total of 163 individual investigators in 2011. During the year, we established several new services and also expanded our existing services. This support was distributed among different departments. Increasingly, we have focused CRP services on junior faculty in recognition of their importance in the clinical research “pipeline”.

The creation of a Clinical Research “Help Desk” makes the process of referral to CRP, PHS and Catalyst resources straightforward, and use of this resource has grown considerably. The hands-on K award workshop was filled within an hour of posting and

we had to turn away others who had wanted to participate. Since this was an intensively interactive workshop with small groups learning from faculty and K24 awardees, the numbers still have to be limited. It was unclear if K award applicants told their mentors that they were participating in the workshop.

ADAPTATION PLAN

1. Expand specific email notices of available CRP services to clinical researchers who would benefit from the CRSO services to enable better access to this information on the website is needed. Such 'push technology' should enhance serving the individual and varied needs of the MGH's clinical research community.
2. Improve the integration of assistance to young investigators with their mentors and communication with mentors and department chiefs.
3. Continually urge all Associate Professors at the MGH involved in clinical research to apply for K24 awards, which are clearly underutilized here.
4. Increase the frequency of the hands-on K award workshop to three times a year, each time to occur three months prior to the submission deadlines.
5. Institute a follow up plan to assess the impact of the workshop. Continued communication between the CRSO faculty and staff and the clinical investigative community as well as with mentors would amplify the impact of the workshop.

Biostatistics Unit

Dianne Finkelstein, Ph.D., Director

GOALS

The broad goal of the CRP's Biostatistics Unit is to support the biostatistical needs of the MGH's clinical research community by providing timely, onsite consultative biostatistical expertise. Specifically, the Biostatistics Unit's faculty:

- assists in the study design for clinical research grant applications prior to submission;
- supports data analysis for IRB-approved clinical studies after funding is obtained;
- guides MGH's clinical investigators in the methodology and interpretation of data for papers intended for submission to journals and;
- serves the CRP's educational mission via a biostatistics Lecture Series and individual tutorials in collaboration with the Education Unit.

These activities have increased the demand for biostatisticians at MGH which has, in turn, led to improved success of our clinical investigative community in the design and execution of their protocol as well as the recruitment, training, and professional mentoring of new faculty in the Unit.

ACCOMPLISHMENTS

Overview of Principal Activities

Dianne Finkelstein, Ph.D., Professor of Medicine and Director of the MGH Biostatistics Center, serves as the Director of the CRP Biostatistics Unit. Five additional biostatistical faculty from the MGH Biostatistics Center participate in the Unit supported in part by the CRP: David Schoenfeld, Ph.D., Hang Lee, Ph.D., Eric Macklin, Ph.D., Hui Zheng, Ph.D., and Brian Healy, Ph.D. Our pool of six Ph.D. statisticians provides a full spectrum of biostatistical expertise to match the needs of the MGH clinical research community. In addition, two master trained statisticians, Alona Muzikansky, M.A. and Douglas Hayden, M.A. support the program.

CRP policy is to offer initial consultations of 4 to 6 hours at no charge to all MGH clinical investigators planning a human research study. Dr. Lee, Assistant Professor of Medicine and Director of the CRP's Biostatistical Consulting Laboratory, personally triages each of these initial inquiries to statistical consultants, taking into consideration the nature of the investigator's need, in-house biostatistical expertise and time required.

The Unit also offers both formal lecture series in biostatistics, coordinated with the CRP's Education Unit. Together, we offered the annual CRP lectures, Basic Biostatistics for Clinical Research, as well as individual tutoring on selected biostatistical topics. We also provide MGH clinical investigators open access to the Unit's computing laboratory for their individualized statistical education and support. This open resource is a powerful

tool that allows our Unit to provide the type of individual support that is required to service the community.

The Unit also maintains and supports the MGH's institutional platform of common statistical IT packages, advanced statistical software, and other high capacity computing tools, including workstations and a protected network system. These programs are fully supported by the MGH Biostatistics Center's computing facility, and managed by the Biostatistics Center's Systems Manager located at the Biostatistics Center. The space also provides a desktop computer loaded with statistical software. Computer programmers and staff research assistants aided the faculty consultations. These programs include (SAS, STATA, Power and Sample Size) connected to Partners Network. This lab also provided updated educational material including on-line tutorial books, and lecture notes developed by Dr. Healy, <http://hedwig.mgh.harvard.edu/biostatistics/software> and <http://hedwig.mgh.harvard.edu/biostatistics/stathelp>.

Education

Dr. Healy offered the annual CRP lecture, "Basic Biostatistics for Clinical Research", as well as individual tutoring on selected biostatistical topics. The computing lab mentioned above supported this course and was used by 112 researchers who received consultation for sessions averaging one hour in length.

Individual Consultations

The CRP supported 36 short consultations which were directed to the Unit from the CRP office. These consultations involved study design or analysis plans, manuscript preparation, handling IRB submissions, and statistical education. A total of 134.25 hours were spent for those consultations. The majority of PIs were junior investigators (Instructors, Assistant Professors, or Fellows, generally functioning in collaboration with senior faculty). We also supported senior investigators at the Associate Professor and Professor levels, and others such as residents, medical students, research associates, and research nurses.

In addition to these consultations, the Unit conducted consultations with 27 PI who contacted the Unit for collaboration on grant submissions. A total of 148.5 hours were spent for those collaborations. This includes discussions on study design, contributing the statistical considerations to the application, and committing a portion of their time to the grant research if it is funded. If the grant is funded, they shift a portion of their activities to new personnel to make their time available to the new project. This requires support in hiring and mentoring new personnel to smoothly transition project work.

Harvard Catalyst also provides a consulting service for Harvard investigators and some of our statisticians provide consultations for both Catalyst and CRP. However the CRP efforts summarized above are distinct from those offered by Catalyst in several ways. First, the CRP short consultations are guided to the statistical group by CRP staff who are assisting with other aspects of supporting their individual projects (such as IRB submission, budget preparation, etc.) and thus these efforts are tightly coordinated by the type of 'one stop shopping' that is unique to the CRP. Second, both the educational and technological support for biostatistics offered by the CRP is local. Thus, courses and computer lab offered by CRP statisticians are available at MGH (in contrast to Catalyst courses which reside solely at the Longwood campus). Finally, statisticians working with investigators on preparations of their individual grant applications are then available to

commit their time to the eventual execution of the grant and research effort as a member of the research team. With Catalyst collaborations, only single consultations for design or analysis plans are supported, and there is no commitment to future collaboration. Thus, the support provided by CRP is complete, local (onsite), and comes with a commitment to be part of the research team – unique features that cover the full spectrum of services and are unavailable from Catalyst.

The following figures summarize the consultations (both grant collaborations and CRP directed short consultations), described by a number of projects as well as the total hours taken. Figures break these numbers down for analysis by faculty ranks (Fig. 1a and 1b), project types (Fig. 2a and 2b) and specialties (Fig. 3a and 3b). The use of the laboratory (by 112 researchers) and the time expended for the educational efforts (to prepare, teach, hold office hours, etc.) are not included in these numbers.

Figure 1a: Number of All Projects by Faculty Ranks

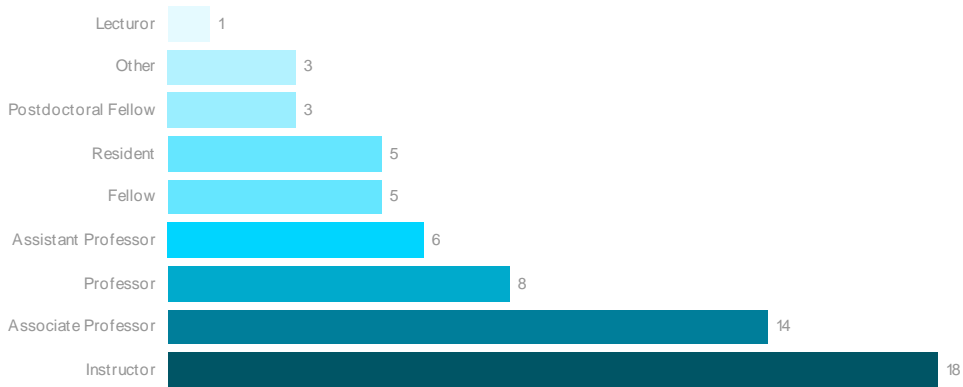


Figure 1b: All Projects Hours by Faculty Ranks

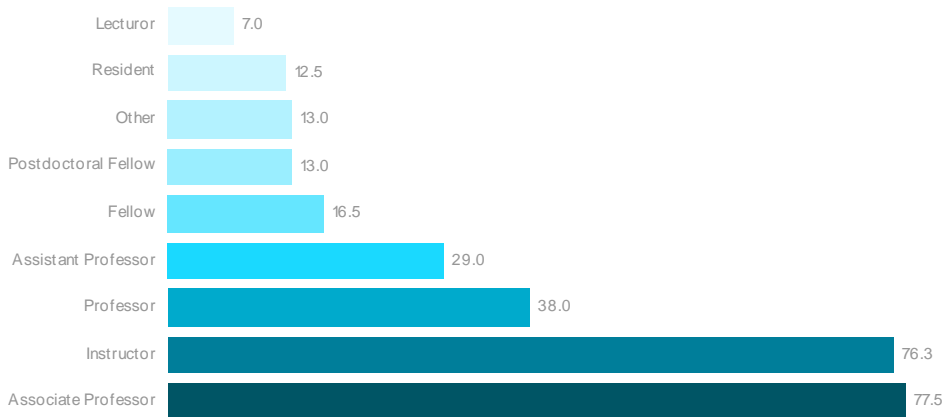


Figure 2a: Number of All Projects by Project Types



Figure 2b: All Projects Hours by Project Types

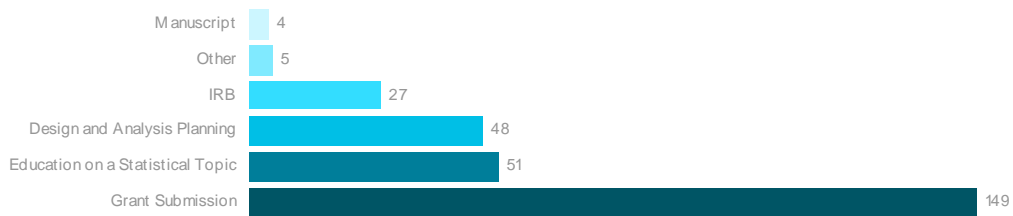


Figure 3a: Number of All Projects by Specialties

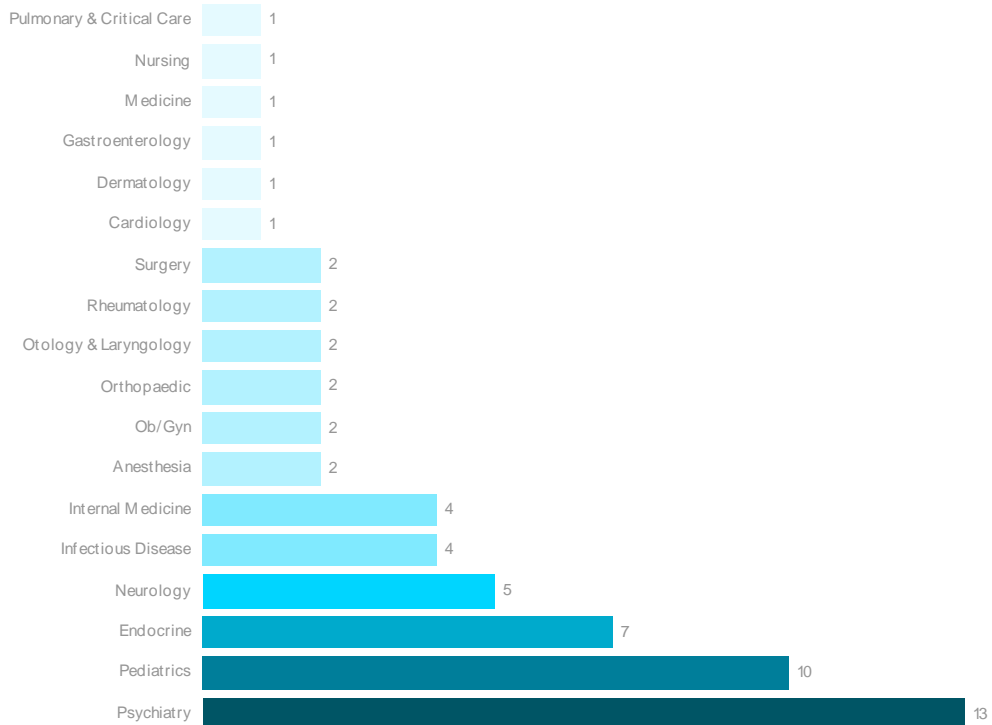
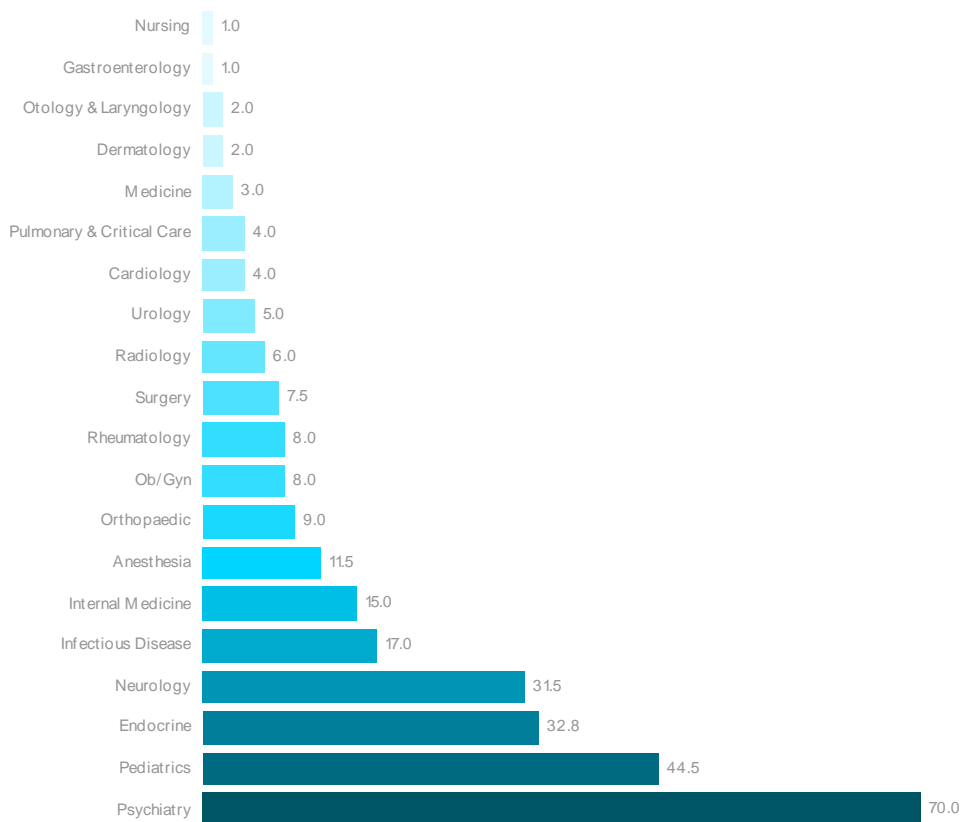


Figure 3b: All Projects Hours by Specialties



LESSONS LEARNED

From Consulting Activities: Locality Matters

A crucial function of the program is to provide MGH's clinical investigative community with local statisticians as interactive collaborators and/or co-investigators on their grant proposals through the consulting activities and laboratory serially over time. These collaborations must lead to the statistician becoming an active member in the research team if the projects are to be fully successful as opposed to merely initial preparatory consultations. The singular and onsite commitment of the CRP Biostatistics Unit to the investigators of the MGH assists such close and evolving interactions.

From the educational mission: The Need is Expanding

The annual CRP Basic Biostatistics Course has enrolled over 100 clinical investigators. Many of the MGH's clinical investigative community are now alumni, and they enjoy a collegial relationship with the Biostatistics Unit through our consultative support activities or tutorials. In many cases, these alumni have become part of research teams that fully integrate the MGH's biostatistical faculty. This improves applications as well as the quality of outcomes. There are also educational components within the individual biostatistical consulting projects, several of which have become important components of NIH career development awards (K series).

These awards often require statistician co-mentors, a role particularly facilitated by our onsite presence. In response to this expanding demand for biostatistics education, we will expand the biostatics offerings in the coming year in collaboration with the CRP's Ed Unit. This collaborative support was launched with a very successful short course in Biostatistics given by Dr. Brian Healy. A particularly popular and unique aspect of his program is the open office hours where investigators are invited to drop in and discuss their research proposals and analyses. This service also includes standing statistical computing and consult lab in dedicated space contiguous to the Biostatistics Unit. There is an interest in providing additional online lectures and tools to allow investigators to learn statistics at their own timing and pace.

From the database support: Locally Available Infrastructure is Essential

Several clinical research teams now require a research database that can be web-based and centrally managed. The Biostatistics Unit has support and infrastructure available for TrialDB and REDCap, both of which satisfy this need.

From the institutions effort on advertisement: The CRP's public relations efforts have increased the visibility and accessibility of our Unit's services; as a result, the Unit supports clinical investigators more widely effectively.

ADAPTATION PLANNED

Unfortunately, many MGH investigators still submit grant proposals with insufficient statistical input and support; these proposals are typically much less successful than those based on our services. Hence, it would be useful if the MGH could establish some new mechanism whereby the CRP's biostatistical review could be inserted into the grant submission process, allowing at least 2-4 weeks prior to submission. This additional support would be especially useful for grants that use the MGH's bridge funding to improve the yield on institutional investment. Similarly, a mandatory statistical review prior to any IRB approval of all clinical studies, coincident with IRB review or even required prior to it, would ensure that study designs are compatible with research goals and might reduce committee time.

Finally, the institution must continue to advertise statistical support to our clinical investigators more widely and effectively. Dr. Finkelstein regularly attends ECOR meetings as a non-voting member of ECOR, thus making Biostatistics more visible at the MGH.

Clinical Research Education Unit (CREU)

Eric Rosenberg, M.D. and Janet Hall, M.D., Co-Directors

GOALS

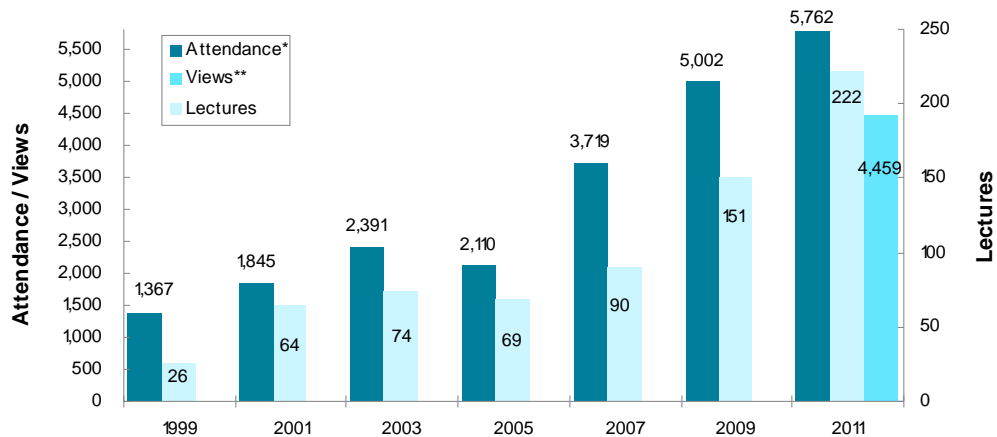
The goal of the Clinical Research Education Unit (CREU) is to improve the quality and quantity of clinical research within the MGH by providing educational opportunities for clinical investigators and their study staff. To meet this goal, we offer courses and seminars that address the unique and rapidly changing educational needs of clinical researchers.

The CREU strives to fulfill the diverse and dynamic educational requirements of clinical investigators through development of innovative course content. In addition, the CREU provides educational programs for research nurses, coordinators and study staff, which are both foundational and responsive to the ever-changing clinical research landscape. We also translate this educational content into web-based learning as swiftly as possible in order to focus on the novel needs of translational research.

ACCOMPLISHMENTS

CREU courses continue to be well attended and well received. The total number of attendees/online viewers increased again in 2011, achieving its highest level since the inception of the program fourteen years ago (Fig. 1). This is a testament to the ongoing need for educational programs for MGH clinical investigators and their study staff. It is also indicative of the CREU's ability to adapt to changing needs, recruit appropriately talented course faculty, and identify timely topics to be covered in course content.

Figure 1: Attendance, Online Views and Lectures, 1999 - 2011



* An attendee is counted once per 'course,' regardless of whether the course is a single lecture or 14 sessions.

** Multiple online resources available; a view counts as a unique user clicking on a single link; individuals may overlap, as an individual may click on several links

A key focus in 2011 was expanding the online access to CREU's educational programs and this initiative was quite successful achieving a remarkable online utilization rate in the first year of its use.

Online courses developed in 2011 include:

1. **Guide to the Research Patient Data Registry (RPDR).** The RPDR is a centralized clinical data registry, originally developed by the CRP, which harvests data from all Partners affiliated hospital systems. The CRP's online training module reviews features of the RPDR Enhanced Query Tool and data wizards and includes multiple walk-through sections which illustrate how to use the RPDR and create queries. In addition, tutorials are available for individuals with specific project needs.
2. **Submitting your Medical Records/Health Information Research Protocol to the IRB.** This online module reviews the process for submitting medical record or health information research protocols to the IRB for expedited review and approval.
3. **Introduction to Phlebotomy.** This online module provides instruction on the basic concepts of phlebotomy and potential adverse events. This portion of the phlebotomy training is required prior to the hands-on course and has proven quite useful for investigators wishing to educate their new study staff.
4. **Clinical Research 101.** In 2011, the CREU revised this course by updating several clinical research-related topics. The online course permits more in-depth information than the prior "live" course and requires the participants to complete a brief quiz to assess comprehension.

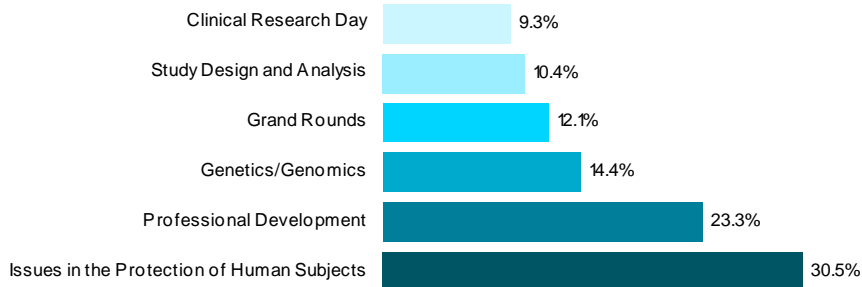
In 2011, the CREU continued to record and post courses on its website and tracked access. The CREU now has an extensive archive of past programs and a growing catalogue of recorded courses. By investing time and effort into online education and in education management, the CRP can now transform courses with consistent content into an online format. This allows us to leverage our staff more effectively to develop new, innovative and interactive live courses.

A second major initiative in 2011 was the development of the **IRB and QI Roundtable Series** in collaboration with the Partners Human Research Committee and the Quality Improvement Program. The goal of this series is to provide instruction to the MGH Community on IRB submissions, regulatory requirements and essential documentation for conducting a clinical study.

Investigator Program

At the forefront of the CREU's agenda in 2011 was the continued development of courses on cutting-edge topics for both junior and senior clinical investigators (Fig. 2).

Figure 2: Percentage of attendees, who were investigators, per course category. Distribution of attendance per course category.



Professional Development is a series of courses focused on skill enhancement and growth; most are eligible for CME credits. Courses provide instruction on Grant Writing, Scientific Writing, Presenting Research Data and Applying for a Career Development Award.

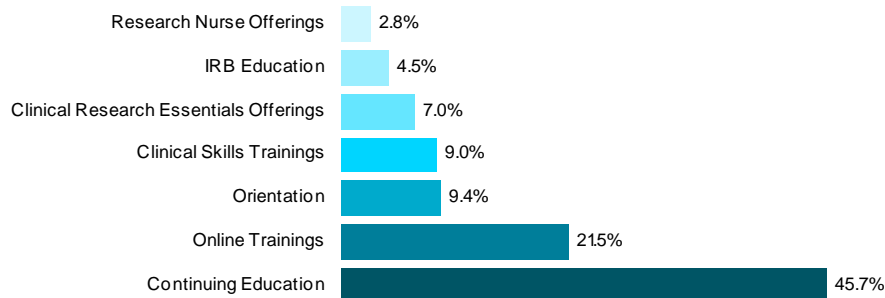
New and revised investigator-focused courses include the following:

Course Category	Investigator Courses	Description	Attendance 2011
Professional Development	Clinical Research Fellows Orientation at MGH	A two-part orientation series focused on the mentor/mentee relationship, navigating the clinical research landscape and accessing resources available for the clinical investigator at MGH.	Attendees: 92 Views: 144
Professional Development	Grant Writing for Clinical and Translational Investigators	Provides essentials of NIH grant writing for the junior investigator with an optional K-Award workshop.	Attendees: 93 Views: 55
Professional Development	From Bench to Bedside: Drug Development in an Academic Medical Center	Overview of the process for how academic discoveries may transition into the development of a new drug or device.	Attendees: 92 Views: 144
Professional Development	An Overview of REDCap: A Free, Web-Based Data Management and Survey	The goal of this course was to introduce Research Electronic data Capture (REDCap), and REDCap Survey. It was developed in collaboration with the Harvard Catalyst. REDCap allows users to create and design data collection tools for research.	Attendees: 200 Views: N/A
Study Design and Analysis	Workshop on Study Design: Using MGH Clinical Care Data for Clinical Effectiveness Research	Introduction to Clinical Effectiveness research using MGH clinical care data.	Attendees: 21 Views: 56
Study Design and Analysis	Basic Biostatistics for Clinical Research	Review of fundamental biostatistical concepts commonly used in clinical research.	Attendees: 75 Views: 385

Study Staff Program

The study staff curriculum supports MGH clinical investigators by providing educational resources for their study staff. This program has been a cornerstone of the CREU since its formation in 1996. At that time, there were no such educational opportunities within the MGH. These educational and community-building opportunities provide study staff with updates on new developments in clinical research regulations and operations, while increasing their knowledge of clinical research essentials. The program continues to be one of the CRP's most successful efforts (Fig. 3).

Figure 3: Percentage of attendees, who were study staff (excluding investigators), per course category. Distribution of attendance per course category.



The following courses were new initiatives specifically designed for clinical research coordinators, project managers, research nurses and assistants:

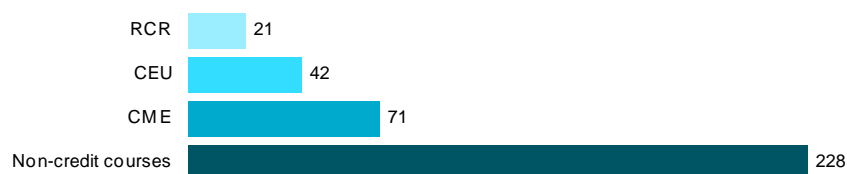
Study Staff Courses	Description	Attendance
Working with Study Subjects with Limited English Proficiency	This course focused on regulatory requirements and IRB policies for obtaining and documenting informed consent from non-English speaking subjects in clinical research studies as well as how to plan for and schedule medical interpretation services.	Attendees: 34 Views: 24
ClinicalTrials.gov Registration	The goal of this course was to explain the requirements set forth by FDAAA and the International Committee of Medical Journal Editors (ICMJE) for registering a clinical trial.	Attendees: 50 Views: 18
Internet Recruitment and Retention: IRB, Security and Web 2.0	The potential ethical and privacy issues involved in recruiting subjects using online bulletin boards was discussed in this course.	Attendees: 110 Views: 141
The Principles and Practice of Clinical Research Data Management	Managing clinical research data in accordance with Good Clinical Practice (GCP) Guidelines was the focus of this course. The course also compared different data capture systems and outlined data management priorities for studies with limited resources.	Attendees: 97 Views: 28
Operationalizing a Clinical Research Protocol	Participants in this course received an overview of how to "operationalize" a clinical research protocol. This was done by explaining the challenges that typically arise from translating a protocol submitted as part of a grant application into a protocol that will be submitted to the IRB.	Attendees: 48 Views: 27

The CREU's course, **Clinical Skills Trainings**, in phlebotomy, ECG and vital signs remained in high demand in 2011.

Continuing Education

The CREU also offered several continuing education courses for physicians and nurses (CME, CEU) and courses eligible for credit in the **Responsible Conduct of Research (RCR)** (Fig. 4).

Figure 4: Credit (CME, RCR, CEU) vs. Non-credit courses (hours)



Clinical Research Day

Clinical Research Day continues to be an institutional linchpin of the CRP's efforts to build a viable community of clinical researchers across the institution. It is recognized as a platform for clinical investigators to present and receive attention and reward from the institution's leadership for their work, as well as a venue for interactions and collaborations amongst investigators. The 2011 theme was **Clinical Effectiveness Research** and Carolyn Clancy, M.D., Director of the Agency for Healthcare Research and Quality (AHRQ), served as the keynote speaker. Participation in clinical research day remained high with 240 submitted abstracts and 17 team nominations. (Fig. 5 and Fig. 6).

Figure 5: Clinical Research Day 2011: Abstracts by Category

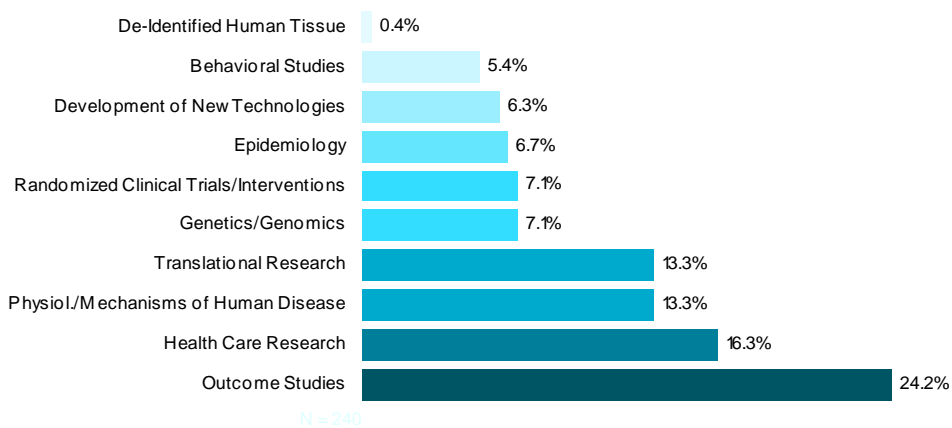
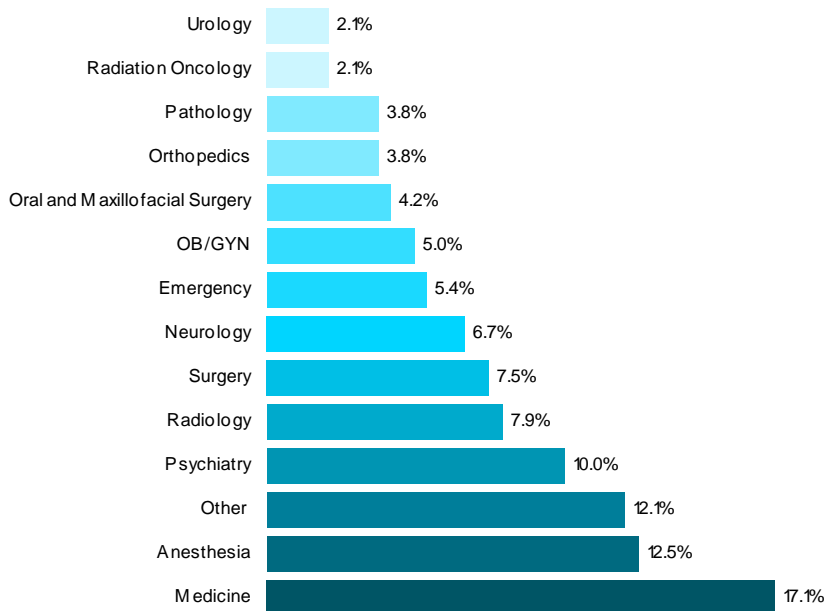


Figure 6: Abstracts Submitted by Department



Following Dr. Clancy's address, there was a panel discussion entitled ***Expanding Funding Opportunities for Clinical Effectiveness Research within Academic Health Center***, moderated by Timothy G. Ferris, M.D., Medical Director, MGPO. Members of the panel included Dr. Clancy, David Blumenthal, M.D., M.P.P., Peter Slavin, M.D., President, MGH and David Torchiana, M.D., Chairman and Chief Executive Officer, MGPO.

Collaboration with Harvard Catalyst

The CREU staff has been an active participant in the development of the Harvard Catalyst's Advanced Curriculum Compendium and has provided leadership to the Catalyst's educational efforts with Eric Rosenberg heading both. The CREU continues to share its courses with the Harvard Catalyst community, thus meeting the needs of MGH investigators and sharing its expertise in clinical research education. Due to the popularity of and demand for CREU courses amongst both MGH and Harvard Catalyst investigators, there also remains a strong local need to produce these courses at MGH while simultaneously serving the needs of the Harvard Catalyst community given the geographic inconvenience and time most MGH investigators encounter in attending the Catalyst courses at the quadrangle. Drs. Rosenberg and Hall's involvement in Harvard Catalyst educational planning efforts places the CREU in a strong position to ensure collaborations and to limit redundancy between the two programs. The CREU has worked closely with Harvard Catalyst team members in 2011, fostering collaborations and supporting the development and execution of many educational initiatives. These included a REDCap survey course, Imaging Basics and a course on Engaging Diverse Communities.

LESSONS LEARNED

1. **Interest.** Interest in CREU educational programming remains high. There is a continuing desire for basic level courses as well as a growing demand for more advanced material from both clinical investigators and study staff that has not been met by the Harvard Catalyst.
2. **Curriculum.** The CREU curriculum is highly adaptable and responsive to course evaluations and requests from the clinical research community. Content areas are suitable for building a foundation for both investigators and study staff and the CREU has identified and addressed some of these topics in 2011 (see Fig. 7 for full 2011 course listing).
3. **Meeting the needs of the MGH clinical research community.** By providing onsite *and* online courses for investigators and their staff, the CREU is able to offer accessible learning opportunities for all members of study teams.
4. **Access.** High attendance at CREU investigator courses in 2011 shows that clinical investigators at MGH make frequent use of onsite continuing education. While Harvard Catalyst education efforts may help to fill specific needs, local availability of courses that fit easily into busy work days combined with timely topics, offering continuing education and RCR credit, and outstanding faculty have been keys to the success of the CREU.
5. **Online Education.** Online education is a highly valuable resource to the MGH clinical research community. By making courses accessible at all times, the CREU is able to increase its impact and provide even better services and resources to the

clinical research community. By placing more foundational and unchanging courses online the CREU can better utilize the highly valuable time of its course faculty, focus its live courses on more current topic areas, and provide more interactive and in-depth in-person education.

6. **Building a Clinical Research Community at MGH.** Clinical Research Day continues to meet this long-term goal. This event is remarkable for its dynamic nature, attendance, participation, and involvement of MGH leadership. Whereas most clinical investigators used to work within their own silos within individuals Departments, they now have begun to establish a cross-group platform of communication, technique sharing, and emotional support that is essential to the future vigor of clinical research at the MGH.

FUTURE ADAPTATIONS TO THE PROGRAM

1. The CREU will continue to build on the Online Education foundation built in 2011 by enhancing and promoting its online education resources and creating additional online educational opportunities. New initiatives include: ***Scientific Writing, Pre-Analytics and Specimen Collection*** and ***Subject Recruitment Basics***.
2. The CREU will continue to develop, innovate, and create dynamic learning opportunities for study staff. Courses in development for 2012 include: ***Overview and Implementation of Good Clinical Practices in a Clinical Research Study, Working on NIH Clinical Research Studies, Recruiting Vulnerable and Disabled Populations in Clinical Research, The Role of Clinical Research in Global Health,*** and ***Basic Genetics in Clinical Research***.
3. The CREU will expand its curricular pathway for investigators and develop a similar "Career Pathway" for clinical research coordinators and research nurses.

Figure 7: CRP Education Unit - Courses and Participation 2011					
Investigator Program	Attended*	Faculty	Lectures	Hours	Views**
<u>Study Design and Analysis</u>					
Basic Biostatistics for Clinical Research (workshop sessions 5-10)	75	1	6	9	301
Applied Biostatistics for Clinical Trialists	135	1	4	6	316
Problem-Based Biostatistics for Physiologic Investigators	57	1	4	8	140
Design and Conduct of Clinical Trials	46	24	14	26	NA
Workshop on Study Design: Using MGH Clinical Care Data for Clinical Effectiveness Research	21	11	5	6.5	82
<u>Genetics/Genomics</u>					
Epigenetics: An Introduction and Applications	147	3	1	3	124
Welcome to the Genetic Code: An Overview of Basic Genetics	121	2	1	3	717
Genetic Literacy: An Intermediate Guide to Understanding the Language and Concepts of Modern Genetic Research	72	4	1	4	24
A Primer on Complex Trait Genetics: Basic Principles for the Beginning Investigator	80	9	1	6.5	NA
Adding Pharmacogenetics to Clinical Investigation: A Practical Guide	45	3	1	4.5	NA
<u>Issues in the Protection of Human Subjects</u>					
Genetics and Clinical Research: Points to Consider	69	1	1	1.5	5
IRB Issues for the Bench and Desk Scientist (Spring)	85	1	1	1.5	13
What Does the IRB Really Want? How to Write a Human Studies Protocol (spring)	83	1	1	1.5	29
ClinicalTrials.gov: The Rules & How Partners is Implementing Them	97	1	1	1.5	64
Maintaining Research Subject Privacy and Information Security: What Clinical Researchers Must Know (Spring)	121	3	1	2	45
Trends in Public and Participant Opinions in Biobanking: Review of the Literature and Legal Case Precedents	62	1	1	1.5	NA
Ethics and Clinical Research Protocols	67	1	1	1.5	14
IRB Issues for the Bench and Desk Scientist (Fall)	33	1	1	1.25	12
FDA Inspections, 483's and Warning Letters: How to Avoid and Survive Them	35	2	1	1.5	15
What Does the IRB Really Want? How to Write a Human Studies Protocol (Fall)	64	1	1	1.5	14
Genetics and Clinical Research: Points to Consider (Fall)	74	1	1	1.5	5
Who Tells the IRB What to Do?: The Effects of Case Law on Research Regulations and Oversight	39	1	1	1.5	9
Maintaining Research Subject Privacy and Information Security: What Clinical Researchers Must Know (Fall)	64	3	1	2	11
Incidental Findings in Clinical Research: Ethical & Regulatory Considerations	90	1	1	1.5	NA
<u>Professional Development</u>					
QUOSA: An Information Manager	24	1	1	1.5	39
Online Overview of Research Patient Data Registry (RPDR) (<i>workshop</i>)	7	1	1	2	NA
An Introduction to the Enhanced RPDR Query Tool (January)	67	1	1	1	50
From Bench to Bedside: Drug Development in an Academic Medical Center	37	3	1	3	56
Using the RPDR Enhanced Query Tool to Obtain Discarded Specimens	43	1	1	1	22
Clinical Research Fellows Orientation Part I: Starting Your Clinical Research Career at MGH (Spring)	33	3	1	2	44
MGH Clinical Research Fellows Orientation Part II: Resources for the MGH Clinical Researcher (Summer)	26	11	1	4.5	107
How to Make a Poster (offered 2x)	37	1	2	2	130
Grant Writing for Clinical and Translational Investigators	93	3	1	2.25	70
Clinical Research Fellows Orientation Part I: Starting Your Clinical Research Career at MGH (Fall)	33	3	1	2	NA
How to Give a Presentation	119	1	1	1.25	71
Applying for an NIH Career Development Award	23	1	1	3	4
REDCap Training: General Overview	47	1	6	1	NA
REDCap Training: Basic Programming	54	1	6	1	NA
REDCap Training: Advanced Programming	31	1	6	1	NA
REDCap Programming Training	75	1	8	16	NA
<u>Grand Rounds</u>					
Medicine Grand Rounds: "A Piscine Approach to Academic Drug Discovery: Bones, Blood, and Brains"	63	1	1	1	NA
Pediatric/Endocrine Grand Rounds: "The Molecular Basis for IGF Deficiency"	78	1	1	1	NA
Medicine Grand Rounds: "Genetic Architecture of Rheumatoid Arthritis: From Genotype to Patient Care"	65	1	1	1	NA
Neurology Grand Rounds: "The Genetics of Intracerebral Hemorrhage"	62	1	1	1	NA
Psychiatry Grand Rounds: "Perspectives on Psychiatric Illness from Genetics"	38	1	1	1	NA
Neurology Grand Rounds: "Genome Scale Sequencing for Neurodevelopmental Disorders"	84	1	1	1	NA
<u>Clinical Research Day</u>					
Overview of Abstract Submissions, Keynote Address, Panel Discussion	300	9	2	4	NA
Total, Investigator Program	3,221	127	99	152.8	2,533

Figure 7: CRP Education Unit - Courses and Participation 2011					
Study Staff Program	Attended*	Faculty	Lectures	Hours	Views**
Orientation					
Clinical Research 101	126	10	9	31.5	NA
Orientation to Clinical Research at MGH	113	13	9	27	NA
IRB Education					
Partners Human Research Committee Updates	9	1	1	1	NA
Tissue Issues in Research: Current IRB Perspectives	17	1	1	1	14
Reliance Agreements and Cede Review Process	5	2	1	1	NA
Review of Human Subjects Research at Convened Meetings of the Partners IRB (Full Board Review)	12	3	1	1	NA
Continuing Review of Human Subjects Research at Convened Meetings of the Partners IRB (Full Board Review)	17	2	1	1	13
Meet the Protocol Administrators and Managers of the Partners Human Research Office	30	25	1	1	NA
New Submissions: Initial Review of Human Subjects Research at Convened Meetings of the IRB (Part I)					
New Submissions: Initial Review of Human Subjects Research at Convened Meetings of the IRB (Full Board Review)	10	3	1	1	22
Continuing Review and Amendments	15	2	1	1	4
Research Nurse Offerings					
RN Roundtable	72	2	7	7	14
Clinical Research Essentials Offerings					
Study Management - Maintaining a Regulatory Binder	22	1	1	1	73
Tools for Web 2.0 Recruitment: Current Choices and Future Opportunities	15	1	1	1	27
Study Management Workshop: Source Documentation and CRFs	16	1	1	1	14
The Process of Informed Consent	11	1	1	1	17
Event Reporting in Clinical Research Studies	19	1	1	1	22
Reading and Understanding a Clinical Research Protocol	11	1	1	1	11
IRB/QI Discussion of Minimal Risk Studies, Requirements and Resources	24	2	1	1	9
Communicating within Study Teams	17	1	1	1	NA
New Submissions (Part II)	27	1	1	1	12
Source Documentation	17	1	1	1	14
Clinical Skills Trainings					
ECG training	61	1	10	25	NA
Phlebotomy	112	2	16	32	NA
Vital signs training	55	1	8	20	NA
Continuing Education					
Budgeting for Industry Sponsored Trials	44	2	1	1.5	50
Internet Recruitment and Retention: IRB, Security and Web 2.0	110	2	1	1	143
Understanding and Writing Clinical Research Literature	44	5	3	4.5	193
An Overview of REDCap: A Free, Web-Based Data Management and Survey Tool (Winter)	72	1	1	1	80
An Introduction to Accounts Payable's New Electronic Research Subject Payment System	117	1	1	1	56
The Cultural Competence in Research Symposium	46	10	1	3.5	NA
Working with the MGH Clinical Research Center (CRC)	34	1	1	1	15
IND/IDEs - Beyond the Basics of Investigational Product Applications	47	10	2	4	78
Clinical Research Subject Remuneration: Policy and Process	62	1	1	1	31
Working with Study Subjects with Limited English Proficiency	34	2	1	1	23
Sponsoring and Managing Multi-Center Clinical Trials	62	2	2	5	41
The Principles and Practice of Clinical Research Data Management	97	1	1	1.5	29
Operationalizing a Clinical Research Protocol (Summer)	48	1	1	2	29
Budgeting for Industry Sponsored Clinical Research & Managing Sponsor Invoicing	47	2	1	1.5	21
An Overview of REDCap: A Free, Web-Based Data Management and Survey Tool (Summer)	80	1	1	1	16
Updates from the Partners IRBs	72	1	1	1	14
ClinicalTrials.gov Registration	50	1	1	1	19
eIRB Training: A Hands-On Introduction to eIRB (offered x4)	29	1	4	8	NA
eIRB Training 2.0: A Hands-On Review of eIRB (offered x 2)	20	1	2	4	NA
Operationalizing a Clinical Research Protocol (Winter)	47	1	1	1	NA
Online Trainings					
Research Patient Data Registry (RPDR) (online)	26	1	9	0.75	81
Good Clinical Practice and Study Management Basics (online)	52	2	4	0.5	216
Submitting your Medical Record/Health Information Research Protocol to the IRB (online)	10	1	5	0.75	31
IATA Shipping Training for Transportation of Biological Materials and Dry Ice (online)	394	1	5	0.5	423
Infection Control Principles and Practice in Clinical Research (online)	64	1	4	0.5	71
Total, Study Staff Program	2,541	130	123	209	1,926
Grand Total	5,762	257	222	361.8	4,459

Clinical Effectiveness Research Unit (CERU)

Richard W. Grant, M.D., M.P.H.

Clemens Hong, M.D., M.P.H.

James B. Meigs, M.D., M.P.H.

Co-Directors

GOALS

The CRP's Clinical Effectiveness Research Unit (CERU) has two main objectives:

- To support clinical research designed to improve the clinical practice of medicine
- To provide mentorship for academic research careers in clinical research

The CERU focuses specifically on that “Translational Block” that exists between clinical trial results and the implementation of their advances into clinical practice. Together with the CRP's Informatics Unit, the CERU seeks to establish and support at MGH the clinical research infrastructure necessary for “clinical effectiveness research.” Such research demands rigorous patient-oriented biomedical investigations that use comparative effectiveness, clinical outcomes and allied research approaches to improve our current healthcare delivery. We support trainees at all levels but are primarily focused on MGH's junior faculty investigators. Given the challenges that we face in improving the effectiveness, efficiency, and equity of healthcare delivery, the CRP believes that patient oriented comparative effectiveness research is one of the most important growth areas in clinical research. Comparative effectiveness research will help us learn how to improve healthcare delivery systems. In the near future, organizations will need to be more accountable and transparent, and this will require high quality information to guide thoughtful, data-driven and value-based changes in patient care. Careers in this area are increasingly fundable, offering the possibility for stable research and data-oriented administrative careers. We will also need to attract many of our best and brightest clinical investigators into this field and provide them with a support matrix like the CRP's CERU. Such support will assure their retention and career development.

ACCOMPLISHMENTS

Focus on Supporting Comparative Effectiveness Research (CER)

In response to increasing health care costs, the need for payment reform, and the continuing gap between evidence and practice, the Federal Government has substantially increased available funding to support comparative effectiveness research (CER). Defined as the conduct of research comparing the benefits and harms of different health care interventions and strategies, CER assesses a wide range of health outcomes for diverse patient populations and subgroups. This research requires the development, expansion, and use of data sources and methods to determine comparative effectiveness and disseminate the results.

The CERU provides MGH's clinical investigative community with individual mentorship in the domains of epidemiology, study design, questionnaire and survey methods, and clinical database use. The CERU also provides data management and analytic support for investigators, operational planning for the use of clinical care data for clinical research,

and assistance with grant and IRB preparation. In addition, the CERU serves as a resource for locating potential funding.

Clinical Innovation Award (CIA): Translating Clinical Insights into Improved Care

The Clinical Innovation Award (CIA) program, initiated in collaboration with the CEO, Peter Slavin, MD, who funded the pilot program and more recently with Gregg Meyer, MD MSc, Senior VP for Quality, has been an outstanding success for the CERU. After five years of success (2005-10), CIA operations were transferred in 2011 to MGH's Department of Quality and Safety, which supports rigorous evaluations of current MGH Care Redesign projects.

The annual Request For Applications (RFA) for this program announces the intent to support 4-5 hypothesis-driven research projects focusing on PHS Care Redesign and Patient Affordability Initiatives and Accelerating Improvements in Efficiency. All MGH Physicians, nurses, and allied health professionals participating in active Care Redesign or Patient Affordability were eligible to apply. Awards support a portion of the PI's salary to allow protected time to devote to the project (up to 20%); research infrastructure support necessary to carry out the project (e.g. biostatistics, project management, informatics development, study coordinators for data collection, and research assistant/study coordinator support); and faculty co-mentorship (with the Quality and Safety Office) from the MGH Clinical Research Program to help design, execute and evaluate the projects.

Seven applications were received in 2011. James B. Meigs, MD, MPH, Co-Director of the CERU, served as the CIA Review Committee's study section chair. Five awards were given for the 2011-2012 cycle. Support for five awards is a testimony to the many excellent applications received and MGH's commitment to rigorous care redesign and patient affordability initiatives. Recipients of the five awards and their projects are as follows:

Elizabeth Martinez, MD, MHS, Arvid Agnihotri, MD, and Thor Sundt, MD: Coronary Disease Care Redesign Team: Building an infrastructure for care improvement in cardiac surgery.

Linda M. Delahanty, MS, RD and Deborah Wexler, MD: Diabetes Care Redesign Team: Improving diabetes outcomes through lifestyle change (IDOLc) translation study.

R. Sacha Bhatia, MD, Michael Picard, MD, and Rory B. Weiner, MD: Coronary Disease: AMI Care redesign team: An educational intervention to reduce inappropriate ordering of transthoracic echocardiograms on the General Medicine Service.

Andrew Freiberg, MD, Richard Pino, MD, and Greg Pauly: Arthroplasty/Total Joint Replacement Care Redesign Team: Total Joint Replacement Accelerated Rehabilitation.

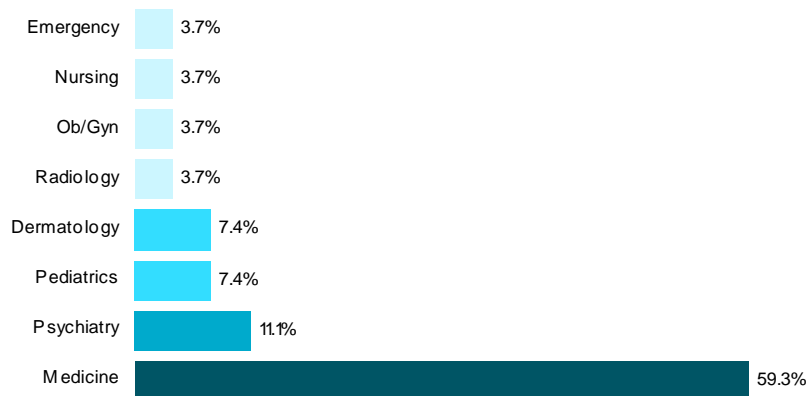
Laura Riley, MD: OB / Vaginal Delivery Team: Redesigning Obstetrical Care with a Focus on Induction of Labor.

Mentorship and Consultation

During 2011, the CERU continued to provide mentoring services, consultation on study design and survey development, and data analysis/data management to the MGH community. The impressive breadth of Departments served by the CERU in 2011 is

shown in Fig.1. These services, available hospital-wide, included advice on hypothesis generation, IRB submissions, data assembly and management, IT implementation and application, and analysis methods. The CERU provides generic consults related to any question or need for any of these services, consults for the CIA program, and consults that continue research mentorship relationships. All of the research that the CERU support addresses second translational block issues, either directly as in the institutional CIA program or more indirectly through methods development or tests of hypotheses derived from first translational step research.

Figure 1: Clinical Effectiveness: Consultation by Department



2011 Collaboration with Harvard Catalyst

The CRP's CERU is a unique resource for MGH clinical investigators engaged in clinical effectiveness research. Consulting, mentoring and resource-linking for clinical effectiveness research are *not* offered through Harvard Catalyst. At MGH the CRP's CERU collaborates with other CRP Units to develop educational programs directed to patient-oriented / clinical effectiveness investigators, provide support for any investigators who wish to develop careers in effectiveness research and provides individual consultation on CER study design and appropriate databases for these studies. The CERU also assists investigators in accessing and interpreting the PHS clinical data warehouse/RPDR for specific studies.

2011 Initiatives

New course offering: In 2010, the CERU initiated a new Clinical Effectiveness Research course in collaboration with the CRP Education Unit. This 4-session workshop took 20 investigators step-by-step through the process of defining a CER question, obtaining IRB approval, designing an RPDR data query, and converting the “raw” clinical data received in a research-caliber analytic database. Based on positive responses (70% rated course Excellent; 27% rated it Good) and helpful feedback from the initial cohort of participants in 2011, the CERU expanded this educational program by creating two separate learning experiences, each operating at a different level of sophistication. One course is designed specifically for MD / PhD clinical investigators. Faculty researchers (whose participation in this course was contingent upon their submitting a 1-page research proposal outline) participated in a CER workshop course on study design, hypothesis testing, and analysis plans. Admission to the workshop was limited to ensure a low instructor-student ratio.

The second course is designed for research project managers, coordinators and other non-faculty study staff. This course will help attendees to understand and formulate RPDR queries and will be linked into an RPDR-user community where solutions to data management can be shared.

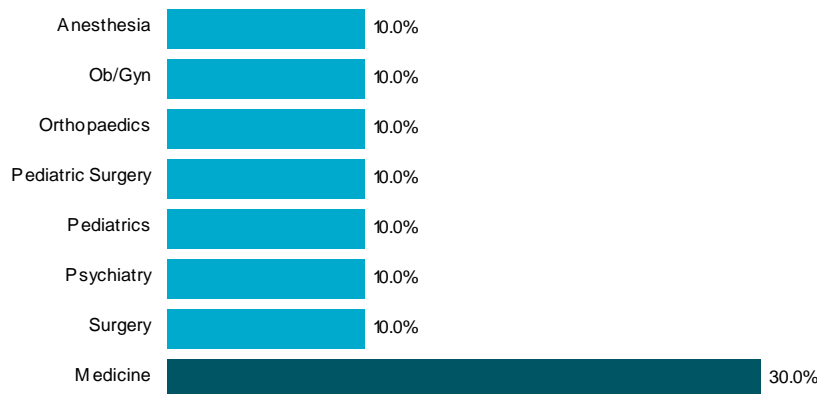
Additional 2011 CERU support

RPDR support: In 2011, Wei He, MPH. joined the DMRU as an RPDR data analyst, manager, and “RPDR Reference Librarian”. Wei provides cleaned data to clinical investigators and offers tutorials for individuals who need a more ‘hands-on’ knowledge of RPDR. In 2011, Wei provided cleaned RPDR searches in Access file format for 10 different projects seeking help with this research need.

Investigator	Project
Wei, Nancy J., M.D.	Readmission database
Florez, Jose C., M.D., Ph.D.	2 projects: MetS for BWH; Pharmgen
Zhang, Mary, M.D.	Genetic study extreme HDL
Elmariah, Sammy, M.D., M.P.H.	2 CAD projects
Januzzi, James Louis, M.D.	Cost data for CHD
Bryant Mantha, Allison S., M.D.,M.P.H.	Postpartum women
Volandes, Angelo E., M.D.	Death info for admitted patients
Wexler, Deborah, M.D.	Diabetes care data

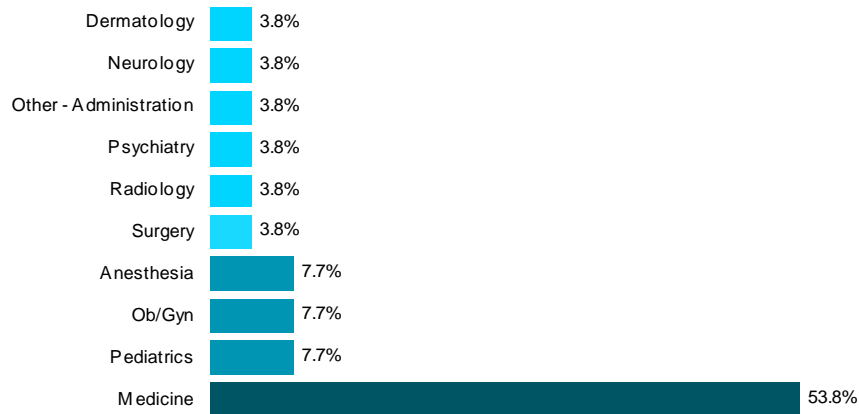
Database Consulting: Data consultation services were made available to the MGH clinical research community in the second quarter of 2011. Under Susan Regan, Ph.D. the data management consultation service offers review of protocol and data collection forms as well review of existing or planned data entry systems. The service also offers training in day-to-day management of ongoing projects in Access databases, including such skills as report and query design, integration of external sources of data (e.g. from laboratories, other sites), and data export for analysis. This program has been expanding since the second quarter of 2011, during which time ten faculty members benefited from the service.

Figure 2: Database Consultation by Department



Survey Consultation Service: Eric Campbell, Ph.D., Associate Professor of Medicine and member of MGH’s Institute for Health Policy and HMS, established and expanded the CERU’s new Survey Consultation Service for a total of 25 formal consults which included all aspect of study design, execution and interpretation. Quantitative results of this outstanding effort are shown in Fig. 3.

Figure 3: Survey Research: Consultation by Department



2011 CERU Leadership Transitions: After 9 years as Co-Director of the CERU Dr. Richard Grant left the MGH to join the research faculty at Kaiser Permanente of Northern California. This is a terrific opportunity for Richard and the CRP thanks him for his many years of creative and energetic contribution to the CRP mission. Clemens Hong, MD, MPH, joined the CRP to become Co-Director of the CRP’s CERU. Clemens completed his general medicine fellowship training at Harvard before taking a faculty position as a primary care physician and health services researcher at MGH. He works in the MGH General Medicine Division and brings a strong focus on implementation research and health care delivery science. Clemens will engage in traditional CERU consultation and resource-linking roles as well as expand our capacity to support health services research and rigorous evaluation of operational endeavors at MGH.

LESSONS LEARNED

After five years, the Clinical Innovation Award Program has become a successful and well-established part of the MGH research mission. In developing the program, the CERU unit has not only created an effective mechanism for eliciting good proposals in areas of critical future need for the MGH (i.e. outcomes and operation research), but also has encouraged an institutional environment of research curiosity and collaboration across different departments and between administrators and researchers. Even more importantly, it has demonstrated that even in an operationally intensive, “just do it” environment that clinical effectiveness studies do not necessarily impede progress, delay implementation.

In 2010, we began the process of transferring administration of the Clinical Innovation Award program to the MGH Center for Safety and Quality. This “hand-off” has allowed CERU faculty in 2011 to concentrate their efforts on building an infrastructure for the MGH and MGPO to support clinical investigators who plan to seek Federal funding for

CER research as the institution begins to function as an ACO. This Unit represents a very strong MGH institutional commitment to research infrastructure, consulting, and career development in Comparative Effectiveness, Clinical Outcomes Clinical Epidemiology, Care Redesign, Patient Affordability and Accelerating Improvements in Efficiency research. In this sense MGH remains a leader in clinical research support, as nothing comparable is available elsewhere in Partners or the Harvard Catalyst systems.

ADAPTATION PLAN

CERU adaptations to its support services for 2012 will enable MGH investigators to:

- Define patient cohorts for further study
- Develop patient and provider recruitment strategies for clinical trials or for survey-based research
- Create patient clinical research databases for epidemiological studies, quality improvement and operations research
- Formulate testable hypotheses and rigorous study designs
- Prepare grant proposals
- Increase support for rigorous operations research, especially that focused on Care Redesign and Patient Affordability

We provide a critical and unique resource to connect clinicians, MGH leadership and clinical investigators with study design and IT expertise. These collaborations are the fount of new solutions to disease management and healthcare delivery problems at MGH. Collaborations also nurture new careers in patient oriented clinical investigation and increasingly support MGH operational leaders seeking data-oriented administrative careers.

As we adapt to change, including the 2012 transition to an ACO model, we will continue to develop clinical research personal capability and clinical research infrastructure. A major adaptive initiative is the establishment of highly detailed retrospective, longitudinal data resources for clinical epidemiology research. Such research will inform ongoing and future real time population research infrastructure development. These efforts are in natural collaboration with Drs. Meigs and Hong's MGH General Medicine Division colleague Steve Atlas, MD, MPH, Director and PI of the MGH Primary Care Operation Improvement's Linked Loyalty Cohort, and the General Medicine Unit's Practice-Based Research Network. The Linked Cohort-PBRN is a mirror-image operations-research resource that will increasingly serve clinical research goals as well as hospital quality improvement and patient care efforts. The MGH CRP CERU will help build a research data infrastructure that in order for MGH to become a learning health care delivery system. The approach leverages high quality data to both improve front line healthcare delivery and conduct clinical effectiveness, clinical outcomes, health services, and operations research. Linked to these efforts is our focus on career mentorship for clinical investigators. We will continue to develop a strong cohort of MGH researchers pursuing academic careers in clinical effectiveness, clinical outcomes, and health services research. These efforts will help the MGH to become an Accountable Core Organization (ACO) and to compete successfully for federal CER support resources.

Additional Adaptations by the CERU in 2012:

Pipelines and Consults. The CERU plans to pursue new ways to identify talented future MGH research faculty by increased interactions with trainees (residents and fellows), and through consulting with faculty in positions to mentor these individuals. As an example, the Harvard Center for Primary Care at Harvard will provide \$5 million in funds to Harvard affiliated teaching hospitals, including MGH, to transform the delivery of primary care in the practices in which internal medicine and primary care residents train. An explicit goal of the funding is to involve residents and medical students that work in these practices in operations improvement and the generation of academic products for this work. CERU will offer consulting and mentoring services to internal medicine and pediatrics faculty that are leading this transformation of care, and provide support for faculty interested in evaluating practice change. This will provide the opportunity to both engage existing MGH faculty in research activities and identify and support trainees with high potential for research careers that work with MGH faculty on operational research projects.

Expand model for Operational Research Engagement. In January 2012, Dr. Hong will begin to attend a monthly MGPO quality improvement meeting. He will meet with Timothy Ferris, MD and others with the aim to identify opportunities to help MGPO faculty evaluate ongoing and newly developed quality improvement projects. The intention is to help faculty involved in hospital operations to be able to develop research questions and methods and publish the results in peer-reviewed literature. Ultimately, the goal is to create a self-supporting model MGPO in operational research activities.

Curriculum development for operations researchers. In 2012 we will consider whether there is interest in expanding the curriculum of the CRP CERU/Education Unit Clinical Effectiveness Research course to include modules of particular interest to those with interests in operational research, alternate study design and program evaluation. We will explore a range of opportunities, but will strongly consider adding a module that provides an overview of study design (e.g. quasi-experimental methods, realistic evaluation, and mixed methods research) pertinent to operational and quality improvement research.

Information Technology Unit (ITU)

Henry C. Chueh, M.D., M.S., Director

GOALS

The broad goal of the CRP's Information Technology Unit (ITU) is to support the increasing information technology needs of the MGH's clinical investigative community. Its specific approaches to meeting this goal is to:

- improve existing information management resources while attempting to create a broad, new information management infrastructure to support the work of the clinical research community at MGH and PHS;
- provide IT management support for MGH clinical investigators, including assisting in the recruitment of study subjects and supporting the CRP's educational initiatives;
- establish ongoing partnerships with clinical researchers to pilot applications and studies with new clinical informatics-based interventions that will create reusable technology platforms for such studies.

ACCOMPLISHMENTS

Our work in 2011 focused principally on building three specific IT solutions targeting different aspects of the clinical research process:

- *Clinical Research Program Hub* – continued development of an online learning management system for clinical research education
- *Monitoring of Online Record Access (MORA)* – completion of the first phase of a platform that supports secured and audited clinical data access for clinical research monitors
- *Dynamic Linkage Cohorts* – creation and maintenance *prospectively* of provider patient panels for research or analysis of operations.

In addition, the IT Unit continued to support:

- *Clinical trials recruitment web sites* – clinicaltrials.partners.org, rsvpforhealth.org
- *Clinical data provisioning for clinical researchers* – exploration of more effective methods of clinical data provisioning to clinical researchers

Clinical Research Program Hub - a site for online learning

Increased use of Hub-based E-Learning courses in previous years revealed a need for better tracking, certification, and recertification support. In 2011, we enhanced the delivery of electronic course content in the Hub and to the Hub's learner tracking tools.

MORA – Monitor Online Record Access

In 2011, we continued our development of MORA (Monitor Online Record Access) in collaboration with Partners Research Computing, the MGH Cancer Center, and the cancer research groups at BWH and Dana-Farber. MORA was successfully piloted with the Clinical Research Program's study coordinators. This pilot successfully demonstrated the key access control features of MORA:

- 1) use of protocol study staff lists in Partners Insight to automatically enable some study staff to manage study monitor access to their protocols;
- 2) creation and management of protocol-linked patient lists by study staff
- 3) limitation of study monitor access to electronic views of data only for patients in protocol-linked patient lists.

MORA eliminates the massive administrative overhead of traditional methods of monitor data access, and applies to numerous monitored studies overseen by the Partners joint IRB. MORA permits outside monitors to access the limited information they require to monitor compliance by outside agencies without burden to the MGH clinical investigator's study coordinator staff and a reduction of their productivity. MORA also offers other opportunities for efficiency within our community. For example, the Dana-Farber IRB oversees MGH cancer studies, but Dana-Farber does not use Partners Insight, and is working on transitioning to a new research management system. Despite this, our team was able to establish an efficient model for MORA that will work for the cancer research centers within their heterogeneous systems environment. The cancer versions of MORA rolled out in December 2011 with general release of the application to researchers at MGH and BWH to follow. As a custom software product, MORA is designed to enhance productivity despite variable workflow across sites.

Dynamic Linkage Cohorts

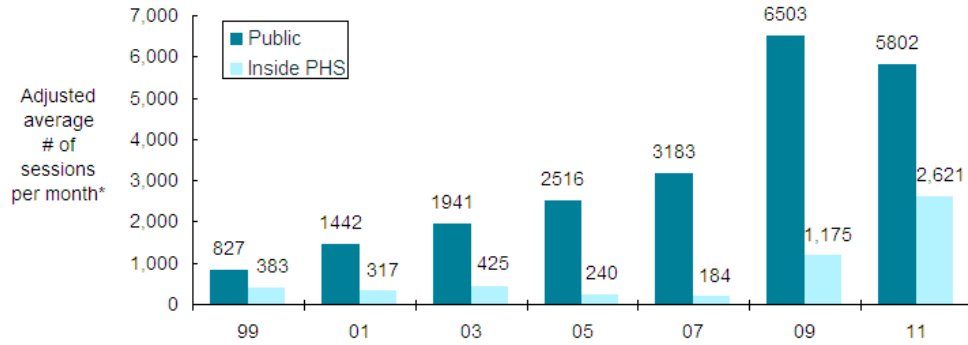
In collaboration with Dr. Steven Atlas of the General Internal Medicine Unit, we have built a framework for a continuously updated representation of provider patient panels ("dynamic linkage cohorts") for use in both clinical research studies and population-based interventions. Since May 2011, these panels have been updated and saved in complete, ready-for-analysis datasets daily. We have integrated them into the TOP-CARE cancer detection and prevention study, of which Dr. Atlas is the principal investigator. They also have been used in a number of operations reporting efforts. As the combined burden of responding to various regulatory requests and the need for understanding and utilizing our patient populations for clinical research mounts, the dynamic linkage cohort is a critical piece of infrastructure. Population management and research will also be fundamental to the ability of MGH and Partners to operate Accountable Care Organization and other risk-based contracts effectively. Dynamic linkage cohorts allow the nimble use of these populations for various innovations in the delivery of patient care.

Clinical Trials Recruitment Sites

We have supported clinical trial listing sites for MGH and Partners since 1998 and the RSVP for Health research volunteer registry since 2003. The clinical trial listing site clinicaltrials.partners.org continues to get robust usage as indicated in Fig. 1. The rise in intramural users in 2011 is particularly encouraging, whereas the drop in extramural use is likely related to the increased availability of national trial listings through tools such as

clinicaltrials.gov. We need to examine how greater use of these other tools can be leveraged through more aggressive promotion and cross-linkage.

Figure 1: Activity (adjusted) on CRP website clinicaltrials.partners.org & crnet.mgh.harvard.edu



* During 1999-2011 three different technologies for counting sessions have been used. The older figures have been adjusted to current equivalents using scale factors derived during periods when the methods of measurement overlapped.

Growth of the RSVP for Health research volunteer registry has continued to slow, continuing the trend of recent years.

Figure 2: CRP Information Technology Unit – Research Recruitment Web Sites	
• Clinical trials at Partners site sessions/month (as of 11/30/2011)	
Sessions/month (12% increase from 2010 total)	8423
• RSVP for Health (as of 11/30/2011)	
New registrations in 2011 (31% decrease from 2010)	2,466
Cumulative registrants (9% increase from 2010)	20,488
Registrants sent one or more mailings (up 7% from 2010)	19376

Research Patient Data Registry (RPDR)

The RPDR project, an innovation developed and driven by the CRP's IT unit, is a successful collaboration between the Laboratory of Computer Science (LCS) and PHS's Research Computing Group. It is now mature and has truly remarkable statistics. The RPDR has ~2,700 users throughout the Partners Healthcare System. It is composed of >6 million patients and 1.4 billion coded records from patient encounters, labs and results, and other medical care data. Most importantly, RPDR is one of the cornerstones for i2b2, Partners effort to create open platforms for data analysis. I2b2 is one of the analytic pillars of the Harvard Catalyst's IT efforts, and has been adopted by over 60 other academic health centers.

The scope and value of the RPDR continues to increase. The registry now contains patient demographic data, diagnoses and procedure data, pharmacy data, inpatient and outpatient encounter information, provider information, and laboratory data. Data from electronic health records, LMR and OnCall, are also included.

LESSONS LEARNED

Clinical Research Program Hub

Requests for Hub-based services have increased as the funding environment has become more difficult. This increased demand requires us to restrict the scope of any custom development we propose to make in the future. To do more with less, we need to make greater use of open source software developed at other institutions. For example, we are collaborating with the UCLA Computing Technologies Research Lab (CTRL) to enhance their profiles module for use with Hub. This profiles module employs the same OpenACS software that we use for the Hub, and it has been used successfully at UCLA departments since 2003. Adding the UCLA CTRL team as a development partner is a logical choice that allows us to meet the needs of our users with fewer internal staff.

MORA

We have learned two major lessons from MORA's development history. One has general relevance to Partners clinical systems development; the other is relevant to the implementation of software in support of MGH oncology initiatives.

The first lesson is that the requirement for monitor access to electronic records needs to be approached differently from most other requirements for clinical data access. Both the expectations for access of this information by extramural monitors and the legal and policy issues that constrain such access apply to all current and future clinical systems. To date, the Partners Information Systems strategy of implementing clinical systems that support clinical data repositories that can be accessed from other applications via data services has served MORA well. However, implementation of this strategy has been incomplete. For instance, data from oncology flow sheets is not available outside the clinical system because these flow sheets are extremely complex and the support of data services has not always been a priority when a specific software feature was developed. Looking ahead, the expected institutional shift toward the use of commercial vendors for clinical systems may further impair our ability to rely on this form of data access. Open systems have not been the norm in the commercial health care information technology market, and the drive toward standardization and efficiency using commercially available software is likely to reduce our flexible access to data created by such systems. We must invest in maintaining research access to clinical data systems; this will likely require custom software "around the edges" of commercial systems, built by teams such as ours.

The second lesson is that the control of decision-making for cancer research-related systems by Dana-Farber, no doubt appropriate in many ways, adds significant additional complexity to collaborative systems development efforts. The multiple pathways for trial governance require MORA to have multiple methods for associating protocols with coordinators, and therefore with monitors.

Dynamic linkage cohorts

Implementation of the dynamic linkage cohorts for immediate use in the TOP-CARE study required daily updates of provider panels as well as extremely high accuracy. We addressed these by adding daily dataset snapshots and automated internal data consistency measures. Supporting these data characteristics will also give researchers who use this data to easily pick the effective date for the start of their analysis and know that the data is accurate from day-to-day. Building this capability upfront would have been much more efficient than retrofitting it later as we have done. A strategy to anticipate

analytic and research requirements in the design and implementation of clinical systems will improve the efficiency of downstream use of data in quality, safety and research analyses when compared to the usual *post hoc* approach to data provisioning. We should accept modestly higher development or acquisition costs in our clinical systems in order to increase analytic efficiency downstream.

Web-based Recruitment Strategies

The two clinical trials recruitment web sites we support, while still useful, are no longer as “leading edge” as they once were when we established them. The growth opportunity in online trials recruitment lies in the challenge of how to leverage social media (especially Facebook) in a way “natural” to these media without encouraging potential recruits to compromise their own privacy. We do not see this as calling for a major new development initiative at this stage. Instead, we need to answer three critical questions at the design and policy levels:

- How can we create campaigns that will trigger personalized adoption of generic recruitment tools (e.g. personalized trials information feeds) within social media sites that will not at the same time leave telltale trails in the profiles or histories of users of those media?
- How can we foster the creation of online communities of potential recruits without encouraging them to disclose information to each other and compromising blinding of studies recruited from these communities?
- Can institutional concerns about patient confidentiality be combined with identification of successful models for recruitment consistent with the radically altered technical and social landscape created by the rise of tools such as Facebook and Twitter?

Patient groups, voluntary disease organizations and even large pharmaceutical companies have moved much more aggressively into experiments with use of social computing tools for recruitment into clinical trials. We feel that too many providers of the platforms for these experiments have failed to ensure that the people who use them understand the long-term implications of linking to public or quasi-public profiles comments and requests rich with implications about personal health issues. Unfortunately, because of our sensitivity to the risks of recruitment in social media we have failed to make any significant innovation in this area. We believe that the risk of falling behind is substantial, but there is still an opportunity for new contributions. We discuss one approach to such innovation below.

Clinical data provisioning for clinical researchers

We have previously worked on methods that simplify data access for clinical researchers. These methods can be broken down into four components: institutional repositories, extraction methods, research registries, and study databases. After false starts with other platforms, it has become clear that the appropriate place to pool MGH clinical data for both analysis of operations and for research is in the Data Warehouse for Quality (D4Q) supported by the MGH Center for Quality and Safety (CQS). Extraction methods, formerly ad hoc, can now be refocused on data in D4Q. At the other end, we have no control over researcher study databases, which are appropriately diverse in technology and design fitted to the individual queries that interest clinical investigators. We have previously made some effort to develop research registries as a way for clinical investigators to aggregate commonly used clinical data in a consistent way. However, to date we have had limited success with this approach in a research unit where we have

been able to build tools into the entire process, from clinical data capture tools that capture granular domain-specific research quality data to the transformation of clinical datasets into research study dataset formats. We believe we were overambitious, and that the nuances of different projects makes a common infrastructure for registries a much more complex endeavor than anticipated, still worthy of pursuit, but requiring additional analysis.

At the same time, we have found that experienced researchers typically have highly customized data sets. Source data from clinical systems needs to be transformed to the format of these sets. This kind of customized target makes it difficult to produce a scalable registry representation. Instead, we frequently end up with the need to have our staff incorporated into protocols so that they can do the extractions requested, in the form requested, on a jobbing basis. We see an opportunity to gain efficiency with a more modest, empirical approach. We know that there are simple patterns to requests we have fulfilled in the past. For instance, full histories within specified date ranges rather than current snapshots are frequently requested for problems, medications, vital signs and some physical findings. In the future, we propose to create software to fulfill these common patterns simply, while continuing to study the new requests that currently require more hands-on support.

ADAPTATIONS PLANNED

Extending the HUB platform through collaboration

In an effort to accelerate ongoing development and reduce the long-term software maintenance overhead, we have started to collaborate with the UCLA David Geffen School of Medicine's Computing Technologies Research Lab on software that supports our common education and research missions. At the start of 2012, we will be porting an open source researcher profile and certification application currently in use at UCLA to meet CRP education and certification needs while reducing long-term costs.

Applying Lessons about the Interdependency of Clinical and Research Systems from the MORA Project.

Implementing a single point of access control for clinical trial monitors and providing these generally extramural monitors from industry with comprehensive read-only clinical data access both remain a valid goal. The first lesson is these are not goals that can be achieved with a one-time development project. The planners responsible for each clinical system that is built or licensed in the future must determine if study monitors will need access to data from that system. If they will, the planners need to make sure that either: 1) the system intrinsically supports the necessary access controls and business rules or 2) the system provides web services to enable real-time access to this data from other applications or 3) the vendor or developer will contract to implement one or another of the changes as an essential first stage deliverable of that clinical system implementation project. We will be pursuing both additional institutional funding to extend the number of clinical data types included in MORA as well as advocating for a broad institutional policy that a cost/benefit analysis of support for research study monitor access must be a part of the planning for all new clinical systems efforts. Extensions to MORA and the policy framework that provides their rationale need to be considered as all of a piece.

Applying the second lesson from the development of MORA – that DFCI-directed information systems decisions have significant impact on MGH cancer researchers –

also requires a modified policy stance on information systems development and acquisition. We will be seeking recognition from DFCI IT decision-makers of the need to account for the consequences of their decisions on research study monitor-related functionality. The change needed in this case is the inverse of the first change in order for clinical systems to be able to support authorization controls based on research program division of labor and workflow, and also to support patient access control based on study patient lists, research system development and acquisition plans need to include provisions for how such connections are to be made. It is all the more important to highlight these interdependencies when MGH cancer researchers are highly dependent on decisions made principally about research studies at Dana-Farber.

Web-based recruitment strategies: a renewed commitment to partnership for research with patients

Due to unexpected staff turnover that affected the development of the patient engagement platform www.ihealthspace.org, we were unable to migrate RSVP for Health registration into that platform. We intend to proceed with this plan in 2012. Once we have completed this migration, clinical researchers will be able to engage volunteers in a partnership in clinical research studies in which the volunteers completely control the terms of engagement. Patients within our system who use www.ihealthspace.org and who are interested in enrolling in studies will be able to access highly specific but still anonymous contact opportunities. They will also be able to block clinical research-related messages completely if they so choose. This will provide us with an environment within which we can explore the appropriate boundary conditions for recruitment strategies based in social media as is already being done by several disease specific voluntary health agencies and foundations who are significantly ahead of academic medical centers in this regard.

Clinical data provisioning for clinical researchers

We will be starting a new development initiative to provide a “self-serve” front end for clinical researchers to request and download specific datasets for their lists of study patients. For this purpose, we will be able to reuse some of the infrastructure built for the MORA project to authorize users to submit such requests based on information from Insight about who is on the study protocol, and the D4Q repository as the underlying clinical data repository. In addition, we will draw on past experience with ad hoc data requests to prioritize certain prespecified data sets: dynamic linkage cohorts, Oncall problem history, Oncall medication history, Oncall vital signs history.

Genetics & Genomics Unit (GGU)

*Susan Slaughaupt, Ph.D. & Jordan Smoller, M.D., Sc.D.,
Co-Directors*

GOALS

The missions of the CRP's Genetics and Genomics Unit (GGU) are threefold:

- provide consultative support to clinical investigators initiating genetic and genomic studies at MGH;
- educate and support clinical investigators already performing such studies through educational programs and process improvements; and
- serve as a link between the MGH clinical research community and the educational and technological platforms in genetics and genomics of the Partners HealthCare System and the greater Harvard Medical community.

As genomic medicine becomes a reality, the GGU continues to make significant progress in arming MGH clinical research teams with the knowledge and tools needed to incorporate or expand genetics in their clinical research studies.

COLLABORATIVE RESOURCES

Genetic and genomic research has arrived at a singular moment in which the technology, expertise, and resources for transformative discovery and clinical translation are now feasible. The GGU is fortunate to be situated within a network of world-class scientific and medical research communities that are driving innovation and translational investigation. To enhance the scientific opportunities and resources available to MGH investigators, the GGU has developed collaborative relationships with other key genetics and genomics centers and investigators. Through this network, the GGU has been able to connect MGH investigators with core facilities, consultation and educational opportunities across the larger Partners, Harvard, and MIT communities.

The *MGH Center for Human Genetic Research (CHGR)* is a trans-disciplinary research center devoted to human genetics and encompassing scientists and laboratories from numerous departments at MGH (including neurology, psychiatry, medicine, surgery, and pediatrics). As senior faculty members at CHGR, Dr. Smoller (Director of CHGR's Psychiatric and Neurodevelopmental Genetics Unit) and Dr. Slaughaupt have been able to enlist other CHGR faculty to participate in the GGU's research consultation and educational programs. The core facilities of CHGR are also available to MGH investigators seeking genotyping services. Dr. Slaughaupt also manages the CHGR's clinical and phenotyping research space on Simches 2, which provides clinical resources (exam rooms, interview/observation rooms, phlebotomy stations, and a specimen preparation lab) for phenotypic characterization of research participants.

The *Partners Center for Personalized Genetic Medicine (PCPGM)* is devoted to promoting genetics and genomics in research and clinical medicine and to realizing the promise of personalized medicine by accelerating the integration of genetic knowledge into clinical care. PCPGM offers CLIA-certified genetic testing for a variety of medical

applications, a research biorepository, core facilities for genotyping, sequencing and gene expression analysis, and IT solutions for the integration of genetics and clinical care.

The *Broad Institute of MIT and Harvard* is a leading research institute in the areas of genomics, molecular medicine, and the development of novel therapeutic approaches. As an Associate Member of the Broad, Dr. Smoller is able to facilitate access to Broad resources and core facilities for MGH researchers involved in genetic and genomic research. Members of the Broad community have also played an active role in the educational offerings of the GGU and the Broad's highly regarded series "Primer on Complex Trait Genetics" has been offered as a one-day course by the GGU for the past several years.

The *Harvard Catalyst* is a pan-Harvard enterprise devoted to facilitating clinical and translational research. Dr. Smoller is Director of the Catalyst's Translational Genetics and Bioinformatics Program (TGBP) and Dr. Slaugenhaupt leads the educational programs of the TGBP. In the collaboration with the Catalyst TGBP, the GGU has expanded consultation services for MGH investigators to include faculty from Harvard Medical School, the Harvard School of Public Health, and the other Harvard hospitals. As a result, MGH investigators seeking individualized research consultation can access the expertise of leading researchers across all of the key domains of genetic, genomic, and bioinformatic research including next-generation sequencing, epigenetics, proteomics, functional genomics, and computational biology. Drs. Smoller and Slaugenhaupt have also worked with their colleagues at the Harvard Catalyst to develop and teach several new genetic courses and expand access to genetic core facilities at the Harvard institutions for MGH investigators. As more investigators are incorporating genetics into their research, there has been a correspondingly greater need for statistical genetics services at MGH that are not the domain of traditional biostatisticians. After a needs assessment, the GGU has addressed this demand by forging close links to the biostatistical and bioinformatics communities at MGH and other Harvard institutions. As a result, consultations in these areas are now available free of charge to all MGH clinical investigators.

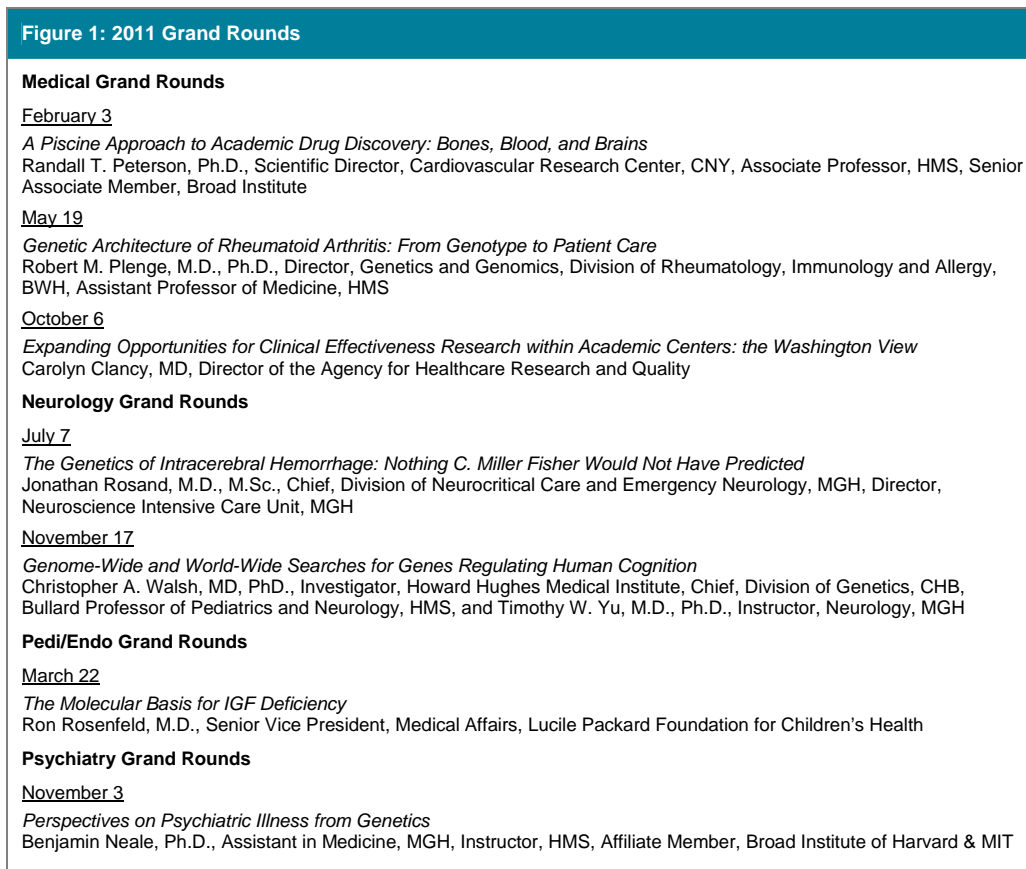
The Genetics and Genomics Unit has effectively bridged the gap between these Harvard-wide resources and has significantly enhanced the interactions and research programs of MGH investigators. The GGU has grown in scope and expertise while broadening the level of service provided to MGH, and it plays a critical role in forging cross-disciplinary and cross-institutional connections while maintaining a focus on MGH.

ACCOMPLISHMENTS

Broad Departmental Grand Rounds Program in Genetics and Genomics

The highly successful MGH Seminars in Genetics and Genomics Clinical Grand Rounds Program is developed annually in collaboration with the CRP's Education Unit. The goal of these seminars is to make maximal utilization of the individual clinical departmental Grand Rounds program settings to highlight opportunities and advances in genetic research that should be of special interest to the clinical community. In this way, both clinicians and clinical investigators can hear of the opportunities made available to them by the latest genetic advances in the context of the individual clinical care issues of their specialty. Such 'context setting' in clinical arenas will ultimately be crucial to the broader adaption of genetics to personalize medicine in several specialties. Each lecture is thus dedicated to a Genetics & Genomics topic based in clinical medicine and centered on a

disease state and clinical case presentation. Through this series, genetic education is embedded within each department and reaches a unique population of clinicians and clinical investigators. The 2011 GGU Grand Rounds Series is illustrated in Fig. 1.



Educational Curriculum

In collaboration with the CRP's Education Unit, the GGU updated its 2011 curriculum primarily in response to feedback from past course participants. This curriculum is primarily aimed at clinical investigators with some specific courses for clinical research coordinators, nurses, and study staff. Course evaluations were extremely positive for each course, rating consistently "very good" to "excellent".

The GGU expanded its curriculum in 2011 by adding a new course, **Epigenetics: An Introduction and Applications**. This course, which was co-sponsored by the Translational Genetics and Bioinformatics Program of the Harvard Catalyst, was extremely well-received.

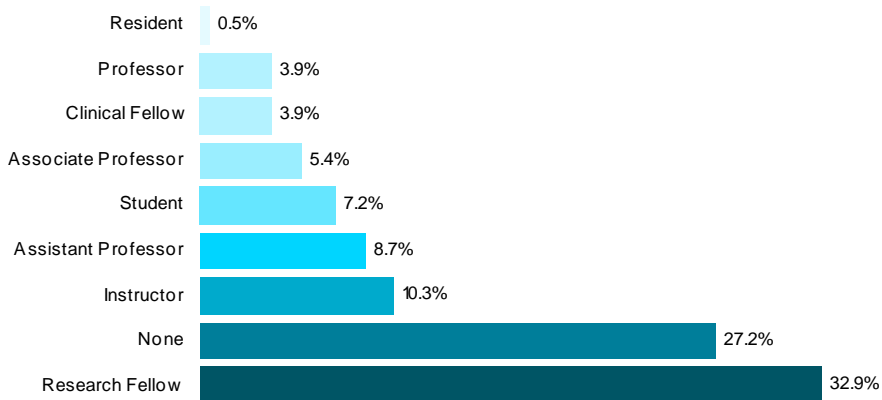
In 2011, the GGU developed a core genetics curriculum to meet the needs of a variety of learning levels in which the GGU draws heavily on faculty in the MGH Center for Human Genetic Research as instructors. We will continue to focus on the needs of MGH clinical investigators as we create the 2012 curriculum are actively working with the Harvard Catalyst education group to expand the MGH's broad educational courses in genetics and genomics to the entire Harvard community. Fig. 2 lists the 2011 GGU courses and faculty.

Figure 2: 2011 Genetics and Genomics Courses

- “Epigenetics: An Introduction and Applications”**
 Distinguished faculty from MGH presented introductory lectures defining epigenetics and its effect on gene regulation and inherited disease.
Attendees – 147
Faculty included: Robert Kingston, Ph.D., Johnathan Whetstone, Ph.D., Bradley Bernstein, M.D., Ph.D.
- “Welcome to the Genetic Code: An Overview of Basic Genetics”**
 This introductory course reviewed fundamental language and concepts including DNA anatomy and genome organization; genotype-phenotype correlations; basic population genetics; and genotyping.
Attendees – 121
Faculty included: Susan Slaughaupt, Ph.D., Jordan Smoller, M.D., M.Sc.
- “Genetic Literacy: A Guide to Understanding the Language & Basic Concepts”**
 A course designed to briefly describe the terminology, technologies, and methodologies of modern genetics. Intended for clinicians, investigators, nurses and other clinical research staff with an interest in genetics and genomics.
Attendees – 72
Faculty included: James Gusella, Ph.D., Benjamin Neale, Ph.D., Mark Borowsky, Ph.D., Roy Perlis, M.D., M.Sc.
- “A Primer on Complex Trait Genetics: Basic Principles for the Beginning Investigator”**
 This course provided clinical investigators who want to keep up with the changing face of genetic research an excellent opportunity to learn the essential elements of complex trait genetics and gain the latest insights from expert faculty from the Center for Human Genetic Research and the Broad Institute of Harvard and MIT.
Attendees – 80
Faculty included: David Altshuler, M.D., Ph.D., Marcy MacDonald, Ph.D., Mark Daly, Ph.D., Shaun Purcell, Ph.D., Christopher Newton-Cheh, M.D., M.P.H., Eric Banks, Ph.D., Jose Florez, M.D., Ph.D., Robert Gerszten, M.D., Ron Do, Ph.D.
- “Adding Pharmacogenomics to Clinical Investigation: A Practical Guide”**
 Distinguished faculty discussed the diverse ways pharmacogenetic studies have been conducted, from small translational studies to clinical trials to large-scale cohort studies. They addressed key principles necessary for clinical researchers to design, conduct, and analyze such studies.
Attendees – 45
Faculty included: Roy Perlis, M.D., M.Sc., Stephen Haggerty, Ph.D., Marc Sabatine, M.D., M.P.H.

As shown in Fig. 3, the GGU’s educational curriculum served a broad range of junior and senior faculty as well as trainees.

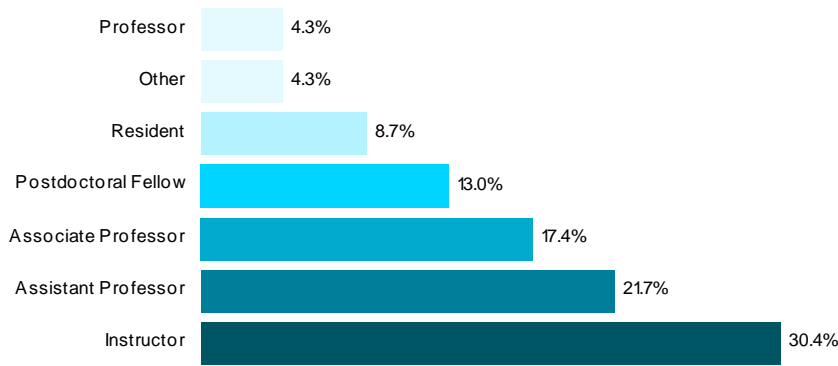
Figure 3: Course Attendee’s Academic Rank



Consultations to Investigators

One of the GGU's primary goals is to provide consultation and triage for the MGH clinical research community. A consult request is completed online by individual investigators at all academic levels requesting help in genetic study design and execution, human subject protection, career advice, and/or identification of particular resources. Requests are triaged by the GGU and assigned to specific consultants depending on expertise and availability. By collaborating with the Harvard Catalyst's Translational Genetics and Bioinformatics Program (TGBP), the GGU has widened the pool of expertise available to clinical investigators at MGH. In 2011, 23 MGH investigators received consultations through joint efforts of the Genetics and Genomics Unit and the Harvard Catalyst. Investigators came from the following departments, centers, or units: Allergy and Immunology, Anesthesia, Endocrine, Infectious Disease, MGH Center on Genomics, Vulnerable Populations, and Health Disparities, Oncology, Orthopedics, Pediatrics, Psychiatry, and Surgery. This represents a **100% increase** in the number of MGH investigator genetics/genomics consultations compared to the prior year, underscoring the increased visibility and perceived value of the service to the MGH community. Fig. 4 shows the breakdown of consults and by academic rank.

Figure 4: Academic Rank of Consults



Access to the GGU Resources

The Genetics and Genomics webpage within the CRP website has been updated with available resources. The website offers the research community a wealth of educational information and links to resources both within the MGH and beyond.

LESSONS LEARNED

1. Collaboration with Harvard Catalyst

Since the establishment of the CRP's Genetics and Genomics Unit antedated the Catalyst by several years, it has served as an important model for the Harvard Catalyst's development of the Translational Genetics and Bioinformatics Program (TGBP). HMS leadership chose Dr. Smoller, (Co-Director of the CRP's GGU) to direct the TGBP, and Dr. Slaugenhaupt directs the educational activities of the TGBP, the GGU has provided the Catalyst with a model for the successful implementation of genetics consultation and

educational offerings, and the Catalyst has provided a platform for expanding MGH investigator's access to genetics expertise and courses throughout the Harvard system. Together the GGU and Catalyst TGBP co-sponsored five highly successful courses on genetics and genomics attended by 465 members of the MGH clinical research community in 2011.

2. Need for basic genetics education and expansion of online resources

Every year our introductory course offerings, Genetic Code and Genetic Literacy, draws large crowds and the course evaluations highly praise the basic level of the material taught. It has become increasingly clear that the MGH's need for basic genetics instruction is growing as research in all disciplines is increasingly incorporating genomics. We also provide the opportunity for students enrolled in Genetic Code to pre-submit specific questions that they would like answered. In 2011, we had over 300 questions, and we tried to touch on most of the topics during our lectures and/or during the question and answer period. This service has proved extremely popular as it provides an accessible and widely used forum for individuals to ask any question in an 'anonymous' fashion which is important since many clinical investigators are embarrassed at their ignorance in these new technologies. Lastly, we recognize the increasing need for additional online courses and resources.

3. Need for diverse and specialized course offerings

The field of genetics and genomics is evolving rapidly, and every year brings new technology and innovations that soon become essential components of clinical research in this area. Thus, we note the continued need for the development of new courses and resource fairs focusing on the latest technology, for example exome and genome sequencing, epigenetics, and proteomics which is a relatively unique problem for our Unit but one that is characteristic of rapidly moving new technologies.

4. Need for expansion of our successful Grand Rounds series

As described above, our collaboration with specific clinical departments to invite speakers focused on using the tools of genetics and genomics to attack a specific clinical problem of interest to the department has been very successful. These talks are very well-received and they have brought in speakers who would not be 'typical' invitees for grand rounds lectures. That said, increasing their number and breadth of clinical departments involved will be a key future goal.

5. Need for novel approaches to translational roadblocks in "-omics" research

The rapid acceleration of "omics" technologies, expanded sample sizes, and an increasingly systems biology approach to genomic research has created a number of new challenges for MGH's clinical investigative community. For example, there has been a deluge of large-scale datasets and the management, integration, and mining of these resources has become both an exciting opportunity and a formidable challenge to progress. The CRP GGU, in collaboration with the Catalyst TGBP, have begun planning an "Innovation" event that will bring together scientists and other stakeholders to share best practices and generate novel solutions to these challenges.

ADAPTATION PLANNED

1. The Genetics and Genomics Unit will continue to work closely with its network of collaborating investigators and centers (CHGR, PCPGM, Broad, and Harvard Catalyst's TGBP) to address the ever-growing needs of the clinical research community at MGH and beyond. These collaborations have led to increased access to resources for MGH investigators, an increased pool of expertise, and expanded opportunities for collaborations. We will continue to serve all academic levels, from clinical fellows to senior investigators, and focus on making connections that will benefit MGH scientists.
2. We will continue to improve our basic genetics curriculum in response to course evaluations and feedback from follow-up surveys. The ability of registrants to ask specific questions at the time of registration has been very well received and enables us to target specific course topics. We will investigate incorporation of this format into other courses. In 2012, we will pilot recording all of our courses for online posting to increase availability and access to the MGH clinical research community.
3. Educational opportunities will be expanded in 2012 in an effort to keep pace with the rapidly evolving technologies in this area. We are already planning an expanded version of our Genome Sequencing course to include a resource fair so that attendees can learn how to access specific technologies, bringing immediate benefit to their research programs. Other new courses planned include "Human Subjects Issues and Responsible Conduct of Research in '-Omics' Research". And a course for clinicians and nurses designed to introduce genetic investigation and patient collection to increase the involvement of all MGH staff in genetics research.
4. To expand the clinical department Grand Rounds series, we will reach out to additional departments with strong research programs, including Anesthesia and Critical Care and Surgery.
5. We will plan the first in a series of "Innovention" events to address translational roadblocks for investigators in clinical "-omics" research, beginning with a focus on the management, integration, and mining of multidimensional datasets. Researchers in genetics/genomics and bioinformatics are facing a data "tsunami": the availability of high-throughput sequencing, transcriptomics, pathway and network analysis, and high-dimension phenotypes including imaging and other tools has created unprecedented opportunities for biological discovery and translational research. At the same time, the overwhelming volume of data presents challenges to its effective utilization including the need for new approaches to multidimensional analytic methods, data integration, functional annotation, and data storage/access. In collaboration with the Harvard Catalyst, we will launch an "innovention" event that will bring together thought leaders and researchers to tackle these challenges and develop novel approaches that can advance translational "-omics" research.

Translational Medicine Unit (TMU)

Mason W. Freeman, M.D., Director

GOALS

The TMU's overall goal is to facilitate research that moves basic scientific discoveries and new technologies toward the clinic to improve diagnostic capabilities and therapeutic interventions.

Specifically, the TMU works with investigators to:

Advance projects from pre-clinical findings that suggest clinical benefit through the required stages of development necessary to test the concepts in human trials. This work involves:

- a) Clarifying the development pathway necessary for a given idea to be taken forward;
- b) Providing an assessment of the feasibility and cost of pre-clinical studies, including pharmacology, manufacturing, and toxicology;
- c) Obtaining an Investigation of a New Drug (IND) license from the FDA;
- d) Preparing the IND for electronic submission;
- d) Conducting meetings with relevant regulators at the FDA; and
- e) Assisting in the writing of clinical protocols for submission to the MGH's Human Studies Committee.

ACCOMPLISHMENTS

- The TMU played the lead role in working with the Partners IRB to streamline its process for review of protocols for novel therapeutics. This program has designated a series of trials as pilot projects and the TMU pre-screens protocols prior to IRB submission to facilitate IRB review. In addition to NIH-sponsored projects, protocols involving novel therapeutics generated by biotechs and pharma companies are eligible for this program. In 2011, protocols for the treatment of amyotrophic lateral sclerosis, inclusion body myositis, hepatitis C, psoriasis, and cancer cachexia were all designated part of this program. The IRB reviews for these protocols were performed in <4 weeks for all and <3 weeks for most. Thus the TMU's facilitation is significantly faster than is typical. Drs. Libby Hohmann and Pearl O'Rourke of the Partners Human Research office have made a major commitment to the success of this pilot program.
- As part of these pilot programs, the TMU is also working closely with the Partners Corporate Sponsored Research Contracting Office (PCRO) in hopes of similarly accelerating their contracting times. This effort led to improvements in contracting time that resulted in new contracts for clinical trials with Gilead and Novartis. Maureen Lawton and Karen Lodigiani of PCRO have been very helpful in this process and are working closely with the TMU to improve the contracting interface for sponsored research aimed at generating novel therapeutics.
- The TMU has interacted with the FDA on multiple occasions on behalf of investigators at the MGH to clarify development pathways for drugs affecting life-threatening hemorrhage, depression, and diabetes, as well as for novel vaccine development.

- The TMU took a drug it developed internally, a novel oral, small molecule SGLT2 inhibitor for the treatment of type 2 diabetes, into a phase 2b/3 trial in 300 patients. The trial is slated for completion in the late spring of 2012.
- The results of the Harvard Catalyst sponsored clinical trial of bevacizumab therapy for respiratory papillomatosis that the TMU organized and executed in concert with Dr. Steve Zeitels of the Voice Center was published in one of the leading otolaryngology journals. This trial demonstrated clinical benefit of the VEGF inhibitor in the control of this disease.
- The TMU has worked closely with Drs. Mark Poznansky and Ed Ryan to develop vaccines for viral hepatitis and cholera. Both projects utilized the expertise of the TMU to apply for major federal funding awards for these therapeutics.
- The TMU played a significant role in developing the content of grant applications for submissions to the NIH, DoD and US Army for Drs. Mark Poznansky and Raymond Chung of the Dept of Medicine and Dr. Hasan Alam of the Dept of Surgery.
- The Harvard-wide translational medicine course that the TMU Director co-directs had another very successful year after its inauguration in 2010. This course, the first of its kind in the country, ran all day for two weeks in June 2011 and had approximately 3 applicants for each of its 55 slots with investigators varying in academic rank from clinical research fellows to Associate Professor. A large contingent from the MGH participated in the course and the course was once again rated as outstanding by the participants.
- Both Drs. Freeman and Halvorsen taught in the fall 2011 Clinical Fellows Orientation to Clinical Research at MGH.

LESSONS LEARNED

- Our pilot program demonstrated that a dedicated Translational Medicine Unit team can dramatically accelerate the process of contracting and IRB review for sponsored research involving new therapeutics across a wide spectrum of diseases at the MGH/PHS system. Were the MGH to develop more of a one-stop front door for this kind of research, the TMU believes it could dramatically increase the number and quality of novel therapeutics being developed at the MGH.
- The number of MGH faculty with a strong interest in moving their bench research into the clinic but who lack experience and knowledge of the regulatory and commercial realities of therapeutic development continues to be impressive. Thus, the TMU has expanded its staff to assist more of these investigators. In several cases, the TMU as an institutional resource is being written into contract and federal grant applications as a part of the research team needed to execute these projects. This represents a strong institutional commitment to this type of research that arguably the MGH has become famous for fostering.
- There is a critical body of translational investigators in need of a facility in which to perform these studies. The Clinical Research Center (formerly General Clinical Research Center) and Catalyst do not fulfill these needs. If the MGH wishes to retain

- its profile as a dynamic and innovative institution, a “proof of concept” facility will need to be constructed in the near future. The costs of a non-investment in this area will soon become apparent by a loss of innovation, leadership in this area, and eventually competitive recruitment/retention of the most innovative faculty.

ADAPTATION PLANNED

- The TMU has expanded its staff to meet the demand for its services by MGH investigators. To cover the cost of this expansion, it is now being incorporated into grant and contract proposals as part of the investigative team. Grants pending to the DoD and the NIH by investigators from the Dept of Medicine and Surgery now have effort and support for the TMU embedded in their budgets.
- With the likely constriction of NIH budgets, the TMU is evaluating whether its proposed plan to create a Translational Medicine inpatient unit can still be realized via alternative funding sources.

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