Clinical Research

Annamarie D. Horan, MPA, PhD

U.S. Regulations General Review

The mention of regulations in any capacity is an easy conversation killer in a mixed group of people. Whether one is discussing environmental protections, Constitutional Rights, or as appropriate to this document, Human Subjects Research, regulations are viewed as either fortresses against progress or guardians of public safety. Perhaps a more pragmatic approach is to view the current regulatory environment in the same way as we do guardrails on a highway. Drive between the guardrails and you stay out of the gutters or prevent yourself from careening off a cliff. Head straightaway into the guardrails and suffer damage.

The regulatory environment for Human Subjects Research includes but is not limited to studies of drugs, devices, biologics, the assurance of Human Subjects protections, quality management systems for producing products for human use, the conduct of post marketing surveillance, and the management and protection of individual privacy rights. In the United States these responsibilities are matrixed across multiple federal agencies in both the Executive and Judicial Branches. The full, searchable, and continually updated Code of Federal Regulations (CFR) can be accessed online at https://www.ecfr.gov/. Currently Titles 1 – 50 are available online.

In the Executive Branch, the Department of Health and Human Services (HHS), *Office of the Secretary* houses the Office for Civil Rights (OCR) which is responsible for enforcing the Privacy and Security Rules. The complete suite of HIPAA Administrative Simplification Regulations can be found at 45 CFR Part 160, Part 162, and Part 164, and includes: Transactions and Code Set Standards, Identifier Standards, Privacy Rule, Security Rule, Enforcement Rule, and Breach Notification Rule. HHS established general rules for the Protection of Human Subjects in Research under 45 CFR 46. The HHS *Operating Divisions* include several agencies engaged in the conduct and oversight of both human and non-human research such as the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the U. S. Food and Drug Administration (FDA). The FDA specific regulations are found under Title 21 CFR. All Human Subjects Research is under the jurisdiction of 45 CFR 46, but not all these activities meet the criteria for FDA oversight.

The FDA jurisdiction is broader than research. FDA sets and enforces rules around Food for human and animal consumption, Cosmetics, Drugs for human and animal use, Medical Devices, Biologics, sets standards for products and activities around Radiologic Health, and oversees some aspects of tobacco regulations. FDA also interacts with other agencies under the Executive Branch in Human Subjects Research with respect to specimen shipping (Department of Transportation Title 49 CFR), United States Customs and Border Protection (CBP) (United States Department of Homeland Security Title 8 CFR Chapter 1). The Judicial Branch of the Federal Government influences Human Subjects Research through the Drug Enforcement Administration (DEA) and the Bureau of Alcohol, Tobacco, Firearms, and Explosives (ATF). Additionally, the FDA works with independent federal authorities such as United States Consumer Product Safety Commission (USCPSC, CPSC) and the Federal Trade Commission (FTC) and innumerable state, local, and international organizations to conduct its myriad duties to ensure safety and efficacy of drugs and devices and other products marketed in the United States.

Penn Orthopaedics Update 2023

At this writing, the Department is quite a bit leaner than it has been in a decade. Dozens of defunct studies were administratively closed with the assistance of IRB Administrators and removed from our regulatory burden. It is critically important for all PIs to ensure regular maintenance of their studies even if the IRB rules the protocol to be *Exempt* or to be *Approved with No Continuing Review Required*. Once a study is opened and active, it must at some point come to a formal close. The best way to ensure this is to assign your Divisional CRC to the protocol as a Study Contact. All protocols are reviewed regularly and the CRCs do stay on top of their dockets to keep the PIs within the guardrails.

Additional compliance requirements applicable to all studies include the ongoing management of every study in the PSOM Clinical Research Management System (CRMS). This now includes the capture of retrospectively "enrolled" patients and excluded/declined patients. There will be more details forthcoming. Again, the Departmental CRC Team all have access to the CRMS and will be undergoing additional training to facilitate this higher compliance standard. We look forward to working with our PIs to further tune up our Institutional presentation.

Activity Report

The data below were presented to the faculty on March 20, 2023. As shown in Table 1, the Department carries a burden of 126 open protocols, only 26 of which are extramurally funded. The funding sources include Industry, Federal, non-Federal, and private. Table 2 provides a breakdown of

Table 1 Open vs Funded Protocols by Sub-Specialty Division

Division	Total Open Protocols	Funded
Adult Reconstruction	22	9
Foot & Ankle	12	2
Hand	25	5
Oncology	7	0
Shoulder & Elbow	9	4
Spine	4	0
Sports	29	3
Trauma	18	3
Grand Total	**126**	**26**

Table 2 Funding by faculty PI

Funded PI's	# Awards
Carey, James L	3
Farber, Daniel C	2
Hume, Eric L	2
Israelite, Craig L	2
Kuntz, Andrew	4
Levin, Lawrence S	3
Lin, Ines C	1
Mehta, Samir	3
Nelson, Charles L	1
Sheth, Neil P	2
Steinberg, David R	1
Tarity, Thomas D	1
Travers, Christopher	1
Grand Total	26

*Awards = Active projects only

the individual faculty funded as of March 20, 2023. Since March 2023, the specific distribution of projects and the number of funded projects has changed and should always be understood to be in flux as old protocols close and new studies begin. Regardless of funding source, in an ideal world, all protocols would be associated with extramural funding. We do not live in an ideal world. Pragmatically, the minimum goal is for every Division to seek sufficient funding to support at least 1 FTE CRC and to not have an unfunded study burden that exceeds the capacity of the CRCs per Division to fully manage, given the totality of administrative regulations applicable to all studies. From the perspective of optimal faculty performance, regardless of source, annual revenues equivalent to an R01 level (e.g. ~ $250K direct costs) would signal great strength in the program. With these values in mind, it is our hope that faculty active in research will focus their energies accordingly. It is not expected that every faculty member engage in research and even distribution across the Department is not practical to expect. For those who are engaged, choosing studies with the greatest chance of full patient follow up is the best way to achieve target revenues.

From the perspective of compliance, the best way to ensure optimal compliance beyond initial IRB approval, combine your desire to engage resident & fellow trainees with the CRC team during initial IRB submission and keep them involved. Keep your data secure. Keep your records in a manner that is aligned with applicable regulations and internal policies. Stay within the guidelines. Become the best PIs you can be.

Adult Reconstruction remains highly productive with 22 open studies, 9 of which are extramurally funded. The myMobility study (NCT03737149) led by Dr. Israelite continues to perform well against our peer institutions. Penn is #1 university enrolling site for 2022. In March of 2023 we reached the 300 subject milestone and continue to be a high enrolling site each month.

Dr. Nelson is having continued success with the PCORI funded PEPPER (NCT02810704) study with ongoing enrollment and 48 Subjects in active follow up. Dr. Nelson has joined the Rush University Medical Center Consortium in their dose finding study of Dexamethasone in TKA (NCT05018091). He has also anticipating funding as a site PI for a multicenter study of Autogenous Bone Marrow Aspirate Concentrate for the Treatment of Osteonecrosis of the Femoral Head (Johns Hopkins, Primary Site). In addition to all these activities, Dr. Nelson will be taking over the final stages of DePuy funded studies of Dr. Hume's Ceramic on Ceramic Hip study (NCT02096211). Dr. Hume will continue to be PI on the Smith & Nephew R3 Delta Ceramic Acetabular System PAS U.S. (R3-PAS) protocol (NCT03056534) as that wraps up this fall. Dr. Travers has nearly completed the DePuy ACTIS study (NCT02783274) and the NIH funded EN20-01 Centrexion Knee OA Study (NCT05025787) has successfully randomized its 1st Subject!

Foot & Ankle is back on track with Dr. Farber's Treace Medical Concepts, Inc.'s Early Weight-Bearing After the Lapiplasty Mini-Incision Procedure (Mini3D) study (NCT05082012). We anticipate that additional updates for the Foot & Ankle Division will be submitted elsewhere in this edition of the UPOJ by colleagues Dr. Josh Baxter and Dr. Casey Humbyrd.

Hand Surgery received notification in March that an academic (UC San Diego)-industry (Auxillium)-federal (NIH) collaborative grant was awarded to Dr. Bozentka. The administrative processes on this award are still pending. We are looking forward to beginning this study!

In the last issue, Dr. Levin's DOD-funded Hand Transplantation Qualitative Research Study (W81XWH1820067) achieved the 1st Manuscript milestone. The publication information was not available at that time and is now available and the link is now presented. https://www.archives-pmr.org/article/S0003-9993(23)00031-X/fulltext This major grant is wrapping up in the fall and additional publications are under development as are other collaborations and funding opportunities. Dr. Andrew Sobel as the Director of the Hand Surgery Clinical Research Program, is striving to develop an educational pipeline within the Division that may also aid the Department. Please follow up with him for details.

Shoulder & Elbow continues its strong Clinical Research presence over the past 10 years with 4 industry funded studies ongoing. We welcomed Dr. John G. Horneff to the Shoulder & Elbow Division, his ASES studies continue to remain active and growing. Shoulder & Elbow has remained a strong and stable Division in Clinical Research under Dr. Kuntz's leadership.

Spine will continue the STRUCTURE study (NCT04294004), a Phase II study enrolling patients undergoing single level transforaminal lumbar interbody fusion. Dr. George Dodge will be handing the role of PI over to Dr. Harvey Smith. Dr. Casper is on the brink of executing a new study with Carlsmed, Inc. to capture registry information for Personalized aprevo® surgery patients.

Sports Medicine continues to have a robust repertoire of active funded projects. Dr. Carey continues in his role as the Local and Global PI on the Vericel sponsored PEAK study (NCT03588975) and also participates in a Vericel sponsored retrospective study. Drs. Kelly and Dodge's study investigating the impact of Kenalog injections on metabolic syndrome biomarkers is drawing to a close. We look forward to the results of this impactful investigation.

Ortho Trauma has several active studies in process, previously described. He is also in pending execution of a new registry study with Curvafix, Inc. Dr. Mehta & Dr. Horan also celebrate the issue of U.S. Patent No. 11,339,436 on May 24, 2022 for their work on Biomarker identification in Fracture Healing. Hopefully, there will be more to follow on this milestone in Orthopaedic Trauma.

Financial Report

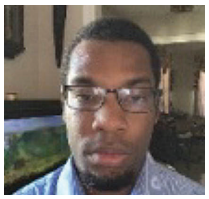
Figure 1 shows the Total Costs (Direct Costs + Indirect Costs) expended during the periods shown for all categories (Personnel and Non-Personnel Costs). The revenue sources for these expenditures include both current sources as shown in Table 1 as well as previously earned revenues that remain available from completed projects. Unless projects are grant funded, revenue supporting Clinical Research is received in a reimbursement method and therefore lags behind the performance period due to the invoicing and payment process. FY21 revenues were considerably lower than FY20 due to the COVID-19 driven full shutdown of non-COVID-19 related and non-life saving clinical research. FY22 revenues show healthy recovery in the program, though the strength and duration of recovery should be interpreted cautiously as the entire industry has irreversibly changed post-COVID-19. Our fingers are crossed that we are truly looking forward to a sustained restorative period.

Division	FY20	FY21	FY22	Sum FY20 - FY22	# Awards
Adult Reconstruction	$324,232	$120,360	$278,474	$723,066	17
Foot & Ankle	$10,138	$42,857	$55,406	$108,401	4
Hand	$337,829	$78,357	$175,873	$592,059	7
Oncology					0
Shoulder & Elbow	$103,053	$131,376	$149,603	$384,033	4
Spine	$500	$21,234	$54,646	$76,380	4
Sports	$76,931	$44,540	$93,926	$215,397	4
Trauma	$44,411	$3,007	$106,238	$153,655	7
Grand Total	**$897,094**	**$441,731**	**$914,165**	**$2,252,990**	**47**

Figure 1. Clinical Research Expenditures FY20-FY22

Our Team. We thank our Team of Dedicated CRCs. Shown below from left to right are Helena Moses, Warren Harding (Adult Recon), Mounika Ponakala (Sports Medicine), Ellen Stinger (Upper Extremity & Spine), Linda To (Ortho Trauma). Not pictured: Artsiom Meliukh (Adult Recon). Ellen Stinger and Warren Harding also serve Foot & Ankle.

Helena Moses
Adult Reconstruction



Warren Harding
Adult Reconstruction

Mounika Ponakala
Sports Medicine

Ellen Stinger
Spine, F&A, Hand

Linda To
Trauma

Samir Mehta, MD
Chief, Division of Orthopaedic Trauma, Medical Director of Clinical Research
Associate Professor of Orthopaedic Surgery

Annamarie Horan, MPA, PhD
Director of Clinical Research
Orthopaedic Surgery and Anesthesiology & Critical Care