

**Recommendations to the Dean, University of
Wisconsin School of Medicine and Public Health and
the CEO, UW Health to improve the conduct of
Industry-sponsored Clinical Trials**

Mary L. Westrick, Ph.D., CRQM

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Contents

<i>Executive Summary</i>	3
Process Summary.....	6
Current Climate.....	7
Ideal Process	10
UW/UWSMPH/UWH Pillars to support Clinical Trials	16
Personnel – Centralized Office.....	16
Personnel – Standardized Training	18
IT	19
Quality Management/Quality Assurance Unit	21
Campus Support for Clinical Trials.....	22
Conflict-of-Interest	22
Health Sciences Institutional Review Board	24
Board of Regents Review	26
Legal.....	27
Pharmacy	27
Procurement.....	27
Clinical Research Unit	28
Culture Change/Public Relations	29
Change Management.....	29
Culture change – Faculty and staff	29
Culture Change – Patients.....	30
Business Plan	30
Conclusion.....	31
References	31
Appendix 1 – Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies	32
Appendix 2 – Process Summary.....	39
Appendix 3 – Report from Covance Quality Assurance and Compliance Vendor Audit	42
Appendix 4 - List of Individuals Interviewed.....	47
Appendix 5 - Biosketch for Mary L. Westrick, Ph.D., CRQM.....	49

Executive Summary

The purpose of this project was to examine how industry-sponsored clinical trials are conducted at the University of Wisconsin-Madison School of Medicine and Public Health (UWSMPH) and UW Health (UWH) and recommend improvements to the process. This project was necessitated by the recognition that significant advances are needed to keep pace with peer institutions in both reputation and sponsored support. This project also supports the strategic goal of UW-Madison, in conjunction with UWH, to be a preferred partner in taking innovation from bench to bedside. To achieve this goal, excellence in clinical research is a necessity.

The scope of the project was defined as those investigations that are sponsored by industry with the intent that many processes and procedures would be common to National Institutes of Health (NIH) and Investigator-Initiated Trials (IIT) and so could be leveraged into those areas. The scope was widened to include all clinical studies for examination of the Health Sciences Institutional Review Board (HS IRB) and Conflict of Interest (COI) committees, as those areas generated considerable feedback and concern from multiple constituencies.

It is important to note that an accreditation scheme for clinical trial sites is on the horizon, and is supported by industry, government and academia. The initiative is spearheaded by the non-profit Alliance for Clinical Research Excellence and Safety (ACRES) and this accreditation will apply to academic, commercial and sponsor-owned sites. A meeting with the FDA was held in early September, 2018, with strong support demonstrated for the initiative, and a meeting with EMA is scheduled for October. ACRES is also in discussion with the National Academy of Medicine (NAM) to access their set of metrics. These recommendations are meant to allow the UWSMPH and UWH to work more easily and efficiently with industry, while keeping patient safety as the primary focus. But they can also form a solid foundation for creating a research system that will meet the accreditation standards. While not a formal recommendation, it is strongly advised that a designated individual be given responsibility to monitor the accreditation scheme progress and advise Senior Leadership as to actions the organizations should undertake to meet those standards.

Over the course of this project, more than 115 meetings were held, and over 140 unique individuals interviewed that spanned the stakeholder horizon – University officials, Physician/Principal Investigators (PIs), Clinical Study Coordinators (CSCs), Budget and Financial staff, and sponsors consisting of both large Pharma and small biotechs. Officials from other Big10 institutions were also consulted in order to attempt to benchmark both common and best practices.

The most concerning and consistent theme emerging from these engagements is the repeated opinion expressed by almost all of those interviewed that the University has evolved to interpreting regulations, requirements, policies and standards in the narrowest sense; commonly gravitating to the most conservative interpretation possible and to protect the Institution from any risk or liability through tight bureaucratic control. This priority creates a situation where patient safety is not given as much weight, attention or effort. The result stifles potentially beneficial – even life-saving – research to patients with no counterbalanced benefit of increased patient protection.

In another consistent theme, it is evident that Faculty need and want to hear from top leadership at the University, UWSMPH and UWH in a consistent, visible, and vocal manner that this industry-sponsored research is a valued and important part of the overall patient care mission. Following on that concern is the essential need for Investigator reward and recognition that is currently lacking for Investigators conducting industry-sponsored studies.

Compounding these issues is recognition that UWSMPH /UWH sits at the bottom of many site lists in the drug development world, a fact reinforced consistently in interviews with internal and external stakeholders. The reputational issues are particularly evident to Contract Research Organizations (CROs). These companies have become a significant conduit for sites to forge and develop partnerships from the largest Pharma to the smallest and most emergent biotech companies seeking to develop and commercialize new therapies.

UWH's plan to assume a greater and more supportive role in clinical research is a very positive development. With the desire from both UWSMPH and UWH to become a leader in healthcare research and innovation and a world class patient care institution, pooling their resources to break down barriers and create efficient processes can form a powerful clinical trials research entity.

These themes mandate major culture change, spearheaded by top leadership, in order for clinical trials, and industry-sponsored clinical trials in particular, to become an ingrained part of the medical system and for UWSMPH and UWH to become a desired and sought-after research partner. Along with culture change must come additional investment. But an increase in the number of clinical trials successfully undertaken, combined with more efficient (and therefore more cost-effective) processes will begin to generate more residual dollars to fund the improvements as well as provide for other activities (IITs, meeting attendance, equipment, etc...)

Structurally, the current model at UWSMPH is very dispersed, with each department and therapeutic area managing trials in its own way. The exception is the Carbone Cancer Center (CCC), which kicked off an initiative to consolidate and centralize clinical trial functions approximately 3 years ago. This effort, while not yet complete, has garnered high marks from everyone interviewed both inside and outside CCC as this consolidation has led to greater efficiencies and even increased staff competency in certain areas (e.g., budget negotiations). Expanding this model is fitting as these benefits can be expanded to other departments. Appropriate metrics must also be collected, tracked and reported regularly to Senior Leadership to monitor progress and identify issues. These metrics must be very transparent, so all stakeholders have confidence in the data and know exactly what is being measured and how it is being measured.

The major recommendations are as follows. Those that are bolded are considered key to changing the culture, focusing on patient safety and creating efficiencies. Additional recommendations along with more specifics can be found in the body of the report. It should be noted that the success of any recommendation is contingent upon:

- Which recommendations are chosen to be implemented – and why
- When and in what order will they be implemented; and most importantly
- How** will they be implemented

The overall goal of these recommendations is to create a clinical trials environment that above all else, protects patient safety, while eliminating needless barriers. Centralizing and standardizing staff and processes is recommended to achieve a more efficient way of working along with an increase in staff competency and retention. It is also critically important that a Quality Management group must be created to take on the quality management role specific to clinical trials, a function that is currently lacking.

- **Provide early, consistent, continuing, vocal, visible and clear messaging from the most senior leadership of UW, UWSMPH and UWH explaining the rationale for the changes and how conducting industry-sponsored**

clinical studies fits with the mission to deliver outstanding, world-class patient care, and to be the preferred partner to take research and innovation from discovery to the people they serve.

- Create incentives for physicians – especially those early in their career – to participate in industry-sponsored studies. Reward and recognition are key if these individuals are to choose to spend their time conducting industry trials.
- Create a single “home” for clinical research staff (coordinators, budgeting, contracting, procurement, etc....) in one office within UWH. Harmonize all job descriptions (e.g., clinical study coordinators), salary scales, and career paths. Create specific competency-based criteria for advancement and incorporate into the job descriptions, including credentialing, if applicable.
- Create a Quality Management function for clinical studies. This group, also to be housed within UWH, has a significant breadth of responsibility, including but not limited to conducting process audits, management (but not ownership) of Standard Operating Procedures (SOPs) and providing support during regulatory inspections.
- Assess the composition of the COI Committee currently residing in the Office of the VCRGE to ensure that its membership reflects sufficient clinicians who understand the most salient and current patient safety and data integrity issues. Remove any logistical barriers, including meeting time and location, to easily allow clinician attendance without impacting patient care time. This will allow these clinical professionals to regularly participate in decisions impacting clinical trials. If this is not possible, consider moving the responsibility for these matters to the Interactions with Industry Review Committee (IIRC), currently residing within the University of Wisconsin Medical Foundation (UWMF). It is recognized that this Committee may need to become a joint SMPH-IIRC body to fulfill this function. However, its membership is very qualified to understand conflicts and risks to patients and create credible safeguards to manage them.
- Address issues in the campus IRB review processes that unnecessarily increase the burden on clinical researchers but do not add value with respect to the safety of human subjects. It is recognized that industry-sponsored clinical trials, the focus of this report, currently utilize an external, rather than a campus IRB. However, many of the “pre-submission” processes of the IRB are imposed on industry-sponsored protocols. Keep the HS IRB where it is currently located, as moving it into the Vice Chancellor’s office and thus farther from its constituents will hamper culture change, encourage a greater disconnect from PIs as well as encourage additional outside tasks (see next bullet) to be foisted on it, all impeding their core mission.
- Remove the University-imposed additional responsibilities placed on the HS IRB which require that body to act as “gatekeeper” and “policeman” for items that are well outside its regulatory function. Significantly change the “pre-review” process to be in line with other accredited academic IRBs and limit question/response loops to one or at most two cycles, eliminating the current unlimited iterative process and expanded timelines currently experienced by submitters.
- Support the initiative to improve the Board of Regents review process for Clinical Trials Agreements (CTAs) to eliminate delays.
- Use the centralized staffing model to devise a single process solution to staff emergent trials, whether in the Department of Emergency Medicine, Cardiovascular group, Department of Surgery, OB-GYN or any other group.

- Redesign the UWSMPH and UWH website to include a user-friendly portal with specific sections for both patients and sponsors, including contact information for a specific individual(s).
- Create a process by which remote monitoring (i.e., access into HealthLink) by sponsors is allowed for clinical trials.
- Develop and require a specific feasibility process, consistent across departments, with the appropriate stakeholders before any study is accepted. This must be a fast and efficient process to be competitive with other sites.
- Develop a Letter of Agreement (LOA) process and template so study start-up activities can be initiated quickly while the contract is being negotiated without fear of being left “high and dry” with no reimbursement for these activities should the study be canceled, pulled from UW or not approved.
- Change processes to require certain tasks to be done in parallel as the norm to decrease timelines.
- Once improvements are made and deficiencies addressed in the Clinical Research Unit (CRU), move qualified trials to that venue to better use that resource and free up Clinic space and staff.
- After significant improvements are made in the overall process and metrics confirm this progress, create a business plan to identify and justify which studies and therapeutic areas are to be pursued initially and create a marketing campaign/plan to identify which clients (Pharma, CROs, biotechs) to target, what professional meetings to attend, etc....

Process Summary

To assess the issues and concerns in conducting industry-sponsored trials at the University of Wisconsin and UW Health, over 115 meetings were held, and more than 140 unique individuals interviewed. Faculty and staff from many different therapeutic areas were involved, as was staff from supporting groups, committees and administration. A variety of opinions was sought, and every effort was made to meet with all constituencies. Many processes were investigated and documents requested. Thus, this report contains recommendations for improvements in the conduct of clinical trials in a variety of areas.

It should be noted that the effectiveness of these recommendations will be based on several factors:

- Which recommendations are chosen to be implemented – and why
- When and in what order will they be implemented; and most importantly
- **How** will they be implemented

Even the best improvement scheme can fail if not implemented properly. Many quality improvement efforts collapse for precisely this reason. As these recommendations are put into practice, the goal should always be to avoid any increase in bureaucracy and, in fact, decrease the bureaucracy currently in place. When forming new groups, the goal should be to create as flat an organization as possible, with special attention to the span of control numbers. Processes should be whittled down to the essential tasks and reviews, without duplicate tasks and reviews in the cascade. And as errors or concerns arise, the culture should move to an examination of the root cause of the problem, rather than adding another layer of oversight, another committee review or another meeting. A full list of the recommendations can be found in Appendix 2.

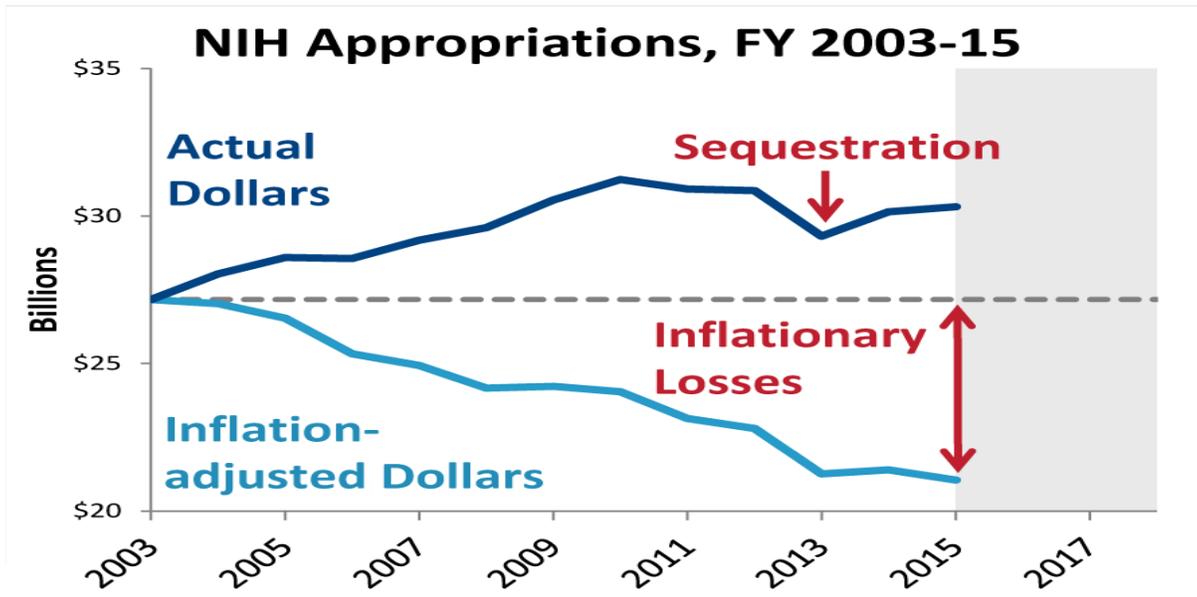
Current Climate

UW-Madison has traditionally lagged and currently lags behind its Big10 peers in industry funded research¹. According to this report from the National Science Foundation (NSF), UW ranks 6th in overall research dollars but 37th in industry research dollars. In addition, NIH funding overall has been decreasing in actual dollars over the period 2003 -2015 (Figure 1). Given the current administration's publicly acknowledged priorities for federal spending, it is unlikely that NIH will receive increased funds, and may have to fight to maintain its current level of funding. Thus, competition for NIH monies will become more intense and forward-looking institutions are seeking other sources for research support. Some institutions have taken this to the next level, as evidenced by the public-private partnerships announced last year by Stanford-Takeda² and Purdue-Lilly³. These relationships are one way to assure guaranteed levels of funding over several years. It is also important to note that clinical trials can have a significant economic impact to the state. Data from 2013 (the last year that data is available) reveals that Wisconsin is second from the bottom in the number of trials, number of patients and dollars brought into the state among the border states of Michigan, Illinois, Minnesota and Iowa along with Indiana (see Appendix 1). All of these states house major research universities and have at least 1 CTSA grant. These numbers include all clinical trials dollars generated throughout the state. So monies generated by the Medical College of Wisconsin, Aurora Healthcare and Marshfield Clinic are included, not just those generated from the University of Wisconsin system.

It is clear that cutting-edge therapies, whether they are new drugs, devices, diagnostics, gene therapies, etc...., are coming into the practice of medicine and becoming standard of care via industry and the clinical trials industry must conduct to achieve regulatory approval. In order to be recognized as a world class patient care center, robust clinical trials participation in multiple therapeutic areas is essential. NIH concentrates on basic research that seeks to understand and explain biological systems and the pathophysiology of disease and concentrates their dollars in those areas, unless there is a demonstrated public health need. Even when a public health crisis is proclaimed, as it was recently for the opioid epidemic, this announcement did not come with any additional funding to deal with the situation. Indeed, the support that Congress has awarded to NIH has been decreasing in real dollars for at least the last 10 years (Figure 1). Thus, it makes sense from both a patient care and financial perspective to endeavor to increase the amount of industry-sponsored trials conducted by UWSMPH and UWH. And it should be noted that more and more responsibility for the placement of clinical trials is in the hands of Contract Research Organizations. Thus, relationships with Pharma companies and biotech firms are not sufficient, as the CRO segment must be recognized as a legitimate sponsor of a growing percentage of clinical protocols. For all this to occur, a significant change in culture will be necessary.

Many Investigators expressed concern that in nearly all phases of the start-up process for clinical investigations too much emphasis is placed on protecting the University from any risk, liability or adverse publicity. Many investigators expressed their perception that UW-Madison very narrowly and conservatively interprets standards and regulations. These views reinforced the results of the IRB survey executed in September 2016. This view was particularly strong in those Investigators who had experience at other institutions, including peer institutions. A lack of centralized focus on patient safety was expressed by numerous PIs during the interview process. In addition, nearly every Principal Investigator expressed concern that currently there is no recognition or reward for participation in industry-sponsored studies, as only NIH studies receive a "gold star" on the Investigator's CV.

Figure 1 – NIH Funding Levels



This is an opportune time to objectively review the current situation, as accreditation for all clinical research sites – whether academic or commercial – is looming on the near horizon. Recent articles in the Proceedings of the Academy of Medicine and a Letter to the Editor in the New England Journal of Medicine both in October 2017 along with another letter in the NEJM on-line in June 2018 demonstrate both the need for site accreditation and the support for site accreditation from academia, industry and government as indicated by the affiliations of the authors^{4,5,6}. Indeed, the ACRES organization, referenced in the article, is well into creating site standards and plotting a timeline for dissemination, feedback and implementation of those standards⁷.

Industry Standards

The UWSMPH and UWH have specific goals related to patient care, translational research and innovation, as well as industry-sponsored trials. They aspire to be a Medical Destination and provide their patients with a “world class experience.” They want to lead in medical innovation and improve the lives and health of people in Wisconsin and across the globe. Participation in industry-sponsored studies can assist in achieving these goals. Providing the option of clinical trial participation for patients, especially those with life-threatening illnesses, gives these patients additional options for their care. Physicians can use clinical trials to determine how promising new therapies perform in “their” hands and with “their” patients. Currently, even many studies sponsored by area-based organizations are not being conducted at the University of Wisconsin/UWH as the barriers to placing these studies locally are viewed as considerable, with this view based on actual experience with the University

Industry has its standards for study placement based on metrics that have been carefully tracked by sponsor organizations for many years. Indeed, big and medium pharma companies and the major Contract Research Organizations all have extensive databases with a myriad of metrics about each clinical site and Investigator. While “Quality” is at the top of every list, it is clear that delivering a quality study is now considered “table stakes;” that is, many organizations can deliver a quality study, and meeting that criteria only puts your institution under

consideration for that trial. Sponsors require quick start-up times and look to metrics from past studies they may have conducted at that site for guidance. They want a reasonable cost, or at the very least a good justification for a high cost. Sponsors want “ease of use” in that they can easily navigate the site organization and have a strong main contact for any problems that may arise. This “ease of use” especially applies to the contracting and invoicing of trials. Contracting of clinical trials appears to be a solid process, but also appears to be dependent on the expertise of a single individual, which puts the process at significant risk without an appropriate and experienced back-up. Finally, sponsors of clinical trials want a “consistency of experience” in that they expect costs, start-up times, coordinator expertise, contract language, invoicing, etc... to be consistent from one study to the next, even if that study is in an entirely different therapeutic area and involves a totally different study team. This is very important, as companies need to predict how much a study will cost and how long it will take to conduct. This information is on the prospective therapy’s master development plan and may likely be on the critical path to approval. Thus, any overruns in either dollars or time will have to be explained to the sponsor’s senior management, and those conversations are never pleasant. Accreditation will soon play a role in industry expectations and requirements as well. It is predicted that standards for clinical sites will be rolled out early 2019, and sponsors have already expressed interest in using the accreditation credential as the first cut for choosing clinical sites.

As stated above, when any sponsoring clinical organization is questioned about their requirements for their clinical research sites, the first response is always “quality.” And this is true, as quality is the utmost concern for sponsors in order to trust that the protocol will be followed and the data generated is accurate and reliable. However, as the industry has evolved sites have improved their study execution and adherence to regulation. The result is that “quality,” in whatever way the client defines it, is now considered an absolute minimum. Any site that does not demonstrate their commitment to quality or have a demonstrated track record of conducting quality studies is not even considered for study placement. Following quality, major reasons that sponsors place studies at sites are that they:

- Are easy to deal with in the business arena (Confidential Disclosure Agreements (CDAs), contracts, budgets)
- Demonstrate a sense of urgency
- Provide quick study start-up
- Enroll in a timely fashion
- Conduct the trial for a reasonable price
- Provide access to the PI during monitoring visits
- Allow remote access to study data
- Have sufficient, well-trained staff to conduct the trial
 - Provide a single point of contact for the trial (typically the Clinical Study Coordinator (CSC))
 - Provide back-up resources should the PI or CSC be out of the office
- Complete data entry and respond to data queries in a timely fashion

In concert with these attributes, sponsors are looking for a “consistency of experience;” that is, costs, timelines and enrollment that can be relied upon study after study. They do not want study start-up to take 90 days for one study and over 200 days for another with no apparent rationale for the disparity. Nor do sponsors want to deal with differences in language or IRB requirements for nearly identical protocols. Sponsors expect the Clinical Study Coordinator in one trial to have the level of knowledge and training and the same study responsibilities as the CSC

assigned to the next study. Processes and procedures must be created that focus on and protect subject safety and comply with regulations, but also are as “client friendly” as possible. This means they are consistent and efficient.

As accreditation looms larger on the horizon, it is assumed that this qualification will quickly become the “bar” which sites must meet to even be considered for studies in the future. Those sites that anticipate the likely standards and move toward meeting them now will be much better positioned to apply for and meet accreditation when the standards go into effect.

Ideal Process

The ideal process for study start-up is both disciplined and transparent. One possible process is depicted in Figure 2. It begins with a website that is both patient- and sponsor-friendly. This means that patients can easily search for clinical trials and access a contact person that will help them with preliminary questions and inclusion criteria. The UWH database should be configured to include an “opt-out” option for all patients to make sending information about clinical trials quicker and more efficient. Experience at other institutions suggests that “opt-out” approaches enhance participation to a greater degree than “opt-in” processes. The website must also be sponsor-friendly, again providing contact information for an individual(s) who can not only answer questions but also help them navigate the UW system for the life of that study. These individuals may be termed “Navigators,” “Ombudsmen,” “Liaisons,” “Guides” or any other title that implies a helper function. They must be chosen carefully, as they need to be well-versed in clinical research trials, yet also have an extensive network within the Institution in order to determine the most appropriate contact in a given situation. That may be a Principal Investigator, a Clinical Study Coordinator, a Contracts person or other contact. This individual would guide the sponsor as needed through the UW processes. They are the sponsor’s main point of contact for problems or obstacles and are charged with removing barriers for the study. The Navigator may need to connect the sponsor with the appropriate department or PI. Once initial contact has been made, the next step is the signing of a CDA, also in an expeditious manner – preferably within 3 days. As a comparison, many sites can turn a CDA around in a matter of hours. Once the CDA is in place, and the details of the study have been shared, the feasibility process kicks in.

The Navigator can coordinate the feasibility process, and direct the sponsor to the most appropriate contact. The feasibility process must include all the relevant departments that would participate in the trial as dictated by the protocol and be fast and efficient. An overall feasibility process map is shown in Figure 3 and a detailed process map for clinical operations depicted in Figure 4. Again, the Navigator would follow-up on the process to ensure it progressed expeditiously and could help the various areas get responses from the sponsor as necessary.

It is very encouraging that the Department of Surgery recently completed a pilot to assess a feasibility process. Early feedback indicates the feasibility process is valuable. In fact, 2 protocols were rejected, thus avoiding waste of staff, time and money for protocols that had little chance of success, and metrics are being assembled to try to quantify the advantages and efficiencies. It is concerning that one of the advantages seen in the pilot was that errors were identified within the protocols. Errors should be caught through the Quality Control/Assurance process, not in feasibility, and this points to the lack of such a process. The purpose of a feasibility review is to determine whether the site can recruit and enroll the required number of qualified patients in the time proscribed and within the budget allotted or submitted.

Nevertheless, this pilot can be used to launch an initiative to both standardize and require the feasibility process across all areas. Standardization is critical, as allowing each department to design its own process will effectively

negate any efficiency. In addition, variation in process leads to an increased chance of error, as well as frustration and confusion for those groups that work across departments in many protocols (egg., Lab, Pharmacy). Surgery's process should be examined with other groups and amended to fit across the enterprise. Best practices must also be identified and shared on a continuing basis to continue to reap the benefits of the initiative.

Figure 2 – Possible “Ideal” Process

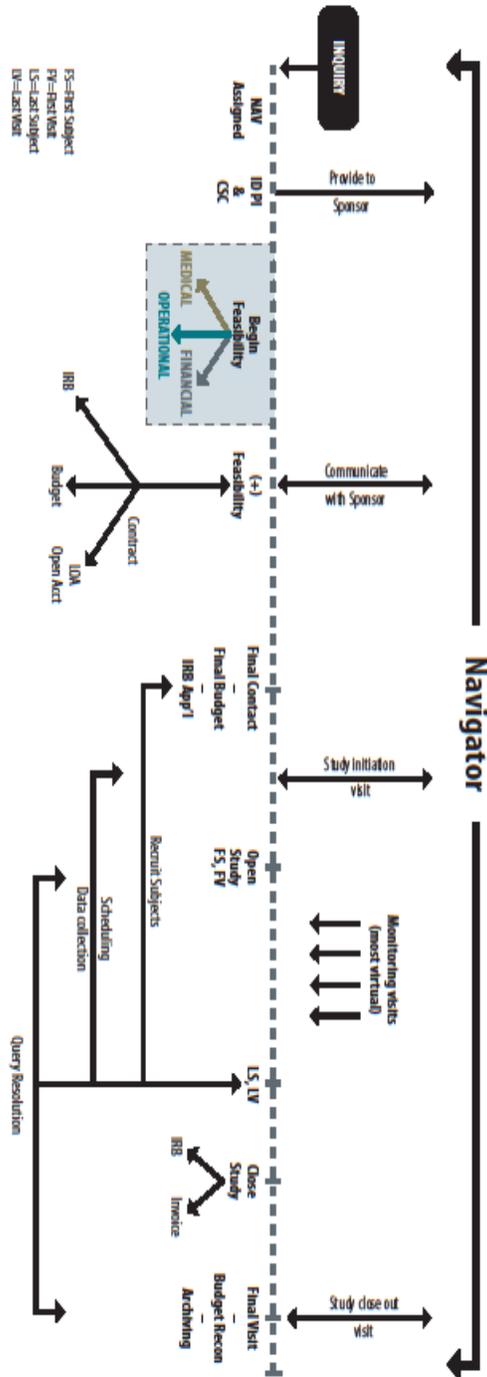
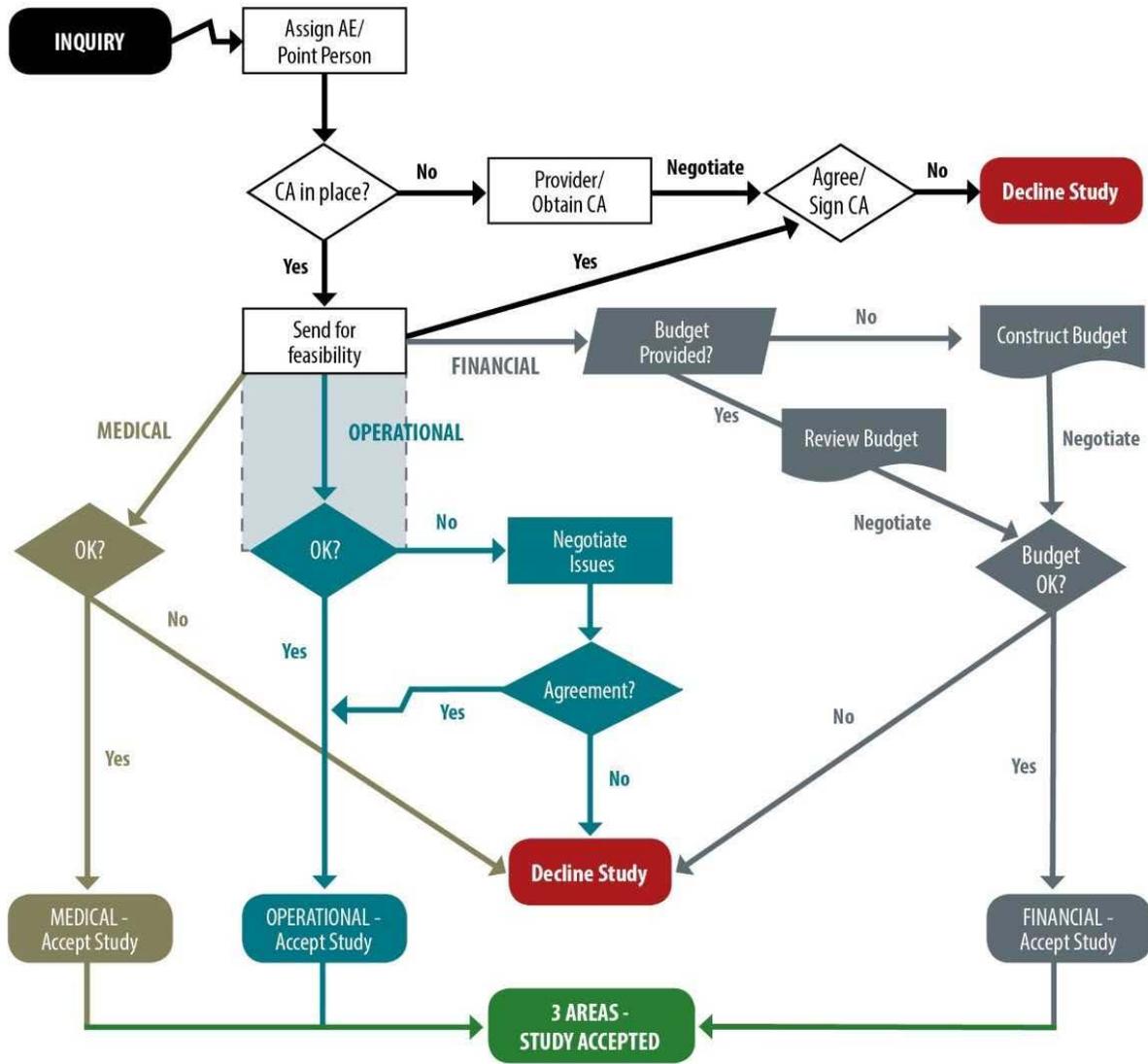


Figure 3 – Overall Feasibility Process Map

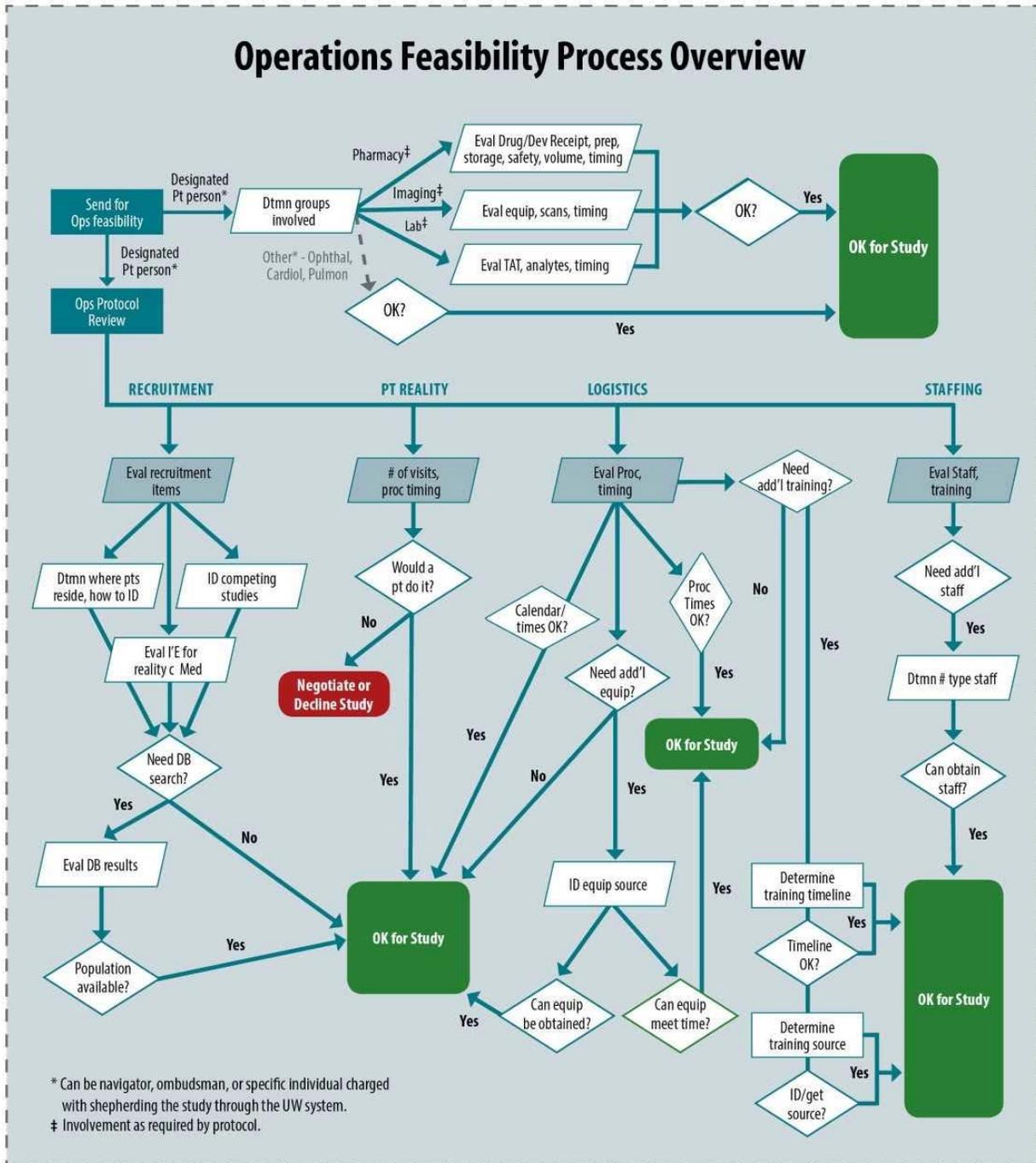
Feasibility Process Overview



CA = Confidentiality Agreement/Non-Disclosure Agreement
 AE = Account Executive

Again, this process should be fast and efficient and include all the relevant departments so there are no surprises once the study commences. The Navigator can facilitate the feasibility by following up on areas that do not respond in time and helping the right people connect to the sponsor if there are questions to be answered. If all the feasibility assessments are positive, the sponsor is contacted and then can determine if the study will be placed at UW.

Figure 4 – Clinical Ops Feasibility Process Map



When the study has been placed, a Letter of Agreement may be generated to allow for study start-up activities to occur with the assurance that they would be reimbursed. Then the budget preparation, contract negotiation and IRB submission can occur in parallel, shortening timelines. Many other institutions have adopted this parallel process (Figure 5) and found it to work well. This Letter of Agreement ensures payment for start-up activities once the site is informed of its selection for the trial. Typically, LOAs begin when the study is formally placed (this can be an email confirmation) and ends either with IRB submission or the IRB decision. LOAs always terminate prior to any patient

contact. This allows time for the contract to be negotiated and signed and guarantees payment for the early study activities, allowing the study to begin much faster once IRB approval is obtained. IT permissions should be in place so the proper personnel can access patient records and identify prospective study subjects without long delays. Again the “opt-out” process will facilitate accessing records and identifying patients.

The Navigator can also gather and report metrics in conjunction with the Quality group. As these individuals may be involved through study close-out, they are a good resource for this task, and limiting the number of people reporting metrics should assist in ensuring the measurements are collected and reported in a consistent manner. An example of the metrics collected by Indiana University is depicted in Figure 6. These metrics do not include IRB measurements which are collected and reported out separately.

Figure 5 – Indiana University Process Map

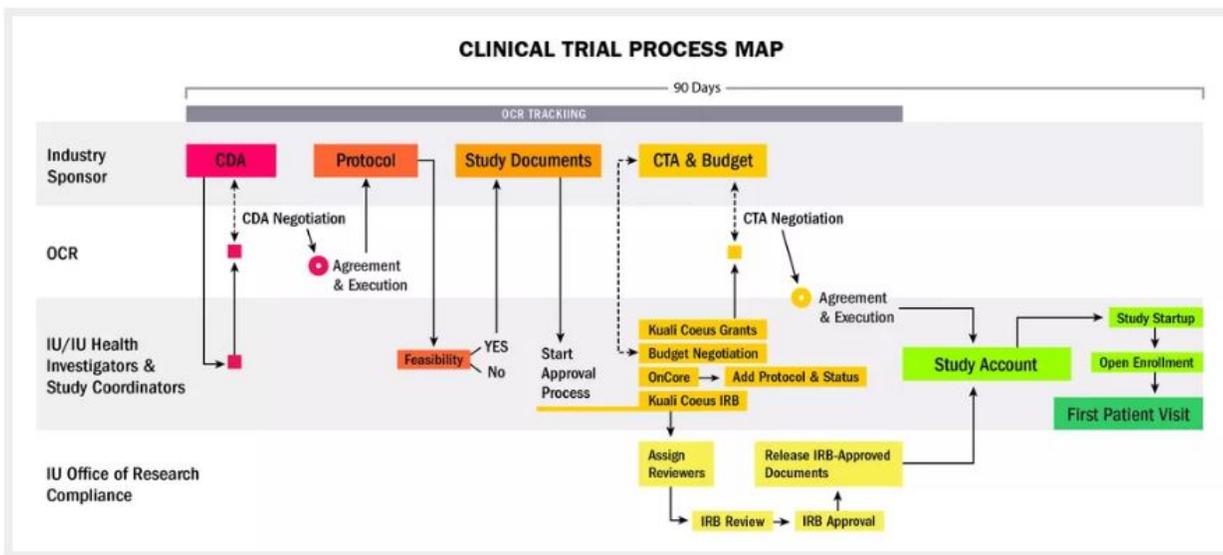
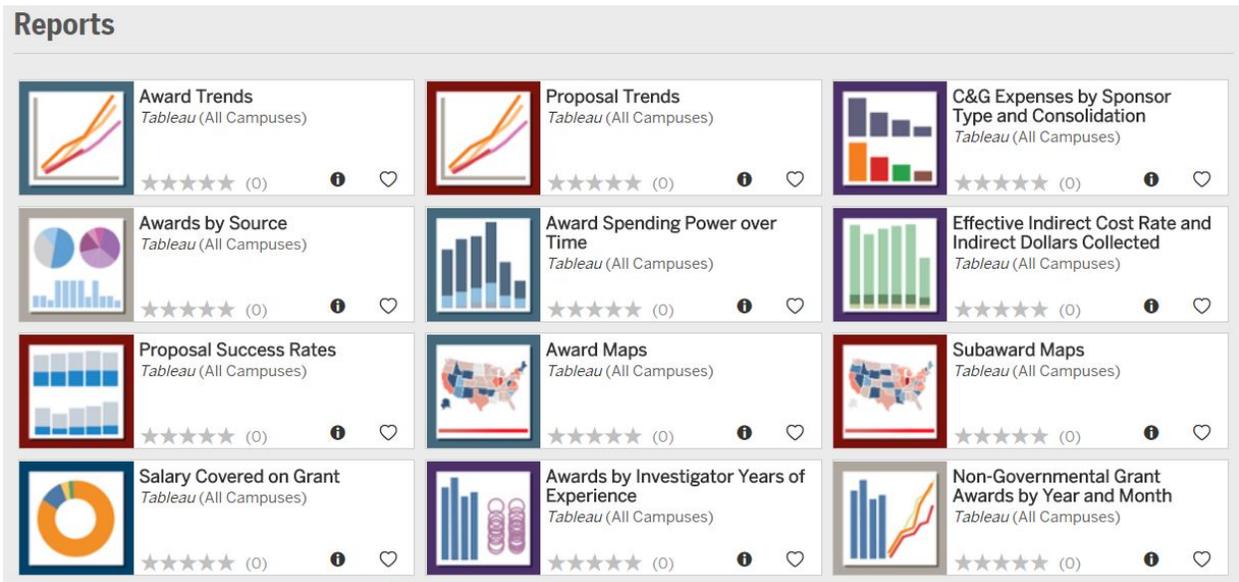


Figure 6 – Indiana University Metrics



UW/UWSMPH/UWH Pillars to support Clinical Trials

Several areas within UW-Madison, UWSMPH and UWH must continue to actively support clinical trials. These areas have been termed “Pillars” and include Personnel, IT and Quality. All areas must create an environment conducive to the protection of patient safety and the efficient conduct of clinical research.

Personnel – Centralized Office

It is recommended that all clinical trials personnel, with the exception of physicians, be transferred into a central office created at UWH. Individuals in the Office of Clinical Trials (OCT) as well as all the clinical research staff embedded in the various departments would transition. This includes Regulatory Specialists, Program Managers and budgeting staff and may include others with unique titles. Consolidation will allow load leveling for study staffing and allow small departments to more efficiently use staff only when they need it. All job descriptions and titles for those acting as Clinical Study Coordinators, for example, should be harmonized, along with salaries, career ladders and competencies for advancement, including credentialing.

At this time, it is also worth noting that the title of Regulatory Specialist at UW differs from that in the industry, and should be reconsidered as it causes confusion with clients. In conversations with these individuals and their departments, their main responsibility appears to be the facilitation of IRB submission and review. Within industry, Regulatory Specialists have a much broader remit and have expertise in IND, NDA and BLA submissions, along with experience in regulatory audits and interacting with individuals at various government regulatory bodies, including those ex-US.

An initiative is ongoing at UW to identify all the various staff that are coordinating trials and create harmonized job descriptions. This effort can be leveraged and the information gathered and employed for the staff to transition into the new central office. A salary survey may be necessary to appropriately set levels of compensation in order to be competitive. Clear and consistent competency-based advancement is particularly critical. While some departments state that advancement in their groups does require demonstration of certain skills, they further state those are “informal” and rarely used to stop the tenure-based promotions. The particular skills used as the basis for promotion also vary from group to group. Creating a central repository for clinical staff will allow for CSC cross-training and cross-coverage for studies. One common client complaint is that, when running a study with a small group that does not have many resources, their studies are essentially put on hold when the CSC is out of the office for any reason. There is no back-up because the department just doesn’t have the staff. Lack of back-up for budget preparation is also heard frequently from clients and can result in needless delays. Cross-training can also provide greater intellectual stimulation for high potential staff, and those that demonstrate they can move between certain therapeutic areas should be compensated accordingly, as they are more versatile and valuable to the group. Demonstrating this type of adaptability can even be a designated step forward in the career ladder.

The concept of “designated” rather than “dedicated” staff can be employed to keep CSCs primarily in their home department but allow flexing to other departments as the need arises. This load leveling can improve staffing efficiency and avoid unnecessary hires. This pool can also be the basis for formulating a solution to staffing emergent studies. The Department of Emergency Medicine is currently devising their own solution, while the Cardiovascular and OB-GYN departments are also trying to create a model that can solve the problem. But creating 3 different solutions is not optimum and leads to inefficiencies. Devising a core process – that may need to be

tweaked slightly for each group – is a better approach. But without bringing the staff together in one department, processes will continue to diverge.

Consolidating clinical trial staff will allow examination and adjustment of the span of control, also leading to better management of staffing levels. In some groups, a supervisor has just 1 or 2 direct reports. Standard span of control is 5-9, and even then, many supervisors are “working supervisors,” taking on a small study load themselves. Conforming to this norm will likely free up a few Full Time Equivalents (FTEs) to take on more study activities and create a more consistent management environment.

Budget personnel are also recommended to move into the new central department. All of the same criteria described above – harmonization of titles, job descriptions, salaries, span of control, cross-training, etc..... would apply. Again, training would be standardized and required. Standardized and systematized training would facilitate the “consistency of experience” that clients require and help ensure that clients receive consistent budgets from study to study. Currently, smaller departments typically have one individual that prepares and negotiates budgets as part of many other duties. These individuals may only negotiate a few budgets per year and can be at a serious disadvantage when bargaining with a “professional” negotiator from the outsourcing department of a sponsor company who wrangles over budgets every day. Combining full time budget staff can transfer this task from those smaller departments and result in a better budget overall. Using the same rationale, Regulatory Specialists and Program Managers are also recommended to move into the central office. Additionally, the single individual currently in Research Billing Compliance who reviews all clinical trials for Medicare utilization should be moved into the central office. An additional FTE is expected to join this function, and the need for more staff should be revisited when the new person has been trained and the clinical trials load assessed. This group needs sufficient bandwidth to be able to perform routine study audits to ensure Medicare coverage compliance, a task which is rarely undertaken at this time because of resource constraints.

Consolidating clinical staff will also allow easy transfer of best practices. Individual departments (e.g., Surgery, Radiology) have some effective tools and processes for clinical trials. But there are no channels for this information to be distributed or discussed so best practices can be in place throughout the organization. Locating all the clinical trials staff in one office, and in one location as much as possible, will facilitate communication and standardization of best practices.

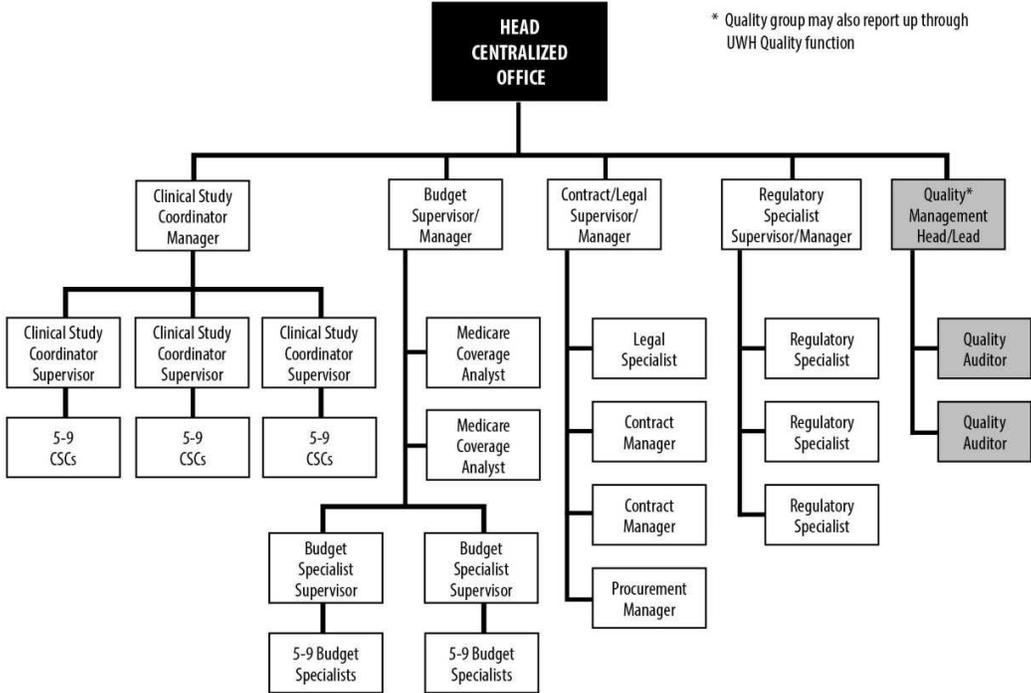
The disparate titles held by clinical trials staff illustrate the challenges of determining just how many staff support clinical trials and in what capacity. Currently, staff carry various titles when performing the same duties, and there is no way to produce a master list of all CSCs, for example. Bringing all clinical trials staff together would allow better control of staffing levels and study loads, as well as provide more timely and higher quality service to both patients and sponsors. These staff would also be eligible for the employee recognition program at UWH. Recognizing appropriate staff for outstanding work will improve morale, job satisfaction and demonstrate the organization’s commitment to clinical trials as an essential part of their healthcare mission.

A leader for this office must be chosen carefully. Someone from industry with a track record of building departments, process improvement expertise and working with clients would be very desirable. The best fit would be an individual with experience in a CRO as and perhaps a Sponsor organization, as CROs are used to doing “more

with less” and have a heightened sense of urgency. They are also extremely process-oriented. The title and level of the person would be set when the number of staff in the group is determined and when it is decided whether the Quality group will reside in this office (see below). Every effort should be made to keep the organization as flat as possible, as the reduction of bureaucracy is a major goal. Other groups that are recommended to move into the central office are discussed later in this report. A mock organization chart is provided (Figure 7).

Figure 7 – Possible Organization of Central Research Office

Proposed Central Office Structure



Personnel – Standardized Training

Training courses must also be developed and required for all clinical trials staff, especially CSCs. In certain groups, coordinators are trained only by shadowing a Principal Investigator for a given period. In some departments, this may be as brief as 2-4 weeks. While that experience provides exposure to some aspects of clinical trials, the Coordinator’s role is very different from the physician’s role and shadowing the physician will not adequately prepare the individual to coordinate a study. Even shadowing a current coordinator is not sufficient, as all aspects of a trial must be included in the shadowing experience (feasibility, recruitment, study conduct, query resolution, etc....), and that may take months to occur. Also, formal training needs to be delivered so the individual understands why certain tasks are accomplished in a certain way and is aware of regulations and best practices.

The modules available through the Institute for Clinical and Translational Research (ICTR) give a good introduction to clinical trials, but do not prepare the student to be a coordinator and are not required for all CSCs. For example, the modules do not address how one “breaks down” a protocol, which is a vital skill to coordinating a trial. Nor do they address Good Documentation Practices, another essential skill for CSCs. Additional modules should be developed,

perhaps within ICTR or within the Central Office, to provide a more comprehensive training program to prepare study coordinators. Other institutions provide robust CSC training, and have additional training modules and programs as the Coordinator progresses from entry level to Senior Coordinator. In some cases, UWSMPH departments have sent their CSCs to these other Institutions for adequate training, as they recognize it currently does not exist at UW. These courses can be used as a benchmark to internally develop training, and until that time require outside training for coordinators. It is essential that all coordinators receive the same training and can demonstrate the same competencies in order to effectively move between trials as needed and provide consistency in delivering quality trials for both the institution and the sponsor. A training matrix must be developed in conjunction with Quality Assurance to ensure that all staff in a given role receive the same training within the same timeframe. This includes Good Clinical Practice (GCP) training, ethics training (CITI), SOPs, Blood borne Pathogens, etc.... The matrix should also dictate how often the training must be refreshed.

The same rationale holds for budget staff, Regulatory Specialists and any other clinical trials personnel. All functions would benefit from standard, required training to provide core competency in each area. CRU staff will also require a training matrix for their clinical trials functions.

IT

It should not come as a surprise that change to IT policy and investments in technology are recommended. It is concerning that numerous individuals stated categorically that no additional IT projects can be taken on or investments made for 2 years. Delaying some of these actions will allow inefficiencies to continue and cause UW to lag farther behind comparable organizations.

First, it is recommended that the PeopleSoft module for time tracking be obtained. This module would benefit all departments (e.g., Engineering) that run projects for non-profits, government organizations or industry as it will allow managers to track their staff time and determine if someone or some project is going off course. It is also useful for clients to prove for example, that the patient population in a given trial is requiring much more time than was originally budgeted. Having data to present to any sponsor, government or industry group, makes a compelling case and can lead to an increase in funding. It can also indicate to a manager if one staff member is taking more time to do the same work. Then the root cause can be found, such as inadequate training. As many University departments can benefit from this improvement, it is recommended that the Institution purchase the module. For this module to be effective, hours must be entered on a timely basis, ideally every day. In some organizations, this is accomplished by tying paychecks to the entry of time data, so staff must enter their hours before they are paid. Appropriate training and subsequent monitoring is essential to ensure the data generated from this module is accurate.

A system for an electronic trial master file (eTMF) should be seriously considered. This is the file that contains many of the standard regulatory documents needed for each protocol. As this is now kept on paper, whenever a new Clinical Monitor is assigned to the study, the current process is to photocopy all the documents and send them for overnight delivery to the new monitor, wasting time and resources. With an eTMF system in place, a new monitor would be given appropriate access and credentials to access their trials in the system electronically and remotely, saving time and money. At the end of the trial, again the documents are photocopied and mailed. With an electronic system the entire study eTMF would be transferred electronically, saving more resources. The CCC is

evaluating eTMF systems, and at least one other department is considering a purchase as well. There is no coordination between departments, so it is quite possible that different systems could be purchased. Again, the consolidation of all budgeting personnel would prevent divergence in systems and keep processes consistent.

Clinical site monitoring has evolved over the last several years to embrace the Risk-Based Monitoring (RBM) philosophy. In this paradigm, Clinical Monitors remotely access study data early in the study for all sites (often after enrollment of the first 1-2 patients) to evaluate the quality of the data and identify any site problems, then match ongoing monitoring frequency and level of scrutiny to the performance of the site. Almost all site monitoring is done remotely, most especially in large Phase 3 studies that may be conducted on several different continents. While remote access is not currently offered at UWH, the ongoing exploration of the use of EpicCare Link is encouraging and should be prioritized as much as possible. When a Clinical Monitor now schedules a visit, the CSC must request logon access for that specific visit for that specific Monitor through IT, then go into the EMR of each patient and specifically grant access for that monitor for that visit for each patient individually. This entire process is repeated for every Monitor visit, wasting hours and hours of CSC time and adding significant cost to the sponsor as the Monitor must physically travel to the site for every visit and the site must budget to cover the hours of CSC time. For many studies which run out for a year or longer, monitor visits approximately every 6 weeks can add significant costs to the study. And that does not include the lack of productivity for that Monitor during travel time. An efficient and secure process to give Monitors appropriate record access throughout the study is essential going forward.

It is recommended that IT would also create the “opt-out” process for patients so that EMRs can be searched and prospective patients contacted regarding clinical trials. Some sort of option for the patient is essential if UWH and UWSMPH are to leverage the vast number of patients they serve. It would also motivate PIs to take on trials if they knew they could search and contact patients that were not just their own or who do not have their own databases of past study patients. One of the great strengths of the UWSMPH/UWH system is access to a large population of patients. And as study entry criteria become more and more detailed and specific, institutions that can leverage their large populations to identify qualified study subjects will be more successful in securing studies.

Also on the IT list is the redesign of the UWSMPH/UWH portal. This has 2 aspects, as improvements need to be made for both patients and sponsors. Following a serious diagnosis, family members are often on their smartphones in a manner of minutes, looking for therapies, expert centers and clinical trials. As designed today, it is extremely difficult to find clinical trials on the UW site, even when one knows all the appropriate buzzwords and terminology. Other Big10 Institutions have patient-friendly web pages that make it much easier and faster for patients who may have little to no clinical knowledge to find clinical study information and contact an appropriate person. The University of Minnesota and Penn State University have a “StudyFinder” function, while Northwestern University has a straightforward search function for clinical trials, and the University of Michigan has a similar “Find Trial” function which also provides information for patients regarding participation in clinical trials. Indiana University has a study search function and offers patients a wealth of information including, “Preparing for Your Visit” and “Making Your Stay Easier.” In some cases, OnCore is interfaced with the web page so, when a study is opened, it automatically shows up in a search from the website. This eliminates duplicate data entry and provides patients with the most current study options. These sites may also offer information on how clinical trials are conducted and what is expected of a patient who chooses to enter a clinical trial.

Similarly, other institutions have well-designed landing pages for sponsors looking for Principal Investigators for a particular study, or who just want to understand if the Institution has any expertise in their area of interest. Again, there is contact information offered for individuals who can provide information and make the right connections. A search function for PIs with certain areas of interest would be useful to sponsors, and serious consideration should be given to adding industry relationships to physician bios. The landing page for the Office of Clinical Research at Indiana University has a specific section for industry, and Rutgers University has Rutgers CRO, which “connects industry, patients and academic collaborators with the University's state-wide academic resources.” This organization is the single point of entry to access lab and analytical services, imaging services and clinical trials services, including Investigator identification. The site includes contact information for sponsors who are interested in engaging the University for clinical trials.

Quality Management/Quality Assurance Unit

A robust Quality Management system is essential to support clinical trials. This function must be created for clinical trials and will be the foundation for site accreditation.

At the University, Quality Management seems to translate into Compliance. Compliance assures the adherence to University policy, along with state and federal law. Quality Assurance has a significantly different function, and in this case, is specific to support clinical trials. The background and training of personnel within the VCRGE's Post Approval Monitoring Program and ICTR's Study Monitoring Service is consistent with a clinical monitoring function, not a quality auditing function. Both clinical monitoring and Quality Assurance have their roles in clinical trials, whether those studies are government funded or sponsored by industry. The University of Michigan includes the descriptions of each on their website to assist PIs in preparing for these different kinds of inspections. The individuals in these functions carry different credentials and often have different backgrounds. Quality Assurance auditors typically are individuals with Bachelor's degrees in the sciences and specific training in quality processes, SOPs and compliance with GxPs (Good “X” Practices, such as Clinical, Laboratory, etc....). They often have earned their Quality credential as a Registered Quality Assurance Professional from the Society of Quality Assurance. A strong Quality Management group or department has a variety of functions including, but not limited to, those listed below:

- Process audits on a regular, scheduled basis as well as ad hoc and for cause inspections
- Internal study audits when necessary or requested
- Fee-for-service audits for sponsors
- Regulatory inspection support for PIs and CSCs
- Host government (FDA, DEA, NRC, etc..) inspections relating to clinical trials
- Host sponsor QA audits
- Administrate (but not own) SOPs
- Participate in process improvement efforts
- Corrective and Preventative Action (CAPA) management and follow-up
- Root Cause Analysis (RCA) assistance and management
- Vendor audits as required
- Monitor regulatory bodies for inspection trends
- Repository for Inspection Reports

All of these functions are essential to ensuring that quality is ingrained in every step of the clinical trials process. This includes the protection of patient safety and privacy and the generation of accurate and reliable data. Both Quality Control and Quality Assurance techniques are employed. Whenever a serious error is uncovered, the QM group plays a significant role in determining the root cause of the error, whether that error can be corrected and assisting in devising measures to prevent future occurrences. This CAPA (Corrective And Preventive Action) process is essential for maintaining quality.

The QM group also typically administrates, but does not own, the Standard Operating Procedures (SOPs). SOPs are owned by the people who perform the tasks; i.e., the staff running the trials. Within UW, SOPs specific to clinical trials are few and far between and vary significantly between groups. For this project, the SOPs reviewed did not adhere to the standard of controlled documents, which is a serious deficiency. The Quality Management group can be the driving force for the stakeholders to come together and create the appropriate SOPs to ensure quality studies and convince both sponsors and regulators that there is a firm commitment to quality at the Institution. They also have the expertise to assist in creating the overall document that controls and describes the SOPs themselves, known as “The SOP on SOPs.”

The leader of this new group must be chosen with care. An individual who is familiar with industry standards and Good Clinical Practices (GCPs) in particular (as opposed to Good Laboratory Practices (GLPs) or current Good Manufacturing Practices (cGMPs)) and is a credentialed Quality professional with a history of building successful organizations would be preferred. Pragmatism should be valued, especially as the current University environment is widely perceived to default to the most conservative interpretation of regulations and policies. The leader should be realistic in creating a quality framework that protects patients, complies with regulations but is also efficient and requires only that level of review and oversight essential to that quality system. This leader should have the mindset that Quality groups are a partner to Operations in helping Ops both comply with regulations and build a culture of continuous process improvement. The first auditors hired should also be Quality professionals and all should have earned their Quality credential (Registered Quality Assurance Professional (RQAP)) from the Society for Quality Assurance (SQA). The leader will be able to assist Human Resources in creating appropriate job descriptions, career paths and salary levels for the auditors.

Campus Support for Clinical Trials

The overall University entity (“Campus”) owns several groups whose efficient functioning is essential to the success of clinical trials. These include the Conflict-of-Interest (COI) committee, the Health Sciences Institutional Review Board (HS IRB) and the Research and Sponsored Programs (RSP), Pharmacy and Legal and Procurement support.

Conflict-of-Interest

This Committee, located in the Office of the Vice Chancellor for Research and Graduate Education (OVRGE) currently does not serve the UWSMPH well. It is interesting to note that common practice in the Big10 and elsewhere is for Medical Schools to convene their own COIs for reasons that will be discussed below. For example, the University of Michigan and Penn State University have COI committees within their Medical Schools to manage clinical COI issues.

At the time the draft of this report was submitted, there were just 2 clinicians on the Committee, and the second one had been recently added. As COI issues and exception requests come before this committee, it is their responsibility to determine how to handle them. Investigators' perceptions of the climate as it stands is consistent with the conservatism noted above with attempts to preferentially eliminate all risk, to the point of informing the Investigator that s/he cannot participate in the research. This creates a very mixed and confusing message for researchers. The University actively encourages autonomy and the pursuit of individual interests among its Faculty to devise innovative therapies and techniques. Then, when that same researcher wants to take that technology, technique or therapy forward, they are faced with a series of obstacles.. It is also clear from email communications that there are no procedures in place for the Committee to meet in an ad hoc fashion. Thus, delays of nearly 3 months can occur merely for scheduling reasons. This does not serve PIs, patients or sponsors well as time is always of the essence and lack of a sense of urgency on the University's part is a common sponsor complaint.

In reviewing some of the management plans dictated by the committee, it appears to be a "one size fits all" no matter the type of research, the degree of the conflict or the design of the clinical trial. Some Committee members interviewed felt that it was solely the IRB's responsibility to protect subject safety. Actually, it is the responsibility of the COI committee to put safeguards in place, based on the degree and extent of the COI and the design of the protocol, to protect patient safety. Current plans seem to focus on the reporting of results and documentation of meetings, rather than the risks should an unscrupulous PI try to manipulate the data at its creation point – the patient. This is a gap that must be filled, as it is not the responsibility of the IRB to put measures in place based on conflict-of-interest concerns. But it is not realistic to expect a committee of members who are inexperienced in clinical research to create a reasonable and effective management plan, especially as no training is currently offered or required for Committee members. The committee members are intelligent and accomplished academicians, but a Professor of Chemical Engineering, or Spanish Literature, or Economics should not be expected to possess the regulatory and operational knowledge of clinical trials to be able to create effective COI management plans. In looking at peer institutions, the University of Michigan has a COI committee within the Medical School, and has categories of risk and conflict, including a category that states, "Conflict exists with no formal plan." This is a useful scheme so that management plans and mitigations can be matched to the degree of risk or exposure. This process can be very useful in preventing draconian requirements for a minimal to nearly nonexistent conflict or risk and ensuring that investigations with significant risk have robust levels of oversight.

Clinicians who understand where patients are put at risk within the protocol are most qualified to recommend safeguards. Thus, membership on the committee should be expanded or revised to include more clinicians, and to remove logistical barriers their attendance. Meeting times and location should recognize the clinicians' patient care commitments and be set accordingly. Meetings should be held each month and scheduled far in advance; if there are no conflicts to review, the meeting can then be cancelled. This allows members to more effectively manage their time and should increase attendance.

If these conditions cannot be met, then it is strongly recommended to move the responsibility for clinical trials COI reviews and exception requests to the Interactions with Industry Review Committee located within the University of Wisconsin Medical Foundation. It is recognized that this Committee may become a joint SMPH-IIRC in order to meet the requirements of the University.

In fact, the IIRC policy states:

UWMF was chartered by the University of Wisconsin Board of Regents in 1996 to support the educational and research missions of the SMPH through the coordination and delivery of clinical care by the faculty of the school. The authority bestowed in the charter carries with it the responsibility to exercise our clinical mission with the highest standards possible. While the UW has policies that speak to conflicts of interest, such policies do not fully reflect the special covenant that exists between clinicians and patients, and do not respond to the urgency felt by academic health centers to formulate specific policy in this area. As a result, UW and the SMPH have delegated the responsibility to implement this Policy on behalf of the UW and SMPH with respect to UW Faculty Physicians and other UW-employed health care professionals. (<https://www.uwhealth.org/files/uwhealth/docs/pdf4/interactions-with-industry-policy.pdf>)

In the past Outside Activities Report (OAR) data has not been supplied to the IIRC in a readily useable format. That situation will be resolved as the Institution moves to the Association of Academic Medical Centers' (AAMC) system of single entry, and the IIRC will have full access. IIRC policies also require a pre-review of the contract before a clinician may sign and may advise the clinician and even prohibit signature. UW employees cannot advise Faculty or staff on matters that involve outside compensation. So it makes sense for one group to consider the entire package.

The IIRC body is populated with multiple physicians/Principal Investigators and has legal resources which give it the necessary experience and expertise to not only shield the Institution from risk and liability, but to focus on patient safety as well. And it is easy to understand how protecting patient safety also protects the Institution. In short, the legal, medical and clinical expertise found within the IIRC is much better suited to reviewing COI issues and creating appropriate management plans than the current COI committee located in the Vice Chancellor's office.

Health Sciences Institutional Review Board

The problems, concerns and issues regarding the HS IRB should be well known, especially following the survey that was completed September 25, 2016, and reported out over 7 months later on May 1, 2017. Interviews with numerous PIs indicate the level of frustration has not diminished and, if anything, has increased. These PIs state they have seen the situation deteriorate or, at best, not change in any way. Several PIs interviewed said they did not participate in the survey as they felt it was for optics purposes only and that substantive changes would never occur. They supported this view with the observation that at the time of the interviews, 16 months had expired since the survey closed and they have seen no progress. Other PIs believed the survey was merely a way to identify "problem" Investigators and worried about retaliation if they supplied negative comments and ratings. Several researchers commented in the survey that they were actively looking to move to other Institutions or at least seriously considering a move due to the frustrations and obstacles of working with the HS IRB, and these comments should be taken seriously. Losing gifted Faculty because the Institution cannot operate an Institutional Review Board efficiently as do other peer organizations is simply unacceptable for a world-class academic Institution and should spur the University to fast track improvements. Following the survey, the Faculty Working Group was created to recommend improvements to the IRB. The report from this group does not have a stated deadline. At the time of the submission of this report, the report of the Faculty Working group was not yet released. When the report is released, it should be noted that there is no requirement for the University to accept the recommendations put forth. It should also be noted that many of the issues described in this report correlate closely with those uncovered in the survey and posted on the website for the Vice Chancellor's Office of Graduate Research and Education⁸.

Administration from the Vice Chancellor's office stated that the HS IRB will be moving into the Vice Chancellor's office in the near future, as the ED/SBS IRB did in September, 2017. This move is *not* recommended, as one of the major problems uncovered with the HS IRB is the amount of "overreach" referred to by PIs. In investigating this feedback, it became clear that the University has imposed tasks on the HS IRB that have nothing to do with its regulatory mission and protecting the rights of patients. The HS IRB is a convenient choke point, as all studies must pass through this body, even those that are delegated to outside Boards. So there are a myriad of tasks that the IRB is currently responsible for, but should not be. The strong recommendation is to divest the HS IRB of those responsibilities as soon as possible and allow this group to concentrate on their core mission. In speaking with officials from peer Institutions, it is apparently common practice for IRBs to be approached by the University or Institution to act as the policeman or checkpoint for a variety of other groups. However, in these peer Institutions, the IRB respectfully declines the additional asks and works with the appropriate body to create a process for that constituency to get the information it needs without the IRB taking on the responsibility for providing or regulating it. In fact, one IRB manager stated that she spends a significant amount of her time with these outside groups, ensuring that the IRB at her Institution can concentrate on fulfilling its mission. Moving the HS IRB into the Vice Chancellor's office would not only make it more difficult to divest these outside responsibilities, but make it even easier for yet more responsibilities to be loaded onto the group. It is easy to see how this could occur, in the guise of "cooperation" and "being a team player" when dealing with other groups also resident in the VC's office. While officially the Board reports up to the Institutional Official, moving the HR IRB farther away from their constituents (PIs) will serve only to exacerbate the issues already identified.

It is clear that the HS IRB is one of the groups that must undergo a significant culture change. Moving into the VCRGE's Office would make culture change nearly impossible to affect. Interpreting the regulations in the narrowest sense and not trusting PIs for even the simplest tasks is just the beginning of a list of attitudes and practices that must evolve. The extensive "pre-review" that currently exists is untenable for the future. Interestingly, when IRB staff was asked about this process, the answer received was a very fast and definite "It is an AAHRPP requirement." (AAHRPP is the Association for the Accreditation of Human Research Protection Programs and is the accrediting body for Institutional Review Boards.) The pre-review is *not* an AAHRPP requirement. AAHRPP does not have *any* requirements; they have standards. In discussion with an Institutional official at another Big10 University who also happened to be an AAHRPP accreditor, it was related that AAHRPP does not even put best practices on their website, for fear that they will be interpreted as requirements. *It is up to the Institution to determine how to meet the standards.* Thus the University devised this pre-review process to meet one or more AAHRPP standards. Peer Institutions do not have this their IRBs have the AAHRPP credential. It is likely that there was no Root Cause Analysis (RCA) done to determine why the standard wasn't being met in the first place. And a page was taken from Quality schemes decades ago in that another, more extensive review was put into place to fix the situation. The staff states the AAHRPP accreditor was very complimentary of the process; however it should be understood that the inspector was only looking at how well the process met the standards, not how efficient the process was or how well it met the needs of the PIs. Adding additional layers of review, more intense review or additional meetings to resolve an issue is an outdated practice and only employed when the RCA indicates it is warranted.

One recurring and significant frustration as expressed by PIs is the iterative nature of the pre-review process. It appears to many PIs that the reviewers are not well qualified to perform the reviews, as they get an initial set of questions, which they answer. Then, several days or a week later, they receive another set of questions, and even a

third and fourth set over several weeks or even months. They suspect that the trailing questions come as the primary reviewer talks to others in the office, and further questions are generated. Several PIs had stacks of emails from IRB staff documenting these cycles. This iterative process is made more frustrating by the lack of assistance on the part of IRB staff to offer suggested language or templates to help the PIs which often increases the number of cycles going back and forth and prolongs the process needlessly. If this pre-review process is optimized and brought in line with other peer Institutions, then these iterations should be eliminated. It is worth noting that, if this review is abbreviated, PIs will likely see an uptick in protocols not approved, although it should be temporary. Other Institutions saw this initially as well when they revamped their Boards. But with improved PI education and a culture change away from the narrowest regulatory interpretations, this is a short-lived situation. Peer Institutions confirm that the advantages to optimizing the process and significantly shortening timelines - *while not impacting the protection of patients' rights* - far outweighs the short-term pain.

So the short cycle time reported is not what the PI or the sponsor (or the patient, for that matter, as there are patients, especially in the CCC, that may be waiting for a study to open) truly feels as the cycle time. This was mentioned by sponsors to the point that they flat out do not believe the metric. And it makes them suspicious of other data provided to them with respect to clinical trials. For the UW HS IRB, the cycle time begins when the staff reviewer feels the study is ready to go on the IRB agenda. For all other Institutions contacted, the cycle start time was defined as the time the "PI pushed the submit button" on their electronic submission system. Any pre-review time is included in other Institutions' metrics. And while the cycle times at other Institutions may be longer – although many aren't that much longer – they are more accurate in describing a time period the PI and sponsor can rely on. This goes back to the issue of creating a "consistent experience" for a client. Northwestern University states that its Center for Clinical Research has decreased the time from *first sponsor contact to first patient/first visit from 8 months to 8 weeks* in early clinical trials.

The HS IRB staff are not credentialed, and the reason given was that "the processes and procedures are so robust it's not necessary." This is precisely why accreditation was created. All institutions feel they have the best practices and believing your group doesn't need or can benefit from outside validation is arrogant and foolhardy. In fact, at some Big 10 IRBs, the credential is required to move out of the entry level position; in others, it is not required but "expected" as soon as the individual has had enough time in position to qualify. The credential is a CIP, for "Certified IRB Professional" and it is granted by PRIM&R, Public Responsibility in Medicine and Research.

The HS IRB does have SOPs, which were supplied for this report by email. as access to them within the system was not granted. However, the majority of documents provided were obviously works in progress, as they were pdf copies of "track changes" Word documents. An "SOP on SOPs" does not exist to describe the contents of SOPs and how the documents are controlled. A document was provided that purported to describe and control the SOPs, but the content is very general and does not describe how SOPs are controlled nor their format or content. In reality these SOPs are not controlled documents. It was also reported that the SOPs are not in one place but in various parts of the system. This makes it much more difficult for staff to be trained on them and for specific documents to be located. A Quality Assurance group can be of great assistance to rectify all these issues.

Board of Regents Review

The UW Board of Regents must review and approve all CTAs that reach a certain dollar amount. Unfortunately, the Board does not meet every month, and can have a very full agenda that delays these reviews. An initiative is

underway to delegate authority to an appropriate individual to approve these agreements, with the Board being notified of all such approvals at their next meeting. In this way, CTAs would be signed in a timely fashion and the Board would still be informed. This initiative is strongly supported so CTAs are not delayed due to the meeting schedule of the Board of Regents.

Research and Sponsored Programs

Staff in the RSP office support clinical trials by handling and negotiating Confidential Disclosure Agreements and Clinical Trial Agreements. It is recommended that the individuals that support trials full-time move into the proposed new central department at UWH. Keeping all clinical trial functions together as much as possible will create better relationships and lead to more efficient processes. One of the common concerns expressed by Investigators is that they will put in significant time and effort and the study will never initiate for a variety of reasons. Then they will have expended time and money with no reimbursement. This can be mitigated with the development of a Letter of Agreement in which the sponsor would agree to cover start-up costs while the contract was being negotiated. Standard language is available for LOAs and UW can certainly create a template. LOAs are quite straightforward, as they generally begin at the time the study is placed at the site and end at either IRB submission or IRB approval. No patient procedures or visits are covered as this agreement is to ensure that work on the study start-up activities can begin immediately, and the PI has comfort their costs will be reimbursed. In this way, finalizing the contract, the budget, preparing documents for IRB submission, planning patient recruitment strategies and creating source documents and orders can begin immediately and occur in parallel.

Legal

Legal support should also be based out of the central office. It is unlikely that UW would allow any trial to move forward without its own legal review, so it is recommended that legal support “sit” in the central office. Metrics collected by both RSP and legal support should be very transparent, using turn-around times (TATs), for example, with concrete start/end times and milestones. For example, initial contract TAT starts when the contract “hits” the office, either electronically or on paper and ends when it goes back out to the client the first time. Templates should be used whenever possible, and this area should be flexible in accepting other contracts and agreements that check all the right boxes for the University, but just don’t contain exactly the same language.

Pharmacy

The Pharmacy generally received high marks from all individuals interviewed. This group is not seen as an obstacle to the conduct of trials. However, it is recommended that a review of their SOPs for clinical trials be undertaken as deficiencies have been found in the SOPs for the IRB and the CRU and could be found here as well. The Quality group can assist in addressing any gaps. One gap previously identified from a sponsor audit is the lack of documentation when transferring study drug from the Pharmacy to the CRU.

Procurement

Several departments (e.g., Radiology, Ophthalmology) have a great need for procurement process improvement. Even when the client is paying for the equipment, it can take months to get the equipment purchased and into the appropriate space. It is recommended a procurement person also sit in the central office and liaise with UW and UWH to speed the process, determining where the equipment will be located, how it will be qualified/calibrated for use and if it can be used for other patient procedures, especially once the study has ended.

Clinical Research Unit

The Clinical Research Unit plays a vital and active role in the conduct of clinical trials. It should be utilized to the fullest, as this will increase their efficiency. Moving qualified studies into the CRU will also free up Clinic space, and as Clinic staff, space and equipment will not be utilized for those study activities, they would be available to generate incremental revenue. However, the CRU has deficiencies that must be rectified if they are to pass sponsor audits and be ready to apply for accreditation. It is strongly recommended that the deficiencies be addressed as soon as possible.

Approximately 2 years ago, a major CRO performed an audit on the CRU as a first step to a potential partnership (Appendix 3). Vendor audits are a standard first step to entering into a long-term partnership with either a sponsor organization or a CRO. Unfortunately, the audit revealed numerous deficiencies that were serious enough to halt the initiative when a response to the audit findings was never received by the CRO. This response was to contain the draft plan to address the deficiencies. Some of the findings are easily corrected, such as ensuring that staff CVs and training records are readily accessible for inspection. Others will take more time and attention. One finding was the lack of a Quality Assurance Unit and accompanying SOPs. This deficiency will prevent the CRU from passing any sponsor audit, as a Quality group is an essential element in ensuring regulatory compliance, adherence to the CRUs own internal SOPs and policies and delivering a quality study along with the other responsibilities listed for the Quality group earlier in this document. A training matrix as described previously for CSCs must be developed for CRU staff which mandates which SOPs, policies and training a staff member must take, the deadline for that training to occur (e.g., within the first month of employment) and the frequency of retraining.

The new Quality group can comprehensively review all the current SOPs for the Unit to ensure they will pass sponsor audits. They can also do a gap analysis to determine if there are additional SOPs that should be added. The current document that controls the SOPs themselves is also deficient, and the Quality group can fix that. It should be noted that the CRU of a peer Institution partnered with a major CRO to bring their SOPs into compliance with auditor expectations. This took time and effort, but once the SOPs were written, the staff was trained on them, and they went live, that CRU passed over 70 sponsor audits and they are now well-positioned to apply for accreditation as soon as the standards are finalized. The CRO is also bringing them studies on a regular basis. Again, these audits are not to be confused with Site Qualification Visits (SQVs) that are made by Clinical Monitors to ensure the site can conduct the study. These SQVs do not go as deeply into the Unit's operations, procedures and training records as an auditor.

Staffing should be reviewed, and when additional staff is needed, non-RN staff should be considered. Currently all staff in the Unit are RNs, and this drives up the cost. Other academic units employ non-RN staff for standard procedures that do not require the expertise of a nurse. Phlebotomy, sample processing and ECG capture are examples of such procedures. Nurses can certainly be used should the patient require more medical expertise, but that can be determined on a study-by-study or even patient-by-patient basis.

Culture Change/Public Relations

The recommendations contained in this document will require significant culture change. This must occur at the University, within the School of Medicine and Public Health and inside UW Health. Attempting to improve processes and increase industry-sponsored research without winning “the hearts and minds” of Faculty and staff is futile. HR professionals state that culture change takes three years under the best of circumstances. Those ideal circumstances include repeated, vocal, visible reinforcement of the mission from the highest levels of each organization and using an established change management paradigm (e.g., Kotter’s Change Model) with a designated Change Manager. It is imperative that physicians feel this research and their efforts are valued, that clinical research staff understand their role and importance in conducting the trial, that non-clinical research staff understand clinical trials are part of the overall mission to deliver world class patient care as well as lead in healthcare innovation, and patients understand how valued they are when they volunteer to participate in clinical trials. A planned Public Relations campaign should be devised to address each stakeholder segment at the appropriate time. This does not have to be involved or expensive, but can include monthly research newsletters, administrative staff training in how to interact with research patients, signage welcoming research patients, regular acknowledgement of excellence (e.g., “Clinical Study Coordinator of the Month”), etc....

Change Management

Many organizations make the mistake of shortchanging themselves in change management, particularly in appointing a leader responsible for leading them through the changes. The leader must be high enough in the organization that they are respected and will be listened to and ideally have a natural enthusiasm for process improvement and vested interest in the success of the initiative. While it is difficult to take a high-level, high-potential person out of the organization for a prolonged period, those organizations that do not commit to a change management leader often face a situation where the changes are struggling to be incorporated into their establishments or strung out much longer than expected. Even worse, they discover that processes have reverted to the “old” ways as they weren’t being monitored and/or the rationale for change hadn’t been explained well to staff. It is recommended that an appropriate person be specifically identified as the point person for the overall initiative and as the individual responsible for applying the principles of an established change management system.

Culture change – Faculty and staff

A formal Public Relations campaign to jump start culture change is recommended and should be seriously considered. Some of the items already described will be incorporated into this campaign, such as the creation of a reward and recognition system for PIs and using the UWH reward and recognition system to honor staff from the new central research office early in the transition. When the University of Michigan’s Research Board of Directors decided to transform clinical research at their institution in 2014, the first strategy was, “Foster a UMHS culture that values, rewards, and supports clinical trial activities.” It is critical that this message is successfully delivered.

Non-clinical research staff also need attention, as these people will interact with researchers and patients, and must understand that clinical research is part of the mission and is a critical component in a world-class healthcare organization and academic institution. For example, check-in staff at UWH must be educated on interacting with research patients. Often, these non-medical staff experience uncertainty when study patients arrive for a study visit. The person assisting them doesn’t really know exactly how to direct them. And even though the staff member

is polite, the patient begins to feel like a burden as the staff member tries to figure out what to do and how to deal with this patient. Ideally, the staff member would know just how to handle that patient and check them in quickly and would also provide a smile and a warm thank-you for their participation in the trial. The ultimate goal is for all individuals within UWSMPH and UWH to understand the mission of the organization and how conducting clinical trials fits into that mission so they create a “world class experience” for every study patient at every visit.

Culture Change – Patients

Patients, too, need to understand the value of clinical research. This starts with the newly redesigned portal that makes it easy for patients to find clinical trials and contact someone who can answer their questions. It also includes the “opt-out” process, and patients who choose to remain in the pool get contacted regarding trials for which they may qualify. Care should be taken to avoid clinical trial “overload,” so patients aren’t inundated with studies once the process goes live. A campaign publicizing the need for clinical trials participation should be undertaken. Many other Institutions have launched these types of campaigns, such as the “Medical Heroes” communications. Little courtesies, such as sending birthday cards to study participants – and continuing to send them well after their participation ends - make patients feel valued and more willing to participate in a trial in the future or recommend participation to a friend or family member. Some departments at UWSMPH currently do this and coordinating all the clinical staff in one office can facilitate the transfer of best practices in interacting with patients across all studies. Notice the current advertisements for Optivo® which thank all the physicians and patients who took part in their trials.

Business Plan

Once significant progress has been made to remove obstacles and decrease timelines for clinical trials, a business plan should be developed to identify which therapeutic areas/study types to pursue initially and identify specific clients to target. It is imperative that this business plan not be launched until there is concrete evidence through metrics that the research climate has improved. Certain disease entities or study types should be chosen carefully to prove to clients that the environment has truly changed. There are certain study types that demand a high per patient price yet are operationally easy to execute. The challenge is identifying and recruiting the patients. This is where the UWSMPH/UWH partnership can excel, as the sheer number of patients in their system increases the odds of successful recruitment and can entice a client to place the study. Given the current climate for clinical trials, Investigators and administration should understand that a client’s trust must be earned, so many large Phase 3 studies that may not be “cutting edge” will have to be delivered successfully before a client will trust that PI and UW with a critical study or even invite them to be the lead PI and author on the resulting paper.

It is also critical to survey the entire landscape of sponsors for evaluation and possible targeting. Large pharma are always considered as they have the most robust pipelines. But CROs should be investigated carefully, as they place a larger and larger percentage of clinical trials year after year. CRO-Pharma partnerships drive this increase, and that trend is continuing.

Conclusion

UWH's interest in becoming a full partner in clinical research and embracing this activity as part of their strategic plan to be a leader in medical innovation is a very positive and exciting development. Sponsors and CROs will be naturally attracted to the UWSMPH due to its reputation as a premier medical school with outstanding Faculty and to UWH with its extensive patient database. But currently the reputation of UW needs improvement, as the culture of the Institution does not encourage the conduct of industry-sponsored trials, nor make them easy to conduct. This situation can be remedied with the firm commitment of all constituents – the University, the UWSMPH and UWH. Changing the culture to value industry-sponsored trials will enable and facilitate process changes to allow clinical trials to be conducted much more efficiently. As more and more clinical trials are successfully completed in a timely fashion, Wisconsin will become a desired partner and climb to the top of the site lists. Increased participation in clinical trials will offer additional options for patients and lead to greater recognition for medical advances and innovations.

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Appendix 1 – Biopharmaceutical Industry-Sponsored Clinical Trials and the
Impact on State Economies

Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies

FROM HOPE TO
cures

ILLINOIS

1,701

total clinical trials



29,294

clinical trial participants



\$249.5 million

invested in clinical trials



\$678.4 million

total economic impact of
clinical trial investments

It takes about 10 years to develop one new medicine. Clinical trials are the most time- and resource-intensive part of the research and development (R&D) process for a new medicine, and biopharmaceutical companies support and conduct the lion's share of this work. Yet without clinical trials, new medicines could not be approved and made available to the patients who need them.

Beyond the profound value that biopharmaceutical industry R&D brings patients in the form of new treatments and potential cures for society's most devastating and costly diseases are the significant economic impacts resulting from clinical trials conducted in communities across the country.

On the left is an overview of industry-sponsored clinical trial activity across the state of Illinois in 2013, including the estimated number of trials active during the year, the number of trial participants, the annual direct investments of biopharmaceutical companies to operate clinical trial sites in the state, and the total economic impact resulting from that investment, including the indirect economic effects that ripple through local economies.

ABOUT THIS ANALYSIS

What does "site-based clinical trial investments" mean?

It means the direct investments made by innovative biopharmaceutical companies to, among other things, identify and operate clinical trial sites; hire staff and contractors; recruit, retain and treat participants; and conduct clinical trial protocols and activities, including monitoring the research sites at the site level.

How is "total economic impact" measured?

The investment in clinical trials by innovative biopharmaceutical companies has an impact on local economies that goes beyond the amounts spent conducting the trials, including payments to vendors and contractors that supply or support clinical trial sites, as well as dollars that are re-circulated into the local economy through consumer purchases by researchers and other workers, vendors and contractors at the clinical trial sites.

What was not measured?

It is important to note that these estimates understate the full economic impact of industry-sponsored clinical trials. These estimates focus solely on the investments made at clinical trial sites, and do not capture all of the trial-wide work that occurs across sites, including activities such as trial design, coordination, and data analysis. It also excludes companies' substantial investments in basic and preclinical research. Finally, it does not reflect the significant and well-documented nationwide **economic impact** associated with the non-R&D activities of the industry, such as manufacturing and distribution.

Additional information is available at fromhopetocures.org.



Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies

FROM HOPE TO
cures

INDIANA

1,111
total clinical trials



19,659
clinical trial participants



\$187.1 million
invested in clinical trials



\$441.6 million
total economic impact of
clinical trial investments

It takes about 10 years to develop one new medicine. Clinical trials are the most time- and resource-intensive part of the research and development (R&D) process for a new medicine, and biopharmaceutical companies support and conduct the lion's share of this work. Yet without clinical trials, new medicines could not be approved and made available to the patients who need them.

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On the left is an overview of industry-sponsored clinical trial activity across the state of Indiana in 2013, including the estimated number of trials active during the year, the number of trial participants, the annual direct investments of biopharmaceutical companies to operate clinical trial sites in the state, and the total economic impact resulting from that investment, including the indirect economic effects that ripple through local economies.

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Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies

FROM HOPE TO
cures

IOWA

444

total clinical trials



4,948

clinical trial participants



\$39.6 million

invested in clinical trials



\$86.9 million

total economic impact of
clinical trial investments

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Additional information is available at fromhopetocures.org.



Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies

FROM HOME TO
cures



MICHIGAN

1,456

total clinical trials



23,600

clinical trial participants



\$191.7 million

invested in clinical trials



\$488.2 million

total economic impact of
clinical trial investments

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Additional information is available at fromhometocures.org.



Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies

FROM HOME TO
cures

MINNESOTA

932

total clinical trials



13,855

clinical trial participants



\$119.2 million

invested in clinical trials



\$318.3 million

total economic impact of
clinical trial investments

It takes about 10 years to develop one new medicine. Clinical trials are the most time- and resource-intensive part of the research and development (R&D) process for a new medicine, and biopharmaceutical companies support and conduct the lion's share of this work. Yet without clinical trials, new medicines could not be approved and made available to the patients who need them.

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Additional information is available at fromhometocures.org.



Biopharmaceutical Industry-Sponsored Clinical Trials and the Impact on State Economies

FROM HOPE TO
Cures



WISCONSIN

725

total clinical trials



9,712

clinical trial participants



\$90.8 million

invested in clinical trials



\$223.3 million

total economic impact of
clinical trial investments

It takes about 10 years to develop one new medicine. Clinical trials are the most time- and resource-intensive part of the research and development (R&D) process for a new medicine, and biopharmaceutical companies support and conduct the lion's share of this work. Yet without clinical trials, new medicines could not be approved and made available to the patients who need them.

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Appendix 2 – Process Summary

The recommendations are as follows:

- Provide early, consistent, continuing, vocal and clear messaging from the most senior leadership of both UWSMPH and UWH explaining the rationale for the changes and how it fits with the mission to deliver outstanding, world-class patient care.
 - Designate a senior person as the Change Manager and make them responsible and accountable for effecting the changes and ensuring the new processes persist.
 - Implement a recognized change management paradigm (e.g., Kotter’s change model) to guide the Change Manager, the institutions and individuals through all the transitions.
- Create incentives for physicians – especially those early in their career – to participate in industry-sponsored studies. Reward and recognition is key if these individuals are to choose to spend their time conducting industry trials.
- Create a single “home” for clinical research staff (coordinators, budgeting, contracting, etc...) within UWH. Harmonize all job descriptions (e.g., clinical study coordinators), salary scales, and career paths. Also create specific competency-based criteria for advancement and incorporate into the job descriptions, including credentialing, if applicable.
 - Use staff centralization to load level staff between departments using the “designated” vs “dedicated” staff approach.
 - Use the centralized model to devise a single process solution to staff emergent trials, whether it be in the Department Emergency Medicine, Cardiovascular group, Department of Surgery, OB-GYN or any other group.
 - Use the centralized model to share best practices across departments.
- Create a Quality Management function for clinical studies. This group, also to be housed within UWH, has a significant breadth of responsibility, including but not limited to conducting process audits, management (but not ownership) of Standard Operating Procedures (SOPs) and providing support during regulatory inspections.
 - Create and track an agreed set of transparent metrics to be reported to the senior levels of the UWSMPH and UWH at least quarterly.
- Assess the composition of the COI Committee currently residing in the Office of the VCRGE to ensure that its membership reflect sufficient clinicians who understand the most salient and current patient safety and data integrity issues. Remove any logistical barriers, including meeting time and location, to easily allow clinician attendance without impacting patient care time. This will allow these clinical professionals to regularly participate in decisions impacting clinical trials. If this is not possible, consider moving the responsibility for these matters to the Interactions with Industry Review Committee (IIRC), currently residing within the University of Wisconsin Medical Foundation (UWMF). It is recognized that this Committee may need to become a joint SMPH-IIRC body to fulfill this function. However, its membership is very qualified to understand conflicts and risks to patients and create credible safeguards to manage them.

- Keep the HS IRB where it is currently located, as moving it into the Vice Chancellor’s office and thus farther from its constituents will hamper culture change, encourage a greater disconnect from PIs as well as encourage additional outside tasks (see next bullet) to be foisted on it, all impeding their core mission.
- Remove the University-imposed additional responsibilities placed on the HS IRB which require that body to act as “gatekeeper” the enforcement entity for items that are outside its regulatory function. Significantly change the “pre-review” process to be in line with other accredited, academic IRBs and limit question/response loops to one or at most two cycles, eliminating the current and unlimited iterative process and expanded timelines currently experienced by submitters.
- Support the initiative to improve the Board of Regents review process for Clinical Trials Agreements (CTAs) to eliminate delays.
- Improve the IT environment to achieve greater efficiency and become more patient- and sponsor-friendly.
 - Implement the PeopleSoft (PS) module for time tracking to accurately record time spent on research studies and allow re-examination (and re-negotiation) of budgets if necessary
 - Consider investing in an electronic Trial Master File (eTMF) system to eliminate manual photocopying and mailing of study documents, which may occur 2 or 3 times in one study as the Clinical Monitor changes.
 - Create a process by which remote monitoring into HealthLink is allowed for clinical trials.
 - Develop and implement an “opt out” process for patients to actively deselect themselves from clinical trials and thus allow patients to be contacted for trials if they do not opt out.
 - Redesign the UWSMPH and UWH website to include a user-friendly sponsor portal, with the contact information of a specific individual(s) who will act as ombudsmen/navigators/guides for placing studies at UW, including recruitment of appropriate investigators and oversight of the entire process if necessary.
 - Redesign the UWSMPH and UWH website to include a user-friendly portal for patients looking for clinical studies in specific disease areas, also with contact information.
- Re-examine the critical path to study start-up and create efficient processes to decrease timelines and the chance of failure.
 - Require a specific feasibility process, consistent across all departments, including all stakeholders as determined by protocol before any study is accepted. A robust feasibility process will guard against agreeing to studies which have only a small chance of success. This must be a fast and efficient process in order to be competitive with other sites. The feasibility pilot carried out by the Department of Surgery is an encouraging first step, and this process should be refined and a consistent process required across all groups which includes metrics. Work on this has begun, and a feasibility pilot was

- Develop a Letter of Agreement (LOA) process and template so study start-up activities can be initiated quickly and without fear of being left with no reimbursement for these activities should the study be canceled, pulled from UW or not approved. Ideally, the LOA process should be designed in collaboration with UW System to prevent any policy conflicts.
- Allow and even encourage tasks to be done in parallel as the norm to decrease timelines. With an LOA in place, the justification of delaying these tasks is gone.
- Create a program/PR campaign to educate staff – including those not working directly on clinical trials (staff at check-in, phlebotomists, etc...) - on why clinical trials are essential to the health care mission and how to provide study patients with a “world class” experience at every visit.
- Once improvements are made and deficiencies addressed in the Clinical Research Unit (CRU), move qualified trials to that venue to better use that resource and free up Clinic space and staff.
- Once significant improvements are made, create a business plan to identify and justify which studies and therapeutic areas are to be pursued initially. Studies can be identified which have a strong chance of success and which are attractive to sponsors for placement at UWSMPH/UWH.
- After significant improvements are made, create a marketing campaign and plan to identify which clients (Pharma, CROs, biotechs) to target, what professional meetings to attend, etc... Include in the plan the metrics to be used to measure the effectiveness of the effort.

Appendix 3 – Report from Covance Quality Assurance and
Compliance Vendor Audit



Global Clinical Pharmacology
 Covance - Madison
 3402 Kinsman Blvd.
 Madison, Wisconsin
 53704
 Tel: 608/442-8200
 Fax: 608/661-8169

03 March 2016

UW Institute for Clinical and Translational Research
 Mary Jane Williams, DNP, MPH, RN, NE-BC
 Nurse Manager Clinical Research Unit
 600 Highland Avenue, Mail Code 673 6
 Madison, WI 53792

Re: Covance Quality Assurance and Compliance Vendor Audit

Dear Mary Jane,

Thank you for hosting the Covance visit to your facility on 23-24 November 2015. Please find below, the observations identified during the audit for your follow-up:

Finding Number: V1					
Impact:	M	Frequency:	M	Action:	M
Category / Sub Category:		Personnel/Training – Training /Qualification documentation			
Requirement:					
ICH E6 section 2.8, 4.1, 4.2					
Finding:					
Evidence of staff qualification and training was not readily available.					
Supporting Evidence:					
<ol style="list-style-type: none"> 1. Staff CVs were not available for review. These are obtained at onboarding and maintained in confidential Human Resources files. 2. No procedure exists requiring CVs to be maintained, or to be updated with a defined frequency. 3. Job Descriptions for each role were not available. It was not clear if any existed. 4. Documentation of SOP reading was only available for CRU SOPs and was not available for hospital policies and procedures. 5. No list of hospital procedures which are applicable to the CRU is maintained. 6. GCP training is completed as a module within CITI Training. This is done once only with no requirement to receive refresher training. 7. There is no separate training provided for Good Documentation Practices. 8. Documentation of protocol reading is not regularly documented. It is not clear how protocol training would be documented if the Office of Clinical Trials was not utilized for study coordination activities. 					

- 9. Other study specific training may occur, but is not regularly documented.
- 10. No training matrix or other document is maintained identifying each training, SOP, policy or procedure which is applicable to each role.
- 11. Since the investigators are not employed by the CRU, it was not clear how their training would be held or documented.

Number of items of evidence:	11
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Recommendation:

1. Evidence of training and education qualifications currently held within HR (e.g. CV and Job Descriptions) should be stored in an individual training file within the CRU for each CRU staff member including any investigators.
2. A training matrix should be developed listing all trainings, SOPs, policies and procedures required for each role. This list should include CRU procedures as well as hospital policies and procedures and should also be applicable to the investigator.
3. A procedure should be created to describe how/where protocol training and other study-specific training will be documented for both CRU staff and the investigator.
4. Good Documentation Practices training should be developed and administered and a frequency for refresher training established for both CRU staff and the investigator.
5. GCP training should have refresher training required at some defined frequency for both CRU staff and the investigator.

Primary Recipient:	Diane Bronson Ted Broering	Function:	Clinic Director CAPA Council Lead
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Response:

Corrective Action Plan:	Owner <Identify who is responsible for action>	Target Completion Date: <Identify when action will be completed>
	Mary Jane Williams	
Preventive Action Plan:	Owner <Identify who is responsible for action>	Target Completion Date: <Identify when action will be completed>

Finding Number:	V2				
Impact:	M	Frequency:	M	Action:	M
Category / Sub Category:	Quality Assurance - Fit for purpose				

Requirement:			
ICH E6 section 5.1			
Finding:			
There is currently no independent Quality Assurance group to oversee the CRU, the OCT, or the independent investigator study teams.			
Supporting Evidence:			
Organizational charts were shown and discussed and the team stated that no QAU is part of the clinical research unit, the Office of Clinical Trials, or the independent investigator study teams.			
Number of items of evidence:	NA		
Recommendation:			
An independent quality assurance system with written SOPs should be implemented to ensure the clinical research unit and applicable research and regulatory support teams conduct trials and record data in compliance with the protocol, GCP, and the applicable regulatory requirements.			
Primary Recipient:	Diane Bronson Ted Broering	Function:	Clinic Director CAPA Council Lead
Response:			
Corrective Action Plan:	Owner <Identify who is responsible for action>	Target Completion Date: <Identify when action will be completed>	
	Mary Jane Williams		
Preventive Action Plan:	Owner <Identify who is responsible for action>	Target Completion Date: <Identify when action will be completed>	

Finding Number:	V3		
Impact:	L	Frequency:	L
Action:	L		
Category / Sub Category:	Data/Data Recording - Availability of source documentation		
Requirement:			
ICH E6 section 2.10			
Finding:			
Current data recording practices would not suffice for complete data reconstruction for a clinical trial.			
Supporting Evidence:			
Sample source records were provided and it was noted that instrument identification is not a standard practice by the clinical research unit. Without this documented it is not possible to investigate potentially compromised data that could be the result of equipment based issues (malfunction, calibration, out of range temperatures, etc.).			

Drug chain of custody is also a concern as the delivery of the study drug from the pharmacy to the clinical research unit is not documented when it transitions from one team to another.			
Number of items of evidence:	NA		
Recommendation:			
Equipment identification should be recorded in all source data. Signatures should be added to identify the movement of the study drug from the pharmacy to the clinical research unit for accountability purposes.			
Primary Recipient:	Diane Bronson	Function:	Madison Site Director
	Ted Broering		CAPA Council Lead
Response:			
Corrective Action Plan:	Owner <Identify who is responsible for action>	Target Completion Date: <Identify when action will be completed>	
	Mary Jane Williams		
Preventive Action Plan:	Owner <Identify who is responsible for action>	Target Completion Date: <Identify when action will be completed>	

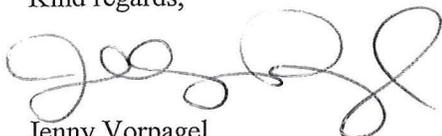
Kindly note that the initial corrective actions should be listed in the corrective action sections, with the person responsible for the completion of each action and the date of the expected completion.

If applicable, the preventive actions taken to prevent this issue from occurring again should be detailed in the preventive actions section, including the person responsible for the completion of each action and the expected completion date.

We would be grateful if you could please return your draft responses to Diane Bronson electronically via email (Diane.Bronson@covance.com) by 31 March 2016.

Once again, let me thank you for hosting our visit.

Kind regards,



Jenny Vorpapel
QA Associate III
jenny.vorpapel@covance.com

cc: Audit Files, Global QA&C, Diane Bronson, Hugh Hauser

Appendix 4 - List of Individuals Interviewed

From Campus, UWSMPH and UWH:

Angie	Adler	Naomi	Holzmann
Donna	Alberti	Terry	Hottenroth
Sanjay	Asthana	Edward	Jackson
Howard	Bailey	Nizar	Jarjour
Julie	Belling	Robert	Jeraj
Mike	Bentz	Susan	Johnston
Barbara	Blodi	Tim	Kamp
Chris	Brandt	Alan	Kaplan
Vielska	Brattingham	Dixon	Kauffman
Mark	Burkard	Tammy	Kiger
Beth	Burnside	Dan	Kolk
Michelle	Chizek	Frank	Korosec
Nichelle	Cobb	David	Kushner
Jennifer	Collins	Susan	LaBelle
Ann	Collura	Josh	Lang
Peter	Connor	Kristie	Lehman
Mike	Dallman	Nancy	Lutz
Brigid	Daly	Rebecca	Marnocho
Davis	Dawn	Mary	Marshall
Jenn	Dawson-Tibbits	Jon	Matsumura
Dave	Demets	Kent	McMillan
Dusty	Deming	Doug	McNeel
Loren	Denlinger	Debbie	Meltzer
Arjang	Djamali	Rick	Moss
Kelsie	Dotie	Mark	Moss
Marc	Drezner	Ken	Mount
Norman	Drinkwater	Andrew	Norman
Dorothy	Edwards	Tracy	Ohrt
Molly	Ellertson	Ruth	O'Regan
Michael	Fiore	Janis	Parkinson
Brian	Fox	Jennifer	Parnell
Dave	Frazier	Jennie	Perry-Ramond
Jacques	Gallipeau	Paul	Rathouz
Matt	Gilles	Amish	Raval
Gemma	Glori	Scott	Reeder
Bob	Gratzl	Laurel	Rice
Ben	Griffiths	Nasia	Safdar
Tom	Grist	Sumona	Saha
Karen	Hansen	Kristie	Schneider
Jenny	Heintz	Manesh	Shah
Greg	Hermus	Kathleen	Shannon

Ann	Sheehy	Kristina	Weaver
Sherry	Shelmar	Oliver	Weiben
Yoram	Shenker	Jennifer	Weiss
Jim	Shull	Lisa	Werning
Kim	Stevenson	Larry	Westby
Sarah	Stewart	Lee	Wilkie
		Mary	
Umberto	Tachinari	Jane	Williams
Fran	Thiesen	Kelly	Wilson
Ann	Traynor	Lisa	Wilson
Andy	Urban	Teri	Young
Ellen	Wald	Terry	Young
		Kurt	Zimmerman

From Sponsor organizations:

Ted	Broering	PRA/Covance
Scott	Button	Venture Investors
John	Centanni	Axogen Inc
Beth	Donely	Stemina
Lisa	Johnson	BioForward
Rock	Lesniewski	Venture Investors
Graham	Lidgard	Exact Sciences
Greg	Lynch	Michael Best & Co
John	Neis	Venture Investors
Sandy	Statz	Exact Sciences
Annika	Swenson	Novartis
Paul	Weiss	Venture Investors

Multiple individuals from the following Peer Institutions agreed to speak on the condition of anonymity:

Indiana University
Northwestern University
The Ohio State University
Rutgers University

Appendix 5 – Biosketch for Mary L. Westrick, Ph.D., CRQM

Dr. Mary Westrick has worked in the fields of early drug development and clinical pharmacology for over 35 years. She earned a Bachelor's degree in Chemistry, and a Master's and Doctorate in Pharmacology and Toxicology (now the Department of Medicinal Chemistry and Molecular Pharmacology) from Purdue University. During her career she oversaw the implementation and management of more than 3000 clinical trials.

Dr. Westrick founded GFI Pharmaceutical Services, a clinical research site in Evansville, IN. The site was a 72-bed professionally managed Phase I – Phase IV research clinic, employing over 200 staff.

Following the acquisition of GFI, Dr. Westrick moved to Covance, Inc. in Madison, WI, where she was Executive Director of the Clinical Research Unit (CRU), and eventually promoted to Global Vice President and General Manager, Clinical Pharmacology, and given responsibility for the Covance CRU in Leeds, England. She added 9 additional clinics and significantly grew the pharmacometrics group, consisting of data management, statistics, programming, pharmacokinetics and medical writing. Eventually she had over 700 people reporting to her in Western Europe and the US, including physicians, nurses, quality professionals and finance staff.

Global Clinical Pharmacology won two Covance awards for “Business Unit of the Year” during her 12-year tenure, an award presented to the one group achieving or over-achieving all their goals in safety metrics, revenue, profitability, and staff turnover.

She next joined Astellas, Inc. as Executive Director, Global Clinical Pharmacology and Experimental Development where she had responsibility for all Phase I operations and led groups in Deerfield, IL, and Leiderdorp, The Netherlands. She then moved to Quintiles as U.S. Vice President for Phase I and General Manager of the Overland Park, KS, site, the 2nd largest site within the Quintiles organization. Dr. Westrick was instrumental in securing preferred partner status with one of the largest Pharma companies in the world, and helped broker a long-term agreement for clinical testing with a world leader in technology. This earned her the highest level of performance achievement.

Dr. Westrick currently donates time to the Alliance for Clinical Research Safety and Excellence (ACRES) where she leads the Site Accreditation and Standards Initiative Domain for First in Human studies and was recently asked to be the Domain Chair for Quality Management (QM) Standard Review and Testing. She has earned her credential as a Clinical Research Quality Manager from the Quality Management Institute.