TRANSLATIONAL SCIENCE AT THE NEURAL INJURY CENTER

MUS Research and Economic Development Initiative

3rd Quarterly Report

February 2016-April 2016

Objective 1: Expand current clinical capabilities of the Neural Injury Center (NIC) and support translational research.

a)   Hirings:

- The Neuropsychologist position has been filled with 1 day per week contracted person with an excellent reputation in the TBI community. He started work with the NIC a few weeks ago and is integrating well into both the clinical and research teams.

- Hours were increased for the Chief Operating Officer, due to expanding duties associated with the NIC.

b)   Equipment:

- N/A

c)   Progress towards milestones:

- mTBI screenings have increased by 40% since January, 2016.

- An article was written about the Neural Injury Center services and research that will appear in the UM *Research View* magazine, to come out this June.

- A short video was written, produced and completed highlighting the NIC's services, technologies and research. It will be posted on the NIC's website and used for presentations and fundraising.

- A decision was made to place the NIC under an existing PT Clinic for establishing Medicare and VA Choice status more quickly. All paperwork has been submitted and we are just waiting on finalization.

- Multiple clinical research opportunities have been identified and are under discussion to determine a fit.

- The new NIC brochure was widely disseminated throughout the community and specifically targeting veterans' organizations.

- Congressman Zinke and staff visited the Neural Injury Center to tour the facility and discuss the VA proposal.

- Meetings were held with Senator Tester's VA and local staff to make them more aware of the activities of the Neural Injury Center

- A social event was held in February for student veterans to build relationships with the community and was well attended.

- Ongoing email blasts were sent to student veterans to continue to increase and maintain awareness of our clinical services.

- Several monthly team meetings were organized and held with the NIC investigators to maintain overall coordination of effort.

Future Program-Building Efforts:

- Dr. Santos and Ms. Laukes wrote a VA Research and Rehabilitation Center draft proposal that was shared with our senatorial and congressional delegation, requesting the NIC to be designated as a Level 1 Research Center. Dr. Rau was designated in the proposal as the "5/8 VA Investigator." This proposal was shared on 3 occasions, most recently a week ago. We are awaiting further feedback and direction, as these asks must come as a political request.

Recent comments from TBI patients utilizing our services:

"I'll be honest, after five and a half years of doctors, counseling and treatment, this was the best experience I've had regarding my injury. Finally found some people who seem to understand what a TBI does physically and mentally to a person. But perhaps more importantly understand that there is real hard science behind the condition instead of the "soft" science of "here's what historically we've been taught about TBI." I'm anxious to get more feedback from the group and I'll definitely avail myself of any opportunity to learn about treating and addressing my challenges. Thanks for your help!"

"The Neural Injury Center gives me hope in helping me to figure out what if anything is wrong. That hope keeps me going. And without it, I would probably fail at what I am doing."

"I went to the Neural Injury Center not knowing what to expect...actually expecting a waste of time. Anything but! Cindi and the doctor were so kind and attentive! I genuinely felt "cared for" and not just another "experiment". They tested me and answered the questions I went in with. I plan on going back and following up with some more involved examinations. Thank you Cindi and to your team of professionals there at the Neural Injury Center! "

"I wanted to thank you for the meetings and for spending the time to listen. Thank you for putting me in touch with Dr. Harrison (the neuropsychologist). All the news I have gotten from the Neural Injury Center so far is good and it is really nice to have fewer worries as finals week approaches."

"I just wanted to thank you for taking the time to see me this afternoon. I tend to ramble on so your patience and understanding was really appreciated. I look forward to our next meeting."

"I want to thank you very much for the help the Neural Injury Center has given me. I really appreciate the regular follow-up and communication. If there's anything I can ever help you with, let me know."

"Thank you for your work. If it helps the progress of science and research I am quite willing to come back in if you need anything further. I really appreciate what you are doing."

Objective 2: Develop a comprehensive panel of objective tests to diagnose mild TBI (mTBI).

a)   *Hirings:*

- A post-doctoral fellow is now being hired to aid the preparation of scientific articles. Two hourly student workers and one graduate assistant continue to work on facilitating the process of recruitment, data collection, and analysis.

b)   *Equipment purchased:*

- N/A

c)   *Progress towards milestones:*

The main objectives for this quarter have been achieved and some excelled. Our continuing studies are on schedule and the following milestones achieved.

- Continuing recruitment, data collection, and preliminary data analysis from control and TBI participants. Initial data analysis has shown exciting results that will be presented in the next quarterly report.

- Development of the balance system (BalanceLab) continues and the 1st clinical viable prototype was delivered in the month of February. Its user interface has also been developed but needs further adjustments to comply with feedback received from clinicians consulted. A dedicated electronic database is also now under development to expedite data management of the system.

- Collaboration established by Drs. Patel & Rau with Vista Therapeutics (Santa Fe, NM) to develop and utilize novel NanoBioSensor technology for the direct rapid detection of miRNA in unprocessed bio-fluids.

- Collaboration established by Dr. Santos with Dr. Guzik resulted in the submission of a new SBIR Phase I proposal for funding to develop a mobile virtual reality (VR) oculomotor testing system.

Objective 3: Develop miRNA inhibitors to reduce neuropathology after TBI.

a)   *Hirings:*

- N/A

b)   *Equipment purchased:*

- N/A

c)   *Progress towards milestones:*

- Review and approval of additional behavioral testing animal use protocol applications by the University of Montana IACUC.

- Continued *in-vitro* testing of candidate miRNA agomiRs and inhibitors on protein expression of miRNA targets by western analysis using the WES System (ProteinSimple, San Jose, CA).

- Tissue processing of samples collected from preliminary study conducted with 16 rats exposed to mild and severe TBI paradigms to assess the effects of TBI on baseline protein and miRNA expression and the efficacy of a novel neuro-protective agent in the lateral fluid percussion animal model.

- Human chronic traumatic encephalopathy (CTE) tissue received from the Center for Traumatic Encephalopathy brain bank, Boston University (Boston, MA), is being processed to quantify changes in miRNA biomarkers and protein targets to establish potential links between acute and chronic TBI.

Objective 4: <u>VAST: Next Generation Learning,</u> Complete the development of a computer-based cognitive training (CCT) system for TBI subjects with cognitive impairment.

a)   Hirings:

- N/A

b)   Equipment purchases:

- *N/A*

c)   Progress towards milestones:

VAST Milestones Completed

Previous (Q1/Q2)

- HTML5 mobile training app completed, including backend/database and user interface (UI), for mTBI treatment on iOS and Android mobile systems;
- Development of set of 8 training levels and 40 training exercises for mTBI identified and completed.
- Testing of prototype with 25 subjects completed and user feedback captured.

Newly Completed (Q3)

- Divergent thinking data obtained and scored from 25 subjects.
- Gamification of 8 levels of mTBI divergent thinking training completed, including intra-exercise scoring feedback and development of incremental training levels necessary for subject engagement and adequate progression through tasks.
- Prototype completed of new variation of figural Trail Making Test as part of updated figural training package.
- Research of RUFF figural test as potential component of mTBI training package.
- Enhancement of front-end UI/UX based on user feedback in Q2.

In Progress (Q4)

- Identification of testing subjects for 8 training levels (mTBI and non-mTBI); preparation for Year 2 controlled testing.
- Development of scoring norms for training exercises.
- Development of new component of training based on Trail Making Test.

Objective 5: Complete the development and testing of a novel post-traumatic epilepsy diagnostic analysis program.

N-SITE LLC Status Report

Project	01030-MUSRI2015-01, Objective 5
Reporting Period	February 2016 – May 3, 2016
Project/Engagement Manager	Alex Philp, Ph.D. - PI

a)   *Hirings:*

- N/A

b)   *Equipment purchases:*

- *N/A*

c)   *Progress towards milestones:*

Abstract

Objective 5 for project 01030-MUSRI2015-01 consists of several high level phases. The first two, acquiring and processing the sample data sample data and the development of the Eidos application have now been completed. This enables the beginning of the third stage, which is data exploration and biomarker identification. Once the research doctors have completed that work, the final stage of clinical evaluation can occur.

Accomplishments: Sample Data

The biomarker discovery activity of objective 5 is predicated on the existence and availability of a substantial amount of EEG recordings for patients that developed Post Traumatic Epilepsy and a corresponding set of control recordings. Working with Dr. Brandon Westover we have received nearly 500GB of deidentified and recordings. These recordings cover both the PTE and control groups and represent nearly 1800 hours of 50 channel 200Hz and 250Hz EDF format data. The recordings range in duration from less than a minute to over 47 hours. The PTE group includes data from 22 distinct individuals and the control group covers 28. Through discussions with the research doctors, it was determined that only 20 of the 50 channels of data were relevant to this effort. The remaining channels did cont contain data collected from head mounted sensors and many were optional and did not contain any data.

While a necessary prerequisite for the subsequent work in this project, the acquisition of this data is of substantial value. Because the onset of PTE can potentially occur many years after the injury, being able to "look back in time" to collect this historical data allows us to cover many years of collection

within the time period of the project. Accompanying this report are two spreadsheets describing the details of each file (EDF file info V5a.xlsx and TBI data collection sheet 3.9.16.xlsx.

Feature Vector Generation

While the simple availability of the sample EEG recordings is critical component of the effort, it is not sufficient to support biomarker discover. The sheer volume of the data along with the potential subtly of the signals of interest makes manually searching it impractical. It must be processed into a more usable form and tools provided for exploring it.

These activities have been completed through the use of a custom stream processing application. This application ingests industry standard EDF format 50 channel data files, resamples the data to uniform 200Hz, applies a bandpass filter and computes a carefully selected set of metadata including discrete wavelet coefficients, entropy, relative energy, rms levels and more. Additionally it byte encodes the actual waveform data for efficient storage and access. Each of the resulting feature vectors correspond to 1 second of EEG data for a single channel with 50% overlap.

Because of the volume of data that needed to be processed a high performance Stream Processing platform (IBM's Infosphere Streams) was employed for this task. Even though the platform and application design results in very high throughput, processing typically 7-10 times the recording rate, the sheer volume of data for 1800 hours of recordings still substantial time to accomplish. The resulting data set produced for this project now consists of over 250 million records occupying 450GB.

Database

In order to effectively explore the computed feature vectors, it was necessary to store them in a way that they could be efficiently accessed. For this project MongoDB was selected for it's combined ability to handle this kind and volume of data as well as providing a rich query language necessary to support evaluation and discovery activities.

Through a process of experimentation, the database schema was gradually refined to provide a compromise between performance, and query support. Each record in the data base includes fields to identify the exact location of the recording that it was produced from, a number of meta data values, a byte compressed set of DWT coefficients, and a bit compressed representation of the waveform.

Once the structure of the database was designed, the process of ingesting all the the feature vector data produced by stream processing application was performed to populate the database. As before, the sheer volume of data made this a non-trivial task. Additional, because of the size of the resulting database, a smaller database containing 10 each of the smaller data files from the control and PTE groups was created to support rapid exploration.

Finally, after the database had been created and various query patterns identified during the development of the Eidos application, a set of indexes were created and evaluated to improve the performance of the data access. To put this in perspective the presence of the correct index could reduce the time for a query that would take hours to evaluate to less than a minute, and many only take a few seconds. Once again the size of the data that is being explored should not be underestimated. It is not unusual for a query to return many millions of records. Optimizing the

performance of the data storage, access, processing, and visualization in the face of these numbers was especially important to create an effective system.

Eidos Application

The final part of the initial phase of this objective was the development of the Eidos application. The purpose of this tool is to allow the researchers to explore the very large dataset to gradually focus on potential signals of value.

Because the researchers are located in different parts of the country and it was not practical to deploy multiple copies of the database, a web-based interface was selected. This approach not only allowed controlled and authorized access to the data, but also supports distributed exploration. The Eidos application leverages the power of many open source data science tools just as Jupyter notebooks, the python language and many data processing packages.

While there are many positive aspects of leveraging the selected tools, the development effort uncovered a number of issues that are largely a result utilizing things that are on the extreme leading edge of adoption. While ultimately worthwhile, dealing with various maturity issues and having to code alternate implementations sometimes backtracking. Complicating matters was the necessity of adapting the tools and methods to remain effective in the presence of the large data volume of sample data set.

Some of the major aspects addressed in the development of the Eidos application included controlled authorization and authentication, effective access and analysis of a very large database, analytical processing to enable the researchers to evaluate the signals, and visualization capabilities to allow them to explore the data.

Although the application is fairly straightforward and intuitive, a User Guide was prepared to facilitate its use by the researchers. Below are a few representative images collected from the Eidos application and supporting notebook. Note that the primary goal of the application was to provide effective infrastructure and capability. Usability and functionality were more important that aesthetic polish.

Database: EEG_Subset2

EEG_Subset2
EEG_MGH

Chart Type:

Multiplot
Multigraph
XY /MP
XY /MG
Table
Dimensional Reduction 2D / MP
Dimensional Reduction 2D / MG
Dimensional Reduction 3D

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18	MGH_TBI_048_01_ARed2.edf	Control
19	MGH_TBI_049_01_ARed2.edf	Control

file

offset

ent

rms

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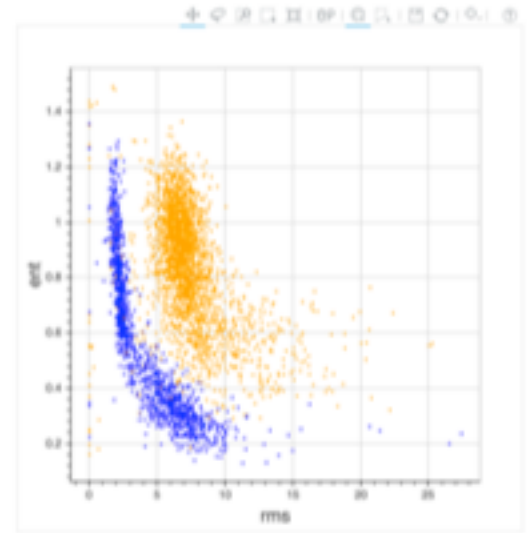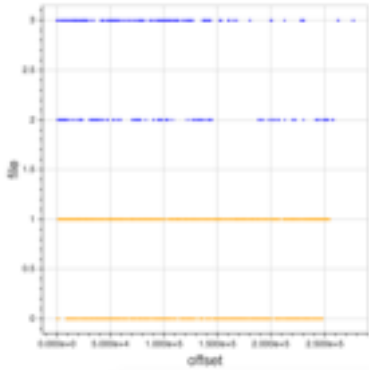
X Axis: rms

Y Axis: ent
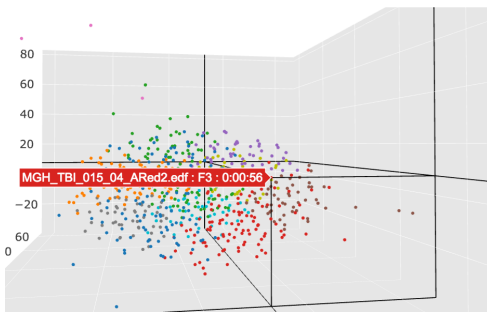
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MGH_TBI_001_03_ARed2.edf	F4	100	0.50	4.26
MGH_TBI_001_03_ARed2.edf	F4	200	0.88	2.46
MGH_TBI_001_03_ARed2.edf	F4	300	0.55	0.07
MGH_TBI_001_03_ARed2.edf	F4	400	1.27	0.00
MGH_TBI_001_03_ARed2.edf	F4	500	1.27	0.00
MGH_TBI_001_03_ARed2.edf	F4	600	1.24	1.47
MGH_TBI_001_03_ARed2.edf	F4	700	1.30	3.27
MGH_TBI_001_03_ARed2.edf	F4	800	0.96	3.04
MGH_TBI_001_03_ARed2.edf	F4	900	0.94	3.04
MGH_TBI_001_03_ARed2.edf	F4	1000	0.88	3.11
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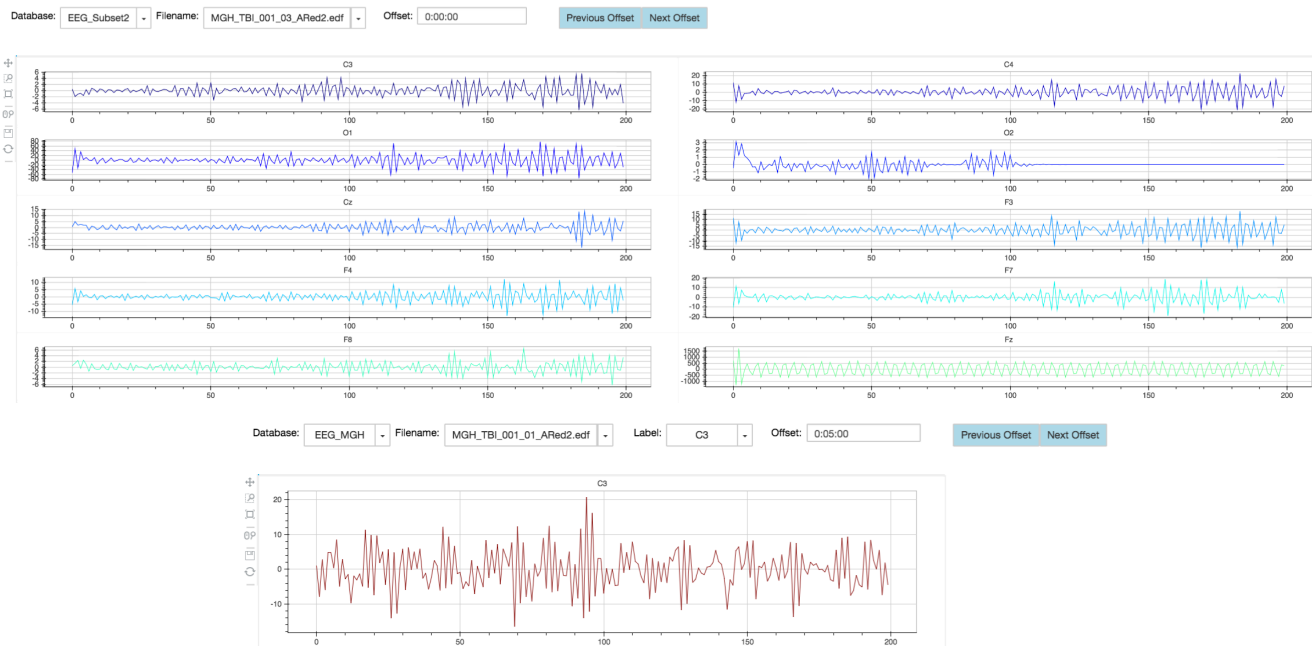
Database and Application Hosting

A separate concern from the development of the Eidos application and supporting database is where and how to host them so they are accessible in a controlled manner over the web. Jupyter notebooks are not inherently multiuser and while it would be technically possible to install the python runtime environment on each of researchers computers, a more desirable option is to host the application in a central location and add a layer of multi-user support. JupyterHub is an open source package that was designed for just such an application and has been utilized in numerous classroom situations. It supports authentication for multiple users and provides support for individual notebook runtime instances.

As of this report The Eidos application and all supporting components (Jupyterhub, Anaconda, etc.) have all been installed and configured on a local development server as well as a Amazon EC2 instance. Because the cost for sufficient storage to host a 450GB database in the commercial cloud would be significant, it is located on the same development server as an interim option. A long-term arrangement has been made with UM to also host it on one LPAR of a Power 8 server currently used to

support InfoSphere Streams CS classes. This arrangement will allow more effective use of that UM asset without interfering with other uses. The database content has been delivered to UM IT staff and installed on that server. The final network configuration is expected to be completed within the next few days. Once done function and performance testing will be done prior to making the application available to the research doctors.

Machine Learning

Although technically not part of the Eidos application, some form of machine learning could potentially be a valuable approach for further analysis of the data produced by the Eidos. When applied in this way the Eidos application would be used to select and prepare the data for input into a deep learning network. In order to validate this capability as well as demonstrate the potential effectiveness, code was written to allow the H20 deep learning open source platform to operate on Eidos generated data. The images below illustrate the application of a deep auto-encoder configured for dimensional reduction on Eidos data from the subset database (about 1M points). This approach demonstrated the ability of a deep network to perform dimensional reduction on millions of points in only a few seconds. For comparison the tSNE algorithm provided in the scikit-learn python library, which is included in the Eidos application, is limited to just a few thousand points, and even then takes many minutes to perform a similar transformation. Other forms of deep belief networks could be applied to the Eidos data for anomaly detection, unsupervised feature generation, supervised classification, etc.

Preliminary validation using H2O based deep learning
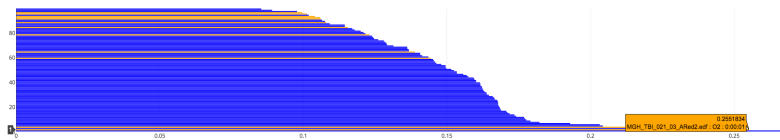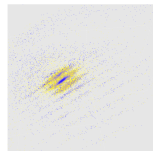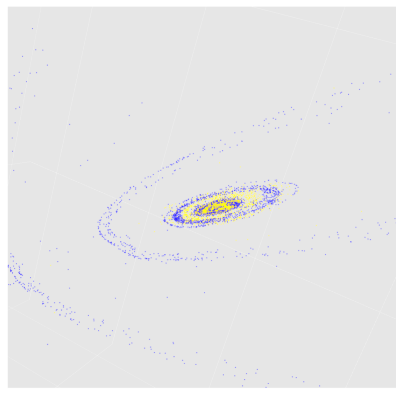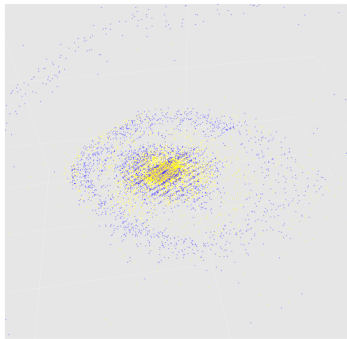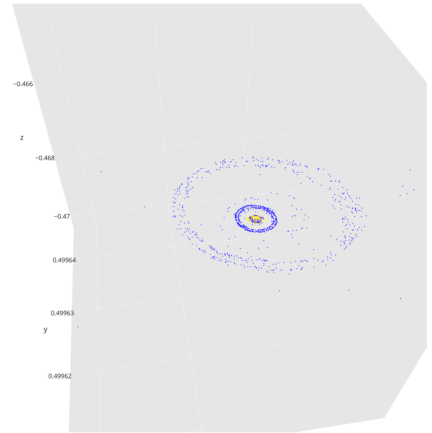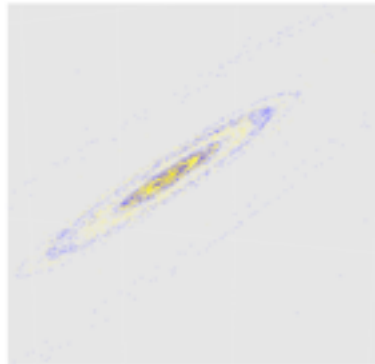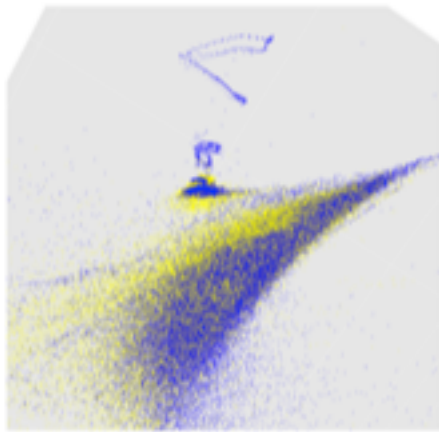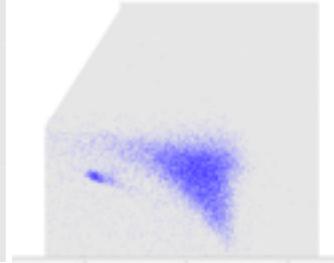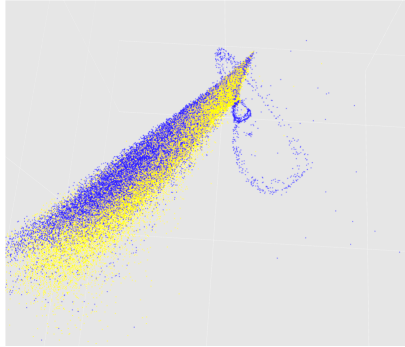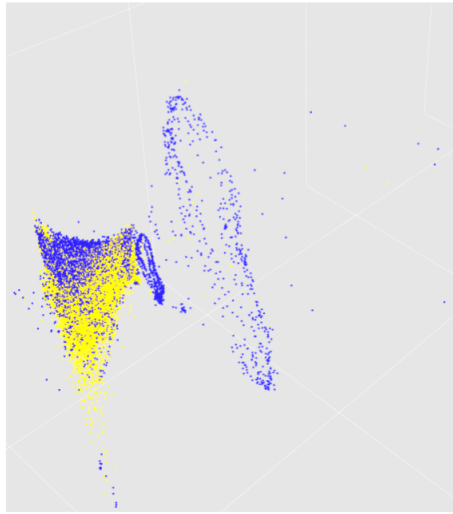
Quarterly Budget Reports

Objective 1:

MUS MREDI Objective 1 - Operating Statement - Inception to Date

Institution: University of Montana (BMED/NIC)
PI: Dr. Sarjubhai Patel
Banner #: MPHR01

Report Date: 5/2/2016

Account	Description	Year 1 Budget	Expenses to Date	Remaining
61124	Contract Professional	-	56359.19	
61125	Classified Employee		5505.84	
61199	**Personnel Services-General**	**145,000.00**	**61,865.03**	**83,134.97**
61401	FICA	-	3816.73	
61402	Retirement		460.84	
61403	Group Insurance	-	16837.67	
61404	Workers Compensation	-	402.2	
61409	Medicare Tax	-	892.64	
61410	State Unemployment Tax	-	154.72	
61415	TIAA-CREF Retirement	-	5405.51	
61415A	TIAA-CREF 1% HB95	-	563.59	
61499	**Benefits-General**	**72,510.00**	**28,533.90**	**43,976.10**
62102	Consult & Professional Services		500.00	
62199	**Contracted Services-General**	**23,500.00**	**500.00**	**23,000.00**
62208	Laboratory Supplies	-	279.63	
62241	Office Supplies		156.70	
62245	Computer Equipment <$5,000		2,581.26	
62282	Ink		110.19	
62299	**Supplies-General**	**-**	**3,127.78**	**(3,127.78)**
62371	Telephone Equipment		132.50	
62382	Data Circuits-Add/Move/Change		42.00	
62399	**Communications-General**	**-**	**174.50**	**(174.50)**
62401	In State Personal Car Mileage		65.07	
62499	**Travel-General**	**-**	**65.07**	**(65.07)**
62815	Recruiting		73.00	
62899	**Other Expenses**	**-**	**73.00**	**(73.00)**
	TOTALS	**241,010.00**	**94,339.28**	**146,670.72**

Objective 2:

MUS MREDI Objective 2 - Operating Statement - Inception to Date

Institution: University of Montana (BMED/NIC)
PI: Dr. Sarjubhai Patel
Banner #: MPHR02

Report Date: | 5/2/2016 |

Account	Description	Year 1 Budget	Expenses to Date	Remaining
61123	Contract Faculty	-	73,729.40	
61126	Graduate Teaching Assistant		5,760.00	
61225	Student		5,520.00	
61199	**Personnel Services-General**	**167,239.00**	**85,009.40**	**82,229.60**
61401	FICA	-	4,364.12	
61403	Group Insurance	-	7,723.02	
61404	Workers Compensation	-	552.71	
61409	Medicare Tax	-	1,020.67	
61410	State Unemployment Tax	-	184.32	
61415	TIAA-CREF Retirement	-	7,040.86	
61415A	TIAA-CREF 1% HB95	-	737.28	
61499	**Benefits-General**	**64,397.00**	**21,622.98**	**42,774.02**
62157	Printing Services-Internal		285.00	
62199	**Contracted Services-General**	**30,000.00**	**285.00**	**29,715.00**
62208	Laboratory Supplies	-	9,383.59	
62245	Computer Equipment <$5,000		186.75	
62249	Minor Software <$100,000		30,349.58	
62299	**General Supplies**	**25,000.00**	**39,919.92**	**(14,919.92)**
62304	Postage & Mailing		4.94	
62399	**Communications-General**	**-**	**4.94**	**(4.94)**
62701	Buildings & Grounds		427.80	
62799	**Repairs & Maintenance**	**-**	**427.80**	**(427.80)**
	TOTALS	**286,636.00**	**147,270.04**	**139,365.96**

MUS MREDI Objectives 3, 4 & 5 - Operating Statement - Inception to Date
Includes Subcontracts to VAST (Obj 4) and N-SITE (Obj 5)*

Institution:	**University of Montana (BMED/NIC)**
PI:	**Dr. Sarjubhai Patel**
Banner #:	**MPHR03**

Report Date:	**5/2/2016**

Account	Description	Year 1 Budget	Expenses to Date	Remaining
61123	Contract Faculty	-	40,716.53	
61125	Classified Employee	-	48,806.24	
61199	**Personnel Services-General**	**125,422.00**	**89,522.77**	**35,899.23**
61401	FICA	-	5,073.32	
61402	Retirement	-	1,942.34	
61402C	ORP-Staff TIAA Cref	-	2,142.76	
61403	Group Insurance	-	20,169.53	
61404	Workers Compensation	-	2,128.95	
61409	Medicare Tax	-	1,186.50	
61410	State Unemployment Tax	-	223.86	
61415	TIAA-CREF Retirement	-	3,913.88	
61415A	TIAA-CREF 1% HB95	-	407.15	
61499	**Benefits-General**	**60,165.00**	**37,188.29**	**22,976.71**
62147	Subcontract Payments*	-	50,000.00	
62147A	Sub Contract Payments > 25,000*	-	234,283.27	
62195	Professional Services-Internal	-	5.48	
62199	**Contracted Services-General**	**281,000.00**	**284,288.75**	**(3,288.75)**
62208	Laboratory Supplies	-	25,703.35	
62208A	Laboratory Supplies - Animals		1,149.95	
62245	Computer Equipment <$5,000		59.99	
62249	Minor Software < $100,000		150.00	
62299	**General Supplies**	**89,945.00**	**27,063.29**	**62,881.71**
62304	Postage & Mailing		158.50	
62399	**Communications-General**	**-**	**158.50**	**(158.50)**

	Year 1 Budget	Expenses to Date	Remaining
TOTALS	**556,532.00**	**438,221.60**	**118,310.40**

Subcontract Totals to Date*			
Company	**Year 1 Budget**	**Expenses to Date**	**Remaining**
VAST (Objective 4)	131,000	60,683.27	**70,316.73**
N-SITE (Objective 5)	150,000	223,600.00	**(73,600.00)**
TOTALS	**281,000**	**284,283.27**	**(3,283.27)**