TRANSLATIONAL SCIENCE AT THE NEURAL INJURY CENTER

MUS Research and Economic Development Initiative

2nd Quarterly Report

November 2016-January 2017

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

a)   *Hirings:*

- N/A

b)   *Equipment:*

- N/A

c)   *Progress towards milestones:*

- Cindi Laukes formed a woman-owned clinical and research consulting and services company.

- Data collection is underway to determine barriers to concussion screening and define best interventions to encourage early screening and treatment in two at-risk Montana populations (student veterans and CSKT). Project target completion date: June 2017 (Laukes)

- Dr. Mohapatra submitted a planning grant through the AI/AN CTR mechanism for he and Cindi Laukes to plan for a Tribal project related to mTBI testing. The grant has received initial approval.

- Testing is ongoing at the Center of mTBI subjects primarily coordinated by Cindi Laukes with initial assessments perform by Dr. Mohapatra.

- Grizzly football athletes were tested for return to play status, as well as an ex-NFL player.

- Progress related to dissemination of information about the Center:

    1) The NIC helped to sponsor a presentation by Dr. John Rush, M.D., an internationally recognized expert on the diagnosis and treatment of depression and other mood disorders. Author of over 800 publications, he helped to develop and test cognitive therapy and medications for unipolar depressive and bipolar mood disorders. As a clinical researcher and practitioner, he is dedicated to advancing science to serve patients with these conditions.

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

a)   Hirings:

- N/A

b)   Equipment purchased:

- N/A

c)   Progress towards milestones:

The work proposed for this objective has up to this date achieved the proposed milestones and extended its reach to the development of new technologies that will facilitate clinical research and services to our community, open new ventures for the delivery of educational content, facilitate positioning the Montana University System and the State of Montana as a silo for the development of translational research.

Specifically, we have achieved the following milestones:

- Data collection for Balance and Oculomotor performances have reached and excelled the number of participants proposed. However, we continue to offer the procedures to our community members as an aid to their health care providers.

- We have found sensitive performance markers indicating the presence of long-term neural impairments. These findings have been included in our daily operations of screening and referrals at the Neural Injury Center. The results of our research (both basic and applied) are now being reported in reputable journals including Scientific Reports/Nature and Brain Injury (copies are available per request). Several other reports are currently being prepared for publication.

- We have extended our reach beyond student veterans and athletes by conducting studies aiming our elderly and children. This initiative is allowing us to establish normative values to be used clinically to establish higher risks of falls and the foundation for future applications on early detection of Parkinson's disease. Data recording for these studies are now completed their results are now being analyzed and reports being prepared.

- A partnership with a Brazilian group of researchers from the Federal University of Piaui has been established where they are currently investigating the ability of our systems to early detect Parkinson's.

- A partnership with a Brazilian company (EMG Systems of Brazil http://www.emgsystem.com.br/) is being established. This partnership allowed the creation of a local company (*Synergy Applied Medical and Research*) to conduct development of instrumented technologies and clinical trials here in the State of Montana. This tech company is now on the track to attract capital and revenue to the Missoula area.

- We also have extended our reach by researching best practices to counter-act the effects of mTBI (mild traumatic brain injury) neural impairments leading to higher risks of falls. A full 16 weeks protocol for balance treatment was carried on by our research assitants. Reporting of results are being prepared for publication. This study is the first one of a series of investigations planned for the years of 2017 to 2019.

- We have also extended our reach by creating new technologies aiming to address the needs of the State of Montana including:

- A prototype of interface to allow mapping of TBI (traumatic brain injuries) occurrences (Figure 1). This interface has been presented to members of the Traumatic Brain Advisory Council. The system would facilitate the process of recognize vulnerable areas, incidence, and quality of care. The first prototype was developed in Matlab language and currently awaits translation to Android/IOS platforms.
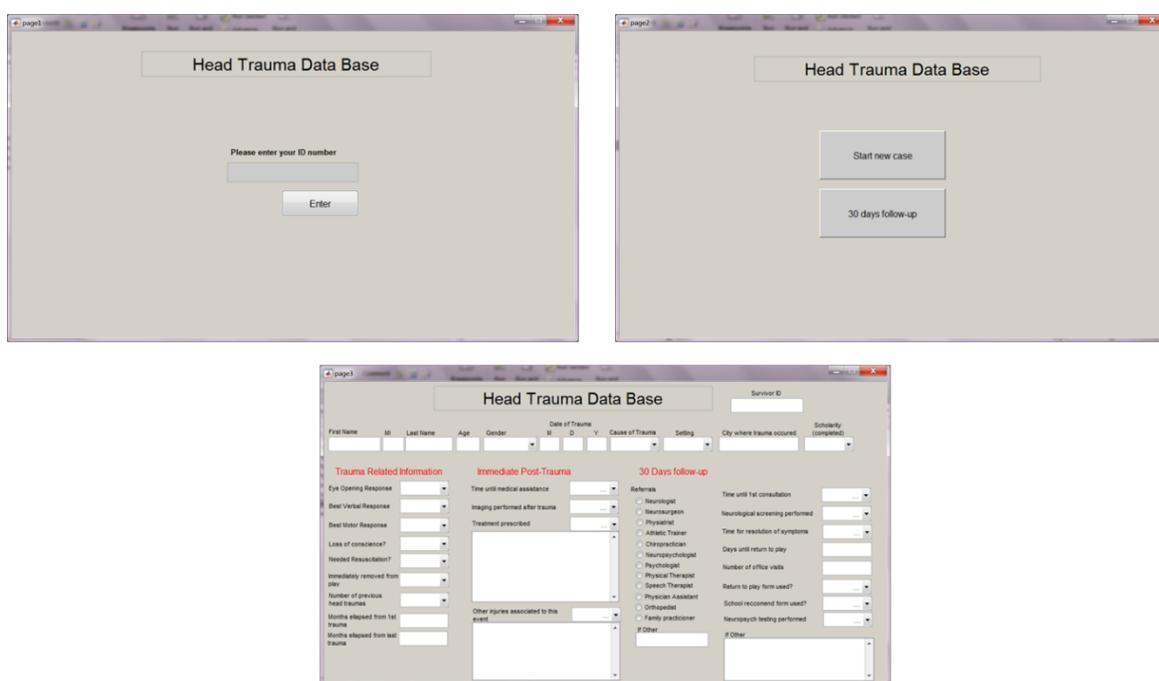

Figure 1. Screenshots of interface developed for tablet application in the field (rurals areas, schools, sport organizations. Analytical interface hosted by Synergy Inc. and UM MCLab.

- A mobile system intended to deliver interventional procedures through interactive virtual reality. This system differs from the current versions in the market by its ability to deliver interactive sessions without the use of tracking cameras. The prototype is in a secondary phase of development and can be used to deliver educational content as well.

Figure 2. 8 year-old boy interacting with virtual setting. Note: the computer screen is only to demonstrate what he sees inside the apparatus. The same system can work on selected cell phones and therefore becomes mobile. Cost of system is below US$ 400.

- System for acquisition and analysis of biological signals (*Lucius vs1.0*). This system allows the acquisition of any signals from instruments to be used in laboratory and clinical settings. Its simplicity of use and customizable interface and analytics will allow the development of several products intended to test performance of patients suffering from traumas and insults to their bodies. O Figure 3 one can see one of the interfaces developed for the University of Montana Motor Control Laboratory (Left panel), integration of instrumentation utilized for balance screenings and electromyography (Middle panel), and its potential use on interfacing systems designed for testing multi-finger coordination and dexterity. This same system is capable of integrating electroencephalography, electrocardiography, goniometers, accelerometer, thermocouples, among many others.
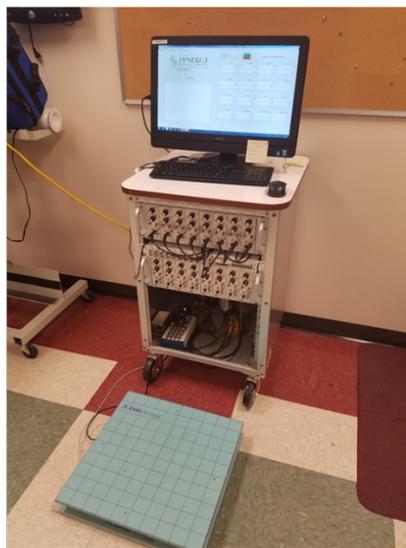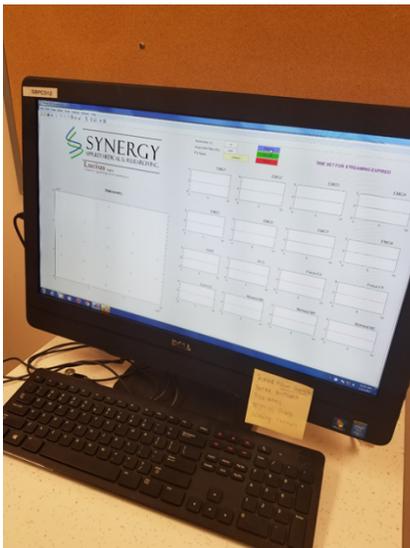

Figure 3. Lucius interface and acquisition system of biological signals (Left panel). Application being used with balance and EMG equipment (Middle panel) and interface created for testing of multi-finger coordination and force production (Right panel). The system can also integrate any other instruments (thermocouples, encephalography, electrocardiography, etc) and produce biofeedback to patients and researchers. Analytical system is customizable for future clinical use and systems are mobile. Lucius is currently being commercialized by one of the spin-off

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companies from awarded financial support (Synergy Applied Medical and Research Inc.) and made available for its use at the MCLab at the University of Montana.

- System for body balance analysis (BalanceLab vs1 to 5). This system was in fact included in our proposal it comprises of a software dedicated to the analysis of body balance control. The system allows on-site analysis and reporting of results including comprisons to normative indices facilitating further investigations of impairments caused by mTBI, progression and subclinical signs of Parkinson's development. We have also focused on using the system as a tool to quantify rates of recovery from injuries and disease, facilitate studies aiming to test the efficacy of rehabilitation interventions as well as to define higher risks of falls in older adults. The system is very portable and can be used in clinical settings. Figure 4 shows the use of BalanceLab v3.

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- Figure 4. Data recording using BalanceLab vs3.

- Drs. Patel and Rau received notice of allowance for patent entitled "Detection of Traumatic Brain Injury" which will issue the first quarter 2017.

- The Office of Technology Transfer is currently negotiating a licensing agreement with Glia Diagnostics for the development of the miRNA TBI panel for a federally approved *in vitro* diagnostic (IVD) test.

- A recent collaboration and partnership with Dr. Stephanie McCalla of Montana State University has been formed to develop new technology for rapid molecular detection of blood-based biomarkers to assess severity of injury and recovery duration.

Continuation of work.

- During the remaining 6 months of this award, a server-based data depository for balance results will be implemented and all initiatives will continue to progress.

- Even though our progress has been considered by us as positive, it is important to clarify that the milestones reached represented only a small fraction of the work that needs to be done. We set our objectives to the development of feasible technology to improve our chances of success in developing interventions that will increase the quality of life of our community. We are positive that with the collaborations in place between the University of Montana, State of Montana, MREDI office, MUS, and our partners around the world we will be able to move this technology in an effective manner towards our schools, universities, and clinics.

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

a)   Hirings:

- N/A

b)   Equipment purchased:

- N/A

c)   Progress towards milestones:

- 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).

- Analysis of rat brain tissue for studies evaluating the effect of a novel neuroprotective agent for TBI.

- Continuing analysis of human chronic traumatic encephalopathy (CTE) tissue received from the Center for Traumatic Encephalopathy brain bank, Boston University (Boston, MA). RNA-seq analysis of 24 human samples is currently in progress to identify miRNA signature for CTE.

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:

<u>VAST Milestones Completed</u>

Previous (Q1-Q5)

- 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.
- 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.
- Development of scoring norms for training exercises.
- Development of new components of training based on Trail Making Test, Ruff Figural Fluency Test, and Reyes Complex Figural Test.
- Additional gamification of exercise presentation, scoring, and presentation of training progress.
- Initial testing of Virtual Reality (VR) prototype and software platform, including eye-tracking.
- Identification of testing subjects for training levels (mTBI and non-mTBI); preparation for controlled testing.
- Research and development of Virtual Reality version of tests.
- Research and development of hardware components of VR necessary to support TBI diagnostics and cognitive rehabilitation.

Newly Completed (Q2_Y2)

<u>Mobile Cognitive Rehabilitation App</u>
- Completion of 10 levels of mobile training based on gamification of divergent thinking tasks.
- Development of 8 new exercise types for assessing executive function using mobile platforms.
- Buildout of training app for iOS, Android, Windows, and Mac platforms.
- Continuing usability and feasibility testing of mobile training levels. Development of specialized version of training for students in grades 6-12.
- Research into problem solving based rehabilitation, with initial development of training screens and levels.

<u>TBI Testing and Training using VR</u>
- Completion of usability and feasibility testing involving all-in-one HMD units versus PC-based units.
- Completion of Virtual Reality (VR) testing environment for TBI subjects using Unity Engine and HTC Vive. March 2017 release in Steam distribution network planned for Oculus Rift, HTC Vive, Google Cardboard, and Fove VR platforms.
- Completion of 9 distinct VR tests, including VR versions of the Trail Making Test, Stroop Task, and working memory tests. Research and development of 3 new, original cognitive tests for VR.
- Completion of backend code and database updates requires to collect VR testing information from subjects via the cloud.
- Completion of testing and data collection with 5 veterans with previous blast exposure, as well as 30 students in grades 8-12.
- Completion of innovative platform for tracking user results, providing basis for future VR-based cognitive testing and rehabilitation.
- Research and development of eye-tracking technology from SMI and incorporation into VR-based testing.
- Research and development of physical therapy training exercises with UM graduate students using Steam sensor technology in VR to track physical movement. Innovative technology will allow patient to complete PT exercises at home, with results sent to clinicians for review over the cloud. Completion of 2 prototype exercises using Unity engine, HTC Vive, and SteamVR sensor technology.
- Research and development into new hardware and sensors required to track physical movement in virtual reality using infrared light detection.

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	November 2016 – January, 2017
Project/Engagement Manager	Alex Philp, Ph.D. - PI

a)   *Hirings:*

- N/A

b)   *Equipment purchases:*

- *N/A*

c)   *Progress towards milestones:*

- EIDOS software is identifying significant differences between our TBI control group and our PTE group using specific statistical analysis. This is focused upon certain statistical analysis of all the data, and the fact that certain signals with nearly all the energy in the lowest two frequency bands, d5 and d6, were significantly more common in many of the PTE group recordings but missing in most of the control group records (Figure 1-3)

- It would appear that the PTE group have EEG measurements of certain frequencies, low frequencies, were most of the relative energy resides, and we are not seeing this in the TBI group .

- EIDOS is performing well and allowing us to conduct this work. Working closely with Dr. Rau.
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- Created updated clean 30 minute sample dataset

  10 of the original EEG recordings were not usable (just noise), 6 had to be observed later in the file
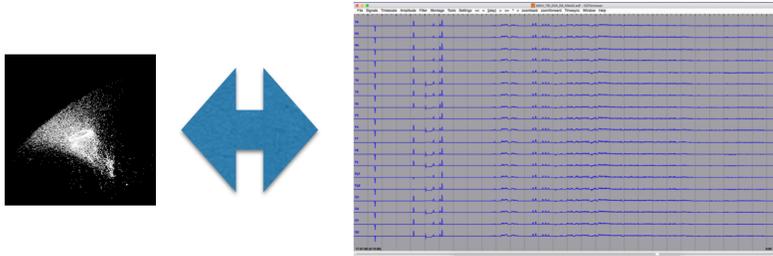
- Deep learning based classification of the 2 histogram images did not pan out. Too few training samples

- Enhancing earlier statistical approach by accounting for how many different recordings a signal appeared did show an interesting result - "Left Edge Bins"

Figure 1

"Left Edge Bins"

Most of the bins "cancel out" with similar probability of those kinds of signals occurring in either group
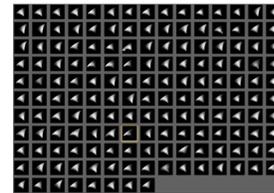
The "left edge bins" contain the most extreme examples of low frequency bias
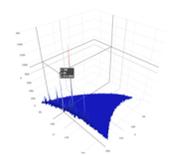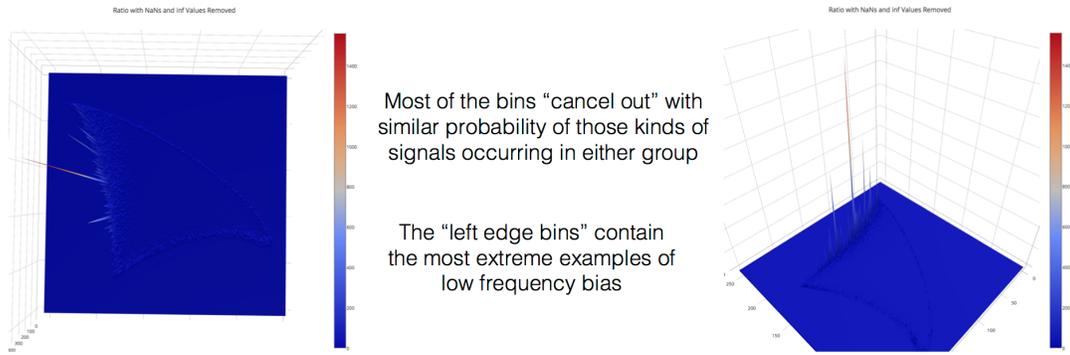
The higher the spike, the greater the ratio of those kinds of signals occurring in the PTE group than the control group
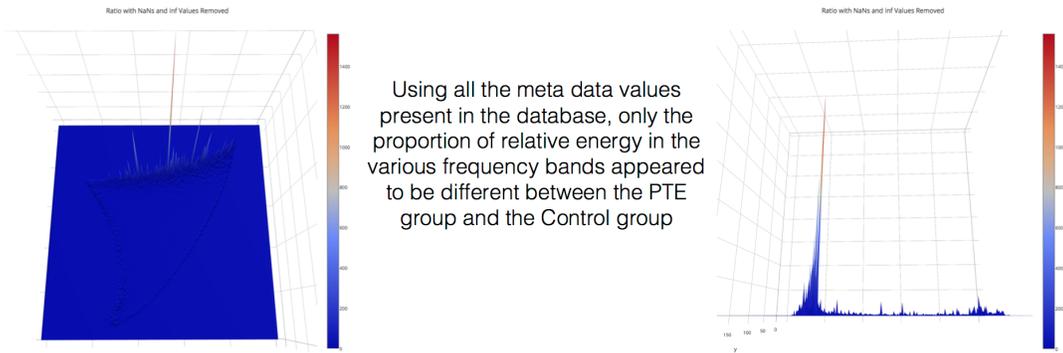
Using all the meta data values present in the database, only the proportion of relative energy in the various frequency bands appeared to be different between the PTE group and the Control group

Figure 2

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"Left Edge Bins"

Band	Range
d2	25-50Hz
d3	12.5-25Hz
d4	6.25-12.5Hz
d5	3.125-6.25Hz
d6	1.5625-3.125Hz
a6	0 : 1.5625Hz

Signals with nearly all the energy in the lowest two frequency bands d5, d6 (approx. theta, delta) were significantly more common in many of the PTE group recordings but missing in most of the control group recordings.

Control   PTE
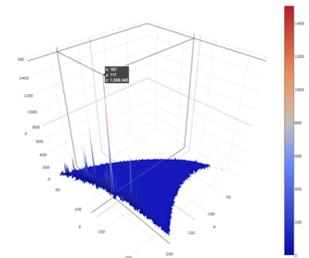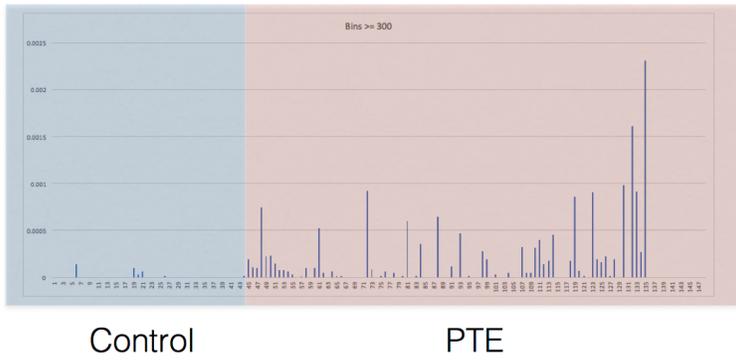
Possibility that drugs might account for PTE group recordings without these signals and that those in the control group that did exhibit those signals did eventually develop PTE but outside the collection period

Figure 3

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: 2/1/2017

Account	Description	Total Budget	Expenses to Date	Remaining
61124	Contract Professional	-	166894	
61125	Classified Employee		14466.88	
61199	**Personnel Services-General**	**250,000.00**	**181,360.88**	**68,639.12**
61401	FICA	-	11188.35	
61402	Retirement		1217.34	
61403	Group Insurance	-	54367.58	
61404	Workers Compensation	-	1084.93	
61409	Medicare Tax	-	2616.67	
61410	State Unemployment Tax	-	453.5	
61415	TIAA-CREF Retirement	-	16102.59	
61415A	TIAA-CREF 1% HB95	-	1674.23	
61498	Grant & Contract Leave Assessmen	-	21588.42	
61499	**Benefits-General**	**155,000.00**	**110,293.61**	**44,706.39**
62102	Consult & Professional Services		16,969.05	
62191	Printing		326.25	
62199	**Contracted Services-General**	**69,000.00**	**17,295.30**	**51,704.70**
62208	Laboratory Supplies	-	2,332.43	
62210	Minor Equipment		4.88	
62241	Office Supplies		156.70	
62245	Computer Equipment <$5,000		3,931.25	
62282	Ink		242.26	
62299	**Supplies-General**	**10,121.00**	**6,667.52**	**3,453.48**
62371	Telephone Equipment		344.50	
62372	Telephone-Add/Move/Change		15.00	
62382	Data Circuits-Add/Move/Change		42.00	
62399	**Communications-General**	**600.00**	**401.50**	**198.50**
62401	In State Personal Car Mileage		65.07	
62408	In state Lodging		207.3	
62497	Non-Employee In State		675.4	
62499	**Travel-General**	**1,000.00**	**947.77**	**52.23**
62815	Recruiting		142.00	
62899	**Other Expenses**	**142.00**	**142.00**	**-**
	TOTALS	**485,863.00**	**317,108.58**	**168,754.42**

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: 2/1/2017

Account	Description	Total Budget	Expenses to Date	Remaining
61123	Contract Faculty	-	217,801.47	
61124	Contract Professional		3,654.99	
61126	Graduate Teaching Assistant		13,533.30	
61127	Graduate Research Assistant		2,674.26	
61225	Student		10,862.74	
61199	**Personnel Services-General**	**334,478.00**	**248,526.76**	**85,951.24**
61401	FICA	-	13,586.43	
61403	Group Insurance	-	19,390.81	
61404	Workers Compensation	-	1,509.27	
61409	Medicare Tax	-	3,177.47	
61410	State Unemployment Tax	-	561.71	
61415	TIAA-CREF Retirement	-	21,334.95	
61415A	TIAA-CREF 1% HB95	-	2,214.56	
61498	Grant & Contract Leave Assessment		11,929.61	
61499	**Benefits-General**	**101,971.00**	**73,704.81**	**28,266.19**
62102	Consultant & Professional Services		5,013.00	
62157	Printing Services-Internal		285.00	
62199	**Contracted Services-General**	**19,000.00**	**5,298.00**	**13,702.00**
62208	Laboratory Supplies	-	13,910.74	
62210	Minor Equipment		1,040.94	
62241	Office Supplies		30.45	
62245	Computer Equipment <$5,000		1,964.50	
62249	Minor Software <$100,000		30,349.58	
62282	Ink		143.88	
62299	**General Supplies**	**65,000.00**	**47,440.09**	**17,559.91**
62304	Postage & Mailing		4.94	
62399	**Communications-General**	**50.00**	**4.94**	**45.06**
62426	Foreign Travel		4,183.74	
62497	Non-employee In State		1,375.55	
62499	**Travel-General**	**7,000.00**	**5,559.29**	**1,440.71**
62701	Buildings & Grounds		427.80	
62799	**Repairs & Maintenance**	**428.00**	**427.80**	**0.20**
	TOTALS	**527,927.00**	**380,961.69**	**146,965.31**

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Objectives 3, 4 & 5

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

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

Report Date: | **2/1/2017**

Account	Description	Total Budget	Expenses to Date	Remaining
61123	Contract Faculty	-	98,588.24	
61125	Classified Employee	-	93,107.15	
61199	**Personnel Services-General**	**250,844.00**	**191,695.39**	**59,148.61**
61401	FICA	-	11,180.78	
61402	Retirement	-	4,468.92	
61402C	ORP-Staff TIAA Cref	-	3,552.09	
61403	Group Insurance	-	41,727.81	
61404	Workers Compensation	-	4,147.92	
61409	Medicare Tax	-	2,614.87	
61410	State Unemployment Tax	-	479.32	
61415	TIAA-CREF Retirement	-	9,292.79	
61415A	TIAA-CREF 1% HB95	-	963.07	
61498	Grant & Contract Leave Assessment		16,301.18	
61499	**Benefits-General**	**124,000.00**	**94,728.75**	**29,271.25**
62106	Laboratory Testing	-	3,721.00	
62147	Subcontract Payments*	-	50,000.00	
62147A	Sub Contract Payments > 25,000*	-	431,143.74	
62195	Professional Services-Internal	-	115.91	
62199	**Contracted Services-General**	**741,658.00**	**484,980.65**	**256,677.35**
62208	Laboratory Supplies	-	47,383.80	
62208A	Laboratory Supplies - Animals	-	3,015.95	
62210	Minor Equipment	-	4,254.09	
62245	Computer Equipment <$5,000	-	411.92	
62249	Minor Software < $100,000	-	150.00	
62263	Veterinary Supplies	-	101.25	
62299	**General Supplies**	**103,231.00**	**55,317.01**	**47,913.99**
62304	Postage & Mailing	-	271.25	
62399	**Communications-General**	**500.00**	**271.25**	**228.75**
62713	Laboratory Equipment	-	711.00	
62799	**Repairs & Maintenance-General**	**711.00**	**711.00**	**-**
62802	Subscriptions	-	99.00	
62899	**Other Expenses**	**100.00**	**99.00**	**1.00**
	TOTALS	**1,221,044.00**	**827,803.05**	**393,240.95**

Subcontract Subtotals Next Page --->

Subcontract Totals to Date*			
Company	Total Budget	Expenses to Date	Remaining
VAST (Objective 4)	312,000	194,745.74	117,254.26
N-SITE (Objective 5)	315,000	286,398.00	28,602.00
MSU/McCalla	15,000	-	15,000.00
Synergy	50,000	-	50,000.00
TOTALS	692,000	481,143.74	210,856.26