November 25, 2020

Dr. Robert "Bobby" Grisso & Dr. Edwards

Department Head & Professor of Biological Systems Engineering

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Dear Dr. Grisso and Dr. Hession,

Enclosed please find the technology review for our project, “Designing an Electronic Clinical Opiate Withdrawal Scale.” This review looks at the best methods to venture away from the current subjective assessment tool measuring opiate withdrawal and addresses faster, more effective alternatives for clinical use. Attached are also appendices containing brainstorming results, challenges faced, a project timeline, and team member responsibilities.

We have neither given nor received unauthorized assistance on this assignment.

Our advisors, Andre A. Muelenaer, Jr, M.D., M.S. and Grace Wusk, have had the opportunity to review this document.

Sincerely,

Kirin Anand

Samantha Brendle

Zixuan Guo

Nicholas Nguyen

Gregory Suliga

# Designing an Electronic Clinical Opiate Withdrawal Scale (eCOWS)

Technology Review

BSE 4125 Comprehensive Design Review

November 25, 2020


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## Introduction

Opiate addiction has become a rising problem in the US, and today can be considered an epidemic. Since the late 1990's, there has been a steady increase in opioid misuse and subsequent death (CDC, 2015). However, the detriments from opioid dependence are more than meets the eye. Withdrawals from opioids negatively impact individuals physically, mentally, and emotionally, but there are even greater consequences. There is a variety of literature depicting the detrimental effects of opiate addiction; for instance, opioid dependence leads to a massive economic burden on society due to increasing health care costs and unemployment rates, and mortality among other things (Huecker et al., 2020). These consequences tear apart families and, in some countries, can cost up to 3% of the GDP (White House, 2017).

The eCOWS group hopes to do our part in fighting this crisis through engineering design. This group consists of Biological Systems Engineering students looking to apply what we have learned to develop a successful wearable device for those going through opiate withdrawal. We look to create an iOS app able to monitor adults undergoing opioid withdrawal. The team has been tasked with developing such a device that can seamlessly monitor different physiological effects based on the clinical opiate withdrawal scale, to then communicate a score indicating whether the user is maintaining sobriety.

In order to develop this wearable system to measure the clinical opiate withdrawal scale (COWS) electronically, the team has established goals and objectives to ensure the project moves forward in the right direction. These goals revolve around designing a user-friendly system that can evaluate opiate withdrawal based on the already made clinical opiate withdrawal scale. This pen-and-paper assessment is frankly outdated, and in need of a more immediate electronic assessment for clinical use. Thus, we hope to use iOS technology to create an app outputting an electronic clinical opiate withdrawal scale (eCOWS). With an app, an eCOWS would be able to be used in hospitals around the country with the same standards. Noting the increased prevalence of iPhones and Apple technology being adopted into hospitals, an eCOWS app will be able to provide faster, more objectively accurate assessments to withdrawal patients, thereby allowing clinicians real-time data used for treatment.

The objectives set for this project include developing a one platform system, ideally a phone application, where the data from all sensors comes together for evaluation. We look to gather sensors or ways to measure all 11 symptoms on the opiate withdrawal scale, and determine if the system is cost effective, user-friendly, and timely through research and testing. The scope of this review is broad; it covers the science behind opiate withdrawal, the current solution, our proposed improved solution, the previous work done, our progress, and challenges encountered, all while including the pertinent literature.

**Review of Technology**

Prior to developing a solution to opioid withdrawal, it is imperative to first understand all facets of the problem. There is an abundance of literature concerning the science of opioid withdrawal that we initially researched. Opioid withdrawal is brought about by the sudden stoppage of opioid consumption or the intake of an opioid partial agonist (Huecker et al., 2020). The body, however, still craves the opioid, which leads to numerous symptoms including restlessness, anxiety, sweating, bone aches, and much more. The severity of these symptoms typically makes it impossible for individuals to go on with their day-to-day lives as normal and immensely reduces their societal productivity. Thus, diagnosis and monitoring of these symptoms is necessary in order for physicians to prescribe medication capable of reducing these symptoms. The most common method of monitoring these symptoms is currently a clinical opioid withdrawal scale (COWS).

While there is minimal literature surrounding an electronic clinical opiate withdrawal scale, there is information regarding a standard pen and paper clinical opiate withdrawal scale. The latter scale is currently the primary method of monitoring withdrawal symptoms and was first developed in the mid 1930s (Ling et al., 2011). Here, a clinician rates eleven potential signals of opiate withdrawal in patients (Figure 1). A higher score indicates a greater likelihood of opioid dependence and thus more severe withdrawal symptoms. While this scale has the potential to correctly identify opiate withdrawal symptoms, it is not ideal. This is because of the variability of results due to the subjectivity of the clinician and patient. One clinician may diagnose a patient with one symptom, while another clinician may have a different viewpoint of the same patient. This is a problem.

Therefore, a more objective measurement would prove beneficial and solve this problem. This is why an electronic clinical opiate withdrawal scale (eCOWS) would prove to be a helpful solution, as it eliminates bias and increases reliability in determining patients' symptoms. After consulting with physicians and through research, we have determined that the benefits an eCOWS outweigh the roughly $3,000 cost necessary for development. This cost is due to the expense of the Raspberry Pi and three sensors (which will be described below). The eCOWS would utilize sensors in order to measure quantifiable symptoms of the patient, as opposed to the current method of guessing. The results of an eCOWS would rely less on opinions and more on data, and thus results would be reproducible no matter where a patient is and which physician they are seeing; this solves the problem of subjectivity.

Prior to getting into how the eCOWS will operate, it is first important to consider outside factors that have the potential to influence the engineering design of the eCOWS. One contemporary issue that may affect the project is the COVID-19 pandemic. Due to the pandemic, hospital access may be more difficult for both patients and physicians; though this is hopefully a relatively short term problem, it needs to be taken into consideration. Furthermore, much of the population, and specifically impoverished communities, have significantly more time due to the job closings during the pandemic. These impoverished communities are the most likely abusers of opiates, and the increased free time and stress levels consequently may lead to more opiate abuse (CDC, 2015). Furthermore, with less jobs and consequently less circulating money, individuals may be more likely to sell opiates in order to generate revenue.

The design of the eCOWS would address these issues in a number of ways. Our biggest fix to the issue of minimal physician contact stems from the creation of an accessible, uniform app. This would allow individuals to get tested for opiate withdrawal symptoms in the safety of their own homes; this high accessibility would help combat the issue of increased opiate abuse as well. Physicians could diagnose and monitor patients without face-to-face contact as well. Furthermore, the app would be uniform in its testing, so results would be able to be generalized, simple, and reproducible, no matter where the individual is.

As previously mentioned, opiate withdrawal is measured on a scale using many different factors, as shown below in the assessment (Figure 1).

## Clinical Opiate Withdrawal Scale (COWS)

**Flow-sheet for measuring symptoms over a period of time during buprenorphine induction.**

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:____________________________ Date: _______________
Buprenorphine induction:
Enter scores at time zero, 30min after first dose, 2 h after first dose, etc.

| Times: | ______ | ______ | ______ | ______ |
|---|---|---|---|---|
| **Resting Pulse Rate**: (record beats per minute)<br>*Measured after patient is sitting or lying for one minute*<br>0 pulse rate 80 or below<br>1 pulse rate 81-100<br>2 pulse rate 101-120<br>4 pulse rate greater than 120 | | | | |
| **Sweating:** *over past ½ hour not accounted for by room temperature or patient activity.*<br>0 no report of chills or flushing<br>1 subjective report of chills or flushing<br>2 flushed or observable moistness on face<br>3 beads of sweat on brow or face<br>4 sweat streaming off face | | | | |
| **Restlessness** *Observation during assessment*<br>0 able to sit still<br>1 reports difficulty sitting still, but is able to do so<br>3 frequent shifting or extraneous movements of legs/arms<br>5 Unable to sit still for more than a few seconds | | | | |
| **Pupil size**<br>0 pupils pinned or normal size for room light<br>1 pupils possibly larger than normal for room light<br>2 pupils moderately dilated<br>5 pupils so dilated that only the rim of the iris is visible | | | | |
| **Bone or Joint aches** *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*<br>0 not present<br>1 mild diffuse discomfort<br>2 patient reports severe diffuse aching of joints/ muscles<br>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort | | | | |
| **Runny nose or tearing** *Not accounted for by cold symptoms or allergies*<br>0 not present<br>1 nasal stuffiness or unusually moist eyes<br>2 nose running or tearing<br>4 nose constantly running or tears streaming down cheeks | | | | |

| | | | | |
|---|---|---|---|---|
| **GI Upset**: *over last ½ hour*<br>0 no GI symptoms<br>1 stomach cramps<br>2 nausea or loose stool<br>3 vomiting or diarrhea<br>5 Multiple episodes of diarrhea or vomiting | | | | |
| **Tremor** *observation of outstretched hands*<br>0 No tremor<br>1 tremor can be felt, but not observed<br>2 slight tremor observable<br>4 gross tremor or muscle twitching | | | | |
| **Yawning** *Observation during assessment*<br>0 no yawning<br>1 yawning once or twice during assessment<br>2 yawning three or more times during assessment<br>4 yawning several times/minute | | | | |
| **Anxiety or Irritability**<br>0 none<br>1 patient reports increasing irritability or anxiousness<br>2 patient obviously irritable anxious<br>4 patient so irritable or anxious that participation in the assessment is difficult | | | | |
| **Gooseflesh skin**<br>0 skin is smooth<br>3 piloerrection of skin can be felt or hairs standing up on arms<br>5 prominent piloerrection | | | | |
| **Total scores**<br><br>**with observer's initials** | | | | |

**Score:**
**5-12 = mild;**
**13-24 = moderate;**
**25-36 = moderately severe;**
**more than 36 = severe withdrawal**

Fig 1. Clinical Opiate Withdrawal Scale (COWS)

Some of these factors are capable of being measured through sensors. These sensors could then communicate to one system, such as a phone app, through Bluetooth, where the total score can be calculated. Depending on the score, certain treatments and drugs will be given to the patients to alleviate some of the withdrawal. These points are thresholds and make it very important to calculate the score at regular intervals. When looking at the factors affecting the score, some factors can be harder to measure than others, so below is a table that summarizes how each feature could be measured using sensors to make the calculation of the score more objective (Table 1).

Table 1. How Each Feature of the COWS Could be Measured

| Feature | Measurement |
|---|---|
| Resting pulse rate | Polar heart rate sensor |
| Sweating | Shimmer3 GSR |
| Restlessness | Accelerometer |
| Pupil size | Reflex Eye Tracker iOS App |
| Bone or joint aches | Questionnaire |
| Runny nose or tearing | Questionnaire |
| GI upset | Questionnaire |
| Tremor | Accelerometer |
| Yawning | Use changes in breathing patterns |
| Anxiety or irritability | Questionnaire |
| Gooseflesh skin | Questionnaire |

A technology such as this has previously not been utilized before. Consequently, there is little to no literature regarding an electronic clinical opiate withdrawal scale. However, this project is a continuation of the work done by a previous design team at Virginia Tech. Their design influenced and helped guide our design, though we made some notable changes as well, specifically concerning app integration. The previous design team approached the issue of developing an eCOWS by first identifying the features needed to measure, and finding sensors to fulfill as many of the COWS categories as possible. Following that, they would go on to use a Raspberry Pi 3 Model

B+ to receive data from the different sensors via bluetooth to process and transmit that to a graphical user interface (GUI) made in MATLAB to display the final results.

Out of the box, the Raspberry Pi acts like a brand new computer, with no interface installed other than the Raspbian operating system (the equivalent to a program such as Windows 7 on a desktop) to allow for simple program and file navigation and execution. USB and HDMI ports allow us to plug in a keyboard, mouse, and monitor to use this computer properly. However, in order to work in conjunction with the different sensors like the Shimmer and Polar (discussed later), those operating systems would have to be coded for on the Raspberry Pi. That is a complex task, so a solution they used was GitHub, an online database for open-source custom software and code for just about anything. There, they found code written in python for the individual sensors that someone else had written and uploaded to GitHub. This now allowed the Raspberry Pi to intake information from the sensors and display it in the GUI.

Building off of this, we were able to update the Raspberry Pi with *sudo apt-get update/upgrade* as well as learn some of the basic commands such as opening and linking the bluetooth channel with *sudo hcitool lescan* and *sudo rfcomm bind 0*. Unfortunately, we ran into an issue where the Pi force updated the Raspbian operating system and wiped the previously obtained python codes for the different sensors. These codes are outdated due to the update, so we are currently at work finding a more recent posting on GitHub, as well as what would be needed to adjust the current code to work with the new and updated software. While this option is currently being pursued in the interest of preserving the work done by the previous team, we are also exploring and working on alternative options that may show more promising and clinically translatable results.

For this year's iteration of the project, we looked to expand on the MATLAB GUI that was made last year. While the MATLAB GUI streamlined the process of delivering the COWS from the original pen and paper method, developing an iOS app that a physician can easily give patients on their phone would further shorten the process. The interface would remain similar to the paper assessment of the COWS, making evaluation familiar to clinicians, thereby making it easy to transition to an app. An iOS app also makes the integration of bluetooth possible for the many wearable devices to communicate with one another with greater ease than the MATLAB GUI does. Bluetooth integration is commonly done on iOS apps, which improves on the struggles the MATLAB interface had with this task. An example usage of this is as follows: the patient walks in with symptoms of opioid withdrawal. The physician then hooks the Polar H10 and Shimmer 3+GSR onto the patient, then gives a phone to the patient with the app readily installed. While the reflex eye tracker iOS app measures pupil size (communicating with our app), the patient answers the remaining subjective questions located on the app. The physician can then use bluetooth to easily transfer the objective data collected from the wearable devices to the iOS app, with the final COWS score being displayed for the physician. Not only is this arguably easier than having to install MATLAB on a desktop computer for eCOWS use, but also an iOS app can be further developed by future iterations of the project to produce real-time data.

**Related Design Standards**

- ISO 13485:2016
  - Medical device safety and quality assurance. This directly applies to our development process to ensure our final design can consistently meet requirements. For us, that would involve a diagnostic process runthrough of our final system to act as a trial run that could be repeated infinitely and not show significant deterioration over time.
- ISO 9001:2015
  - Specifies requirements for a quality management system. Effective application of system, proof that our methods will record the data we describe with accuracy. This works in conjunction with the previously mentioned standard as it requires us to provide an exact success rate for our final design (once complete) to fulfill for this standard to be met.
- ISO 10993-1:2018
  - Medical device safety as well as hazards. Despite the non-invasiveness of both our design options, there are still many potential safety hazards that

must be considered. Small components may present potential choking hazards, or sharp edges as part of the sensors must be considered in development.

- IEC 62366-1:2015
    - Application of usability engineering to medical devices. Describes medical device manufacturing and the risk associated with production error. As we move more towards the iPhone app approach, this is less relevant but still should be considered. Using additional sensors from other companies must be developed with their own standards already in place, but our implementation of a quality assurance test as mentioned before will satisfy this.

As it stands, the devices in the possession of the eCOWS team yield a range of possible solutions to the problem of subjectivity. This is because these devices are capable of objectively measuring pulse rate, sweating, pupil size, tremor, and gooseflesh. Pulse rate is measured by the Polar H10's ECG (electrocardiogram) sensors. While the Shimmer3 is capable of measuring pulse rate as well, it uses PPG (photoplethysmography) which is largely not as accurate as ECG measurements. ECG sensors utilizes electrical signals that are directly made through heart activity. On the other hand, PPG uses electrical signals that are found from light reflected because of variations in blood flow when the heart is active. Thus, PPG is better used for averages or moving averages, while ECG is the standard for measuring pulse rate; the Polar H10 was therefore deemed better in measuring heart rate, and was consequently chosen as the eCOWS sensor of choice.

The Shimmer3 is capable of measuring EDA (electrodermal activity), at other times referred to as GSR (galvanic skin response), which can identify sweat secretion. When sweat occurs, the electrical properties of the skin change; the EDA can then pick up on this change to determine a quantity of sweat (Benedek et al., 2010). More specifically, EDA comes from the autonomic activation of the skins' sweat glands. It can measure the changes in resistance of the skin to an electric current, which reflects the action of sympathetic nerve traffic on sweat glands (Critchley et al., 2013). The

Shimmer3 also contains an accelerometer, which can measure acceleration forces such as movement or vibration. An important facet of the accelerometer is the piezoelectric effect, which uses highly sensitive crystal structures that are stressed by accelerative forces. This stress causes a voltage to generate, which is interpreted to determine velocity and orientation. In this instance, vibrations are used to measure two symptoms of opiate withdrawal: restlessness and tremor.

The other features, namely bone aches, runny nose, GI upset, yawning, and anxiety, require a questionnaire and were not able to be measured through the sensors in our possession.

**Summary and Conclusions**

Through the review of this project, there are some important things we learned including the objectability this project presents, the need for software communication and integration, the timeliness of the assessment, and the effectiveness. This project, using sensors and quantitative data, allows for a more universal way to measure opiate withdrawal. This is important because it provides physicians with comparable and more accurate results. Another important aspect of this project includes the connection of all of the sensors to a one platform system that is then used to produce a score with the eCOWS. This allows for a more user-friendly interface with less complications. In addition, it allows for a more timely interpretation of the assessment as the physician only needs to reference one source opposed to many. Lastly, the effectiveness of the eCOWS is also an important thing we learned through the review of this project. Since this device could be utilized in clinical settings, it is important that it measures opiate withdrawal more accurately than the current pen and paper method with repeatable and consistent results.

Throughout the development of this project, there are still some topics that require further investigation and review. Some of these topics are related to producing real time data. This would allow for constant measurement of the withdrawal symptoms and could alert the physicians of any changes in the score. This would better show how the patient is going through opiate withdrawal and how prescribed medications, if any, were affecting the patient's withdrawal. The physician could then set up alerts with the iOS app that notify them when the patient hits a certain threshold. This would provide a more timely response to combat opiate withdrawal in the patient.

In addition, other areas of investigation include looking into how the symptoms measured through the questionnaire could be measured electronically through sensors. This may be very challenging as these symptoms are not typically measured with sensors. Further research with the eCOWS assessment could be done to determine how much impact these symptoms have on the overall assessment. In other words, does the measurement of these symptoms affect the opiate withdrawal score? This could be answered through research and would allow for a better understanding of what symptoms are greatly impacted by opiate withdrawal. In the end, this project has been moving in the right direction, but still has more work to be done before it can be used in clinical settings.

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**Appendices**

*Appendix 1. Brainstorming Results*

Ideas for the Project in September:

- Need sensors to talk with one another
    - System should gather the same information the COWS form currently measures
    - Take in all withdrawal systems at once--all data into one main interface to calculate withdrawal score
- Build a system that could be used to determine if this approach would be equivalent to doing the scale on paper
- Want to obtain data from restlessness (accelerometers), aching bones, yawning (breathing), anxiety with an objective measurement like sensors
    - Research into other sensors

Ideas for the Project in October:

- Contact old team member to understand Raspberry Pi
- Look at pupil diameter, there are apps that can measure this
    - Have the App integrate to MATLAB code or the Raspberry Pi
- Is there a way to measure anxiety?
    - Saliva cortisol stress kit
    - Takes time to send and process results
    - Wearable device measuring cortisol

(Current) Ideas for the Project in November:

- Rankings of thresholds for score—do they change over time?
    - Do we still need the trendline that was in the GUI for threshold?
- How do you objectively measure pupil size, sweating, and tremor?
- Want to generate a iOS App that takes in the data from the sensors and generates a score based on the COWS

*Appendix 2. Challenges Faced*

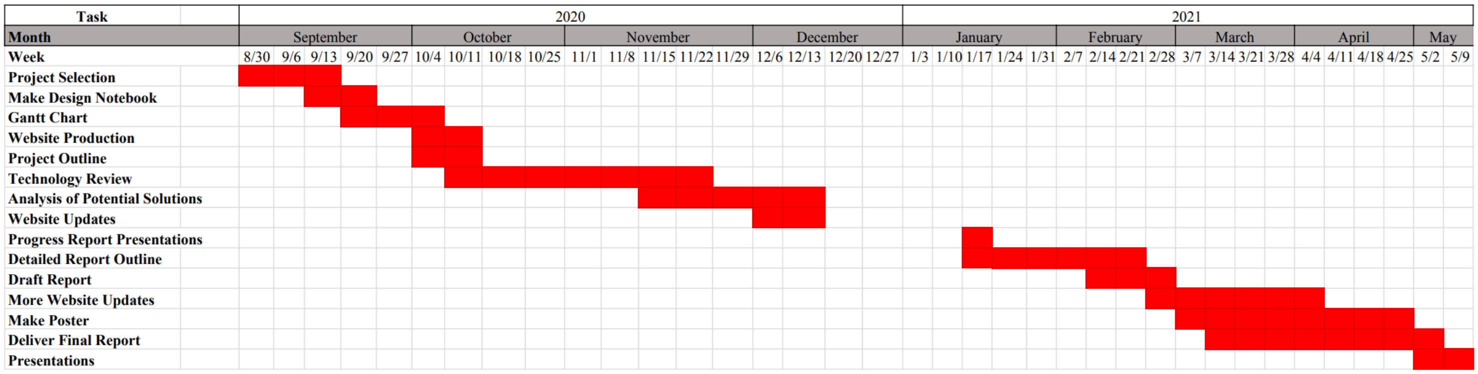
Since this semester is proceeding during a pandemic, there are some general challenges associated with this in addition to the technology challenges of the eCOWS project faced by the team. With the restrictions brought on from the pandemic, meeting in person has become a challenge which puts a strain on communication. As a result, our team relies more on Zoom meetings and GroupMe messages opposed to face-to-face communication. There are also restrictions on lab times which makes it harder to work in the lab as our team only has a time block scheduled once a week. As a result of this, the technology and sensors are kept at a member’s apartment making it harder to work collectively on this portion of the project. In addition to challenges faced by the pandemic, our team also ran into problems with the technology itself.

Some of the challenges our team faced with the technology had to do with the Raspberry Pi. Since it was kept in storage from last semester, it needed to be updated. In updating, the Raspberry Pi ran into an error and needed to be reset. This resulted in the team losing some of the crucial data that was on there from the previous team. Our team was then set back from this and is in the process of getting back the files important for using the Raspberry Pi with the sensors. Another challenge our team faced was not having a member especially skilled in coding. This project uses different sensors that communicate via bluetooth to the Raspberry Pi where the data is transferred to a MATLAB code to produce a score based on the COWS.

Despite these challenges, our team has been able to come up with plans to address these concerns. For communication, our team has set up regular Zoom meetings and makes an attempt to meet in person during the scheduled class time to work on assignments collectively and talk through ideas face-to-face. For the technology challenges, we were able to reach out to a member from the previous year to help us work with the Raspberry Pi. Lastly, for the coding we have been able to refer to the codes from the previous year and use GitHub to help bring the project together.

*Appendix 3.Project Timeline*

Below is the Gantt chart used to outline the project timeline and key tasks.



*Appendix 4. Member Responsibilities*

Below are the members on the eCOWS and what their roles and responsibilities have been thus far.

| Team Member/Partner | Responsibilities |
|---|---|
| Kirin Anand<br><br>Samantha Brendle | ● Background and literature research<br>● Eye sensor and integration to overall eCOWS system<br>● Technology review |
| Zixuan Guo<br><br>Gregory Suliga | ● MATLAB and Python coding<br>● Raspberry Pi system<br>● Shimmer/Polar sensors<br>● Research in coding for the App<br>● Technology review |
| Nicholas Nguyen | ● Creation of the iOS App<br>● Technology review |
| eCOWS Team | ● Attend weekly meetings<br>● Facilitate communication between team and advisors<br>● Update team and advisors on progress made<br>● Have a positive attitude! |