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Presenter: David Cifu

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Moderator: We are at the top of the hour now so I would like to turn it over to Dr. Ralph Depoma who will be introducing our presenter today. Ralph?

Ralph Depoma: Thank you, Molly. It is a pleasure to present David Cifu who is a senior TBI specialist with the Department of Veterans Affairs. He is chairman and the Flax professor of Rehabilitative Medicine at Virginia Commonwealth University. Importantly, also, a principle investigator on the chronic effects of neurotrauma, a joint program of DOD and VA. David?

David Cifu: Thank you, Ralph, and thank you Molly. I appreciate it. We are going to be talking today about the latest updates on the use of hyperbaric oxygen primarily for mild traumatic brain injury and concussion, but will also include information on posttraumatic stress disorder, particularly when seen in combination with mTBI. I would certainly welcome any and all of your comments and questions. Please type those as we go along. I imagine you can see my slides. It just switched to the disclosure. The view I am going to present are mine and mine alone. Although I funded and hired by the Department of Veterans Affairs, these are my specific views.

A topic outline, we are going to look very briefly at the theory behind potential role for hyperbaric oxygen in general, but more specifically for mild TBI, as I mentioned for PTSD, and then we are going to jump to an update on several trials that have now been completed, are impressed and are continuing to be debated across the U.S. and beyond. We will try to give you a definitive answer by the end of this talk. I am going to just temporarily turn it back to Molly, who is going to go through some polling information so we can understand where you are coming from. Molly. To you.

Moderator: Thank you so much. So for our attendees, you will see up on your screen now a poll question. We would like to get an idea of what best describes your research experience. Please click the circle next to the answer option that best fits your experience. Have you not done research? Have collaborated on research? Have conducted research yourself? Have applied for research funding? Have led a funded research grant? It looks like we have a nice responsive audience today, so thank you very much. We are already at 80 percent response rate. We will give people a few more seconds to click their answer. We will close it out. All right, I think I see a pretty good trend. I am going to go ahead and share those results now. As you can see, nearly half of our audience have not done research. A quarter of our respondents have collaborated on research. Fifteen percent have conducted research themselves. Four percent have applied for funding. Twelve percent have lead a funded research grant. Thank you again to those respondents. David, do you want to say anything about this before we move on to the next poll?

David Cifu: Only that I will say that I will make sure I keep this talk at the level that is appropriate for that. We are not going to talk about P values too much. We are not certainly going to talk about the role of grants or even a ton on the research methodology. We will give you just enough so you know I am telling you the truth, but hopefully, you will be able to trust me on my assessment of this research. Thanks, Molly, back to you for the second question.

Moderator: Okay, we appreciate that. Okay, for the next question, we have up on your screen, we would like to get an idea of your TBI research experience. For those of you that have done some research, well, actually one of the answer options is have not done research; have collaborated on research; have conducted research myself; have applied for research funding; or have led a funded research grant. Again, we appreciate you submitting your responses because as Dr. Cifu just said, it does help him have an idea of how to gauge the talk content. All right, we have had about 80 percent response rate again. We will go ahead and close this out and share the results. Just over half of our audience have not done TBI research. About a third have collaborated on it. Twelve percent have conducted it themselves. Two percent have applied for research funding, and another two percent have led a funded research grant. Thank you once again to our respondents. I will turn it back to you.

David Cifu: Thank you, Molly, okay. We are going to move on. I certainly do not want to overlook the concept that we are talking about concussions here or mild traumatic brain injuries. Again, same thing. They are not any different. There are a number of ways of getting concussions. The one that has been in the new most recently certainly has been in professional sports or in all sports. Whether that is the sport which has a goal of causing concussion that allows you to win which is boxing or MMA, mixed martial arts, or the one that is really getting most of the press is the NFL with the new movie *Concussion* coming out with Will Smith. It talks about the long-term effects of repeated concussions. I noted there was a lawsuit yesterday against the National Hockey League by a former player who is claiming dementia or cognitive decline as a result of his repeated injuries. Suddenly, the one that is in the news is concussions. It is sports, but it certainly occurs also very commonly. The largest numbers actually are in motor vehicle collisions or in traffic accidents, whether you are a pedestrian or whether you are on a motorcycle or if you are on a bicycle. This is the most common cause. The same mechanism of injury is rapid acceleration and deceleration. Airbags certainly have helped just as some of the rule changes in sports or perhaps even some of the subtle padding in boxing may help a little bit, but the head and neck are still moving more rapidly than can be accommodated by the differences in densities between the grey and the white matters of the brain. We get micro areas of stretch for shear, which is causing diffuse axonal injury or focal axonal injury. You are just getting stretch injury or shear injury to the axon, which is causing the momentary alteration in neurologic function that we see with concussions.

Certainly, you can get it just from falling, not usually falling while holding a suitcase. It is usually falling while out of bed if you are in a hospital or a nursing home or if you are an elder in your own home perhaps. Certainly, there can be other causes, gunshot wounds, which happened to Gabby Gifford and did not cause mild traumatic brain injury. She is kind of famous and I wanted to put that into here. Certainly, just being assaulted. In this picture, this is not policemen assaulting an innocent bystander. Those are just people helping them, but certainly assault of any type whether it is criminal or one that occurs in the process of other activities, that can certainly be caused during a bar fight for example. That certainly can cause concussions. The one that we are most familiar with in terms of the VA and over the fence is certainly in the military where about half of it is due to motor vehicle type collisions. The other half or more is due to blast injury or exposure to the forces from a blast wave. We do not yet have significant evidence that the mechanism of injury would cause the acceleration or deceleration is in fact changing the outcomes, whether those be the acute symptoms or long-term effects but that is still being explored. Certainly, there is not a great belief that blast injuries look that much different when it comes to mild brain injury versus the other mechanisms of injury. All these causes are out there. There are certainly challenges in documenting whether veterans who have had their experiences weeks or months or sometimes years before have had one concussion or had 50 concussions. We are certainly exploring that to figure that out. One thing we do see is a full range of symptoms. Many of these symptoms are occurring acutely, in which case we can associate it more specifically with the concussion that we are evaluating, but sometimes these symptoms occur over time or maybe are not reported until over time so that it becomes a little bit more difficult to figure out is the concussion a primary source of the light sensitivity or the dizziness or the balance problems or is it a secondary effect? Is the concussion causing some secondary behavioral challenges which are then resulting in these symptoms or whether they are a combinant of acute stress response as a result of the near death experience where they were close to a blast or motor vehicle collisions that has caused an acute stress response that then over time can become PTSD, which can then cause these symptoms. We cannot always tell the specific association or the primary association between the concussion or the concussive event and the symptoms, but certainly the source of the concussion is one that can lead to a number of symptoms for the research we are going to talk about, we could not always associate whether the symptoms we saw were due to the exact concussion was reported or multiple other concussions or difficulties with chronic pain from other sources that result in insomnia, or other symptoms of PTSD, etc., but we saw a lot of these symptoms in the research that we did and others did. We are very aware of the overlap of symptoms. This has been caused anything from post concussive syndrome, which is not a term that most people are using. Poly trauma can be a term that is used for TBI, along with behavioral dysfunction or pain disorder or other somatic issues. Certainly, just depression and anxiety without evidence of concussion can cause many of these symptoms, as can just chronic health issues. These are common symptoms. They are ones, which are a challenge clinically. As a result of that, there are a lot of modalities that are being looked at to try to improve these symptoms. One of them we are going to talk about today is the use of hyperbaric oxygen.

It is not clear why people with concussions continue to have symptoms in many cases. Again, even if we assumed there are no other behavioral dysfunctions or pain dysfunctions, that the patient has a “pure concussion.” Even with that, we are still seeing individuals that are having some persistence of symptoms beyond the acute period when acute cell injury and cell recovery, let us say the first zero to eight to 12 weeks after that period of time are still seeing symptoms. We cannot always explain that by the cell biology that we are aware of itself. We are challenged to figure these things out and whether that is due to secondary mechanisms that may be the result of behavioral or somatic complaints or due to some other known neurodegenerative process, which is what we are examining in many of our large studies is unclear. Certainly, we are aware that there are acute changes that occur even in concussion that have been well documented in the basic science, as well as in the human model. We can understand why individuals are having difficulty with acute level of arousal with challenges to balance and dizziness perhaps with pain as manifest with tinnitus or light sensitivity or noise sensitivity and certainly headache. Some of these are due to abnormalities within the skull so within the brain. Some of these are the result of acute changes that occur to the tissues around the skull at that.

Certainly, within the brain, we are seeing direct tissue trauma. Those could be on a microscopic level as with a mild TBI. We may be seeing some changes in blood flow that are occurring acutely after a concussions for the first several hours from days to weeks. There is certainly basic science suggestion that there is impaired regulation metabolism within a cell level with glucose and lactate imbalance. There are some secondary stages of injuries with cellular ischemia that may occur after concussion, which are being recognized in individuals that are not getting well and certainly in lab model as well. These may be causing some of the impairments in function whether they be neurologic or somatic that we are seeing for the first several hours to days to perhaps weeks. It is unclear that there is any persistent or ongoing secondary stages of injuries in concussion beyond six weeks, eight at the most. Certainly, for that period of time, we are seeing some difficulties. These secondary factors may be those maybe the causes of some of the longstanding behavioral difficulties that folks are having, as well as some of the pain issues. These factors themselves, the fact that they began a syndrome or behavioral dysfunction, maybe the ongoing generators of some of the symptoms that we see. There are a number of research projects that are within our program here at VCU at the Richmond VA, as well as others that are looking at ways to intervene acutely as a way of perhaps blocking this cascade of injury that occurs acute in a way to prevent some of the more long term difficulties, specifically looking at some of the prevention of neurodegenerative changes that they are believed to be associated with multiple or large numbers of concussions, but perhaps even after a single concussion or two concussions that occur that close enough together, there may be some interventions to prevent some of the acute chronic symptoms which we are looking at. The mechanisms have been elucidated within the basic science model and not so much in the human model, but we assume that we were are on course for that. As a result of some of these findings in the basic science model, there were a large number of studies that were completed in the animal model, which we will highlight.

Let us look at the theory as to why the HBOT might actually work for traumatic brain injury. The question is are these theoretical constructs snake oil as a way of selling something that is a large lobby in Washington that is a very high dollar item or is there truly science behind it? I would say that anybody that is using hyperbaric oxygen was on the phone or in your setting, there are a number of indications that are approved by the CMS or by Medicare/Medicaid that have FDA approval. There are some that the UHMS, which is the Undersea Hyperbaric Medicine Society also approve or recommend. I would recommend that if you were using it for any of these indications, you also take a look at that literature because the most I dive into this and this is a topic in HBO in general, the more I dive into it, the more I wonder how much of that science is a little suspect as well because of what I read on wound healing and skin care does not convince me that it is overwhelmingly a valid treatment for that as well. I know it is CMS approved for certain things, for diabetic wounds and it is used for spinal cord injury wounds. I would challenge you to look at that literature. There are indications and these things did meet the guidelines for CMS for FDA approval, but I am not overly convinced on how well they compared to some of the other standards. Where the yellow arrow is, you can see there is a CMS accepted indication for crush injury , severe acute trauma, particularly that involving ischemia and the folks in the hyperbaric world are hanging their hat on it that perhaps this is supportive of traumatic brain injury insult where there is some vascular abnormality. Again, that would be more for moderate to severe, but may occur in mild as well, but clearly the FDA and CMS is not providing a support for its use in TBI based on that alone. There are six basic areas of effect that the folks who propose a hyperbaric oxygen say that it works under, you can read these things yourself. When we look at traumatic brain injury for acute injury, perhaps in some of the cellular repair and vascular improvement for acute, we may see some effect but since we are talking about individuals with chronic traumatic brain injury. In this case, chronic concussion, the ones that may have some effect is there perhaps some chronic cellular hypoxia that is seen in a certain number of nerve cells, as well as glial support cells and can that hyper oxygenation that accompanies HBOT perhaps have some effect. Also, in terms of cellular repair, are there some cells that have been damaged but are trying to recover after concussion or mild traumatic brain injury that it may be having some effect on. The other ones certainly seem far less likely. The areas that are associated with that, certainly acutely we can see the reduction in cerebral edema, but not relevant to a chronic mild TBI. We look at is there an enhanced oxygen availability and possible oxygenation of those nerve central neurons that are still surviving but not functioning at full capabilities are in their penumbra or area where there is cell damage, but not death. Can there be some influence through the hyper oxygenation and improved vascularity for neurotransmitter function and the availability. Again, this would be more of the acute function. Is there some immune modulation and stem cell mobilization as a result of hyperbaric oxygen? There are the areas that if we propose that perhaps there may be a cellular role for HBOT whether that is improving the oxygenation of cells that have bene partially injured and are not functioning fully, or the mobilization of new cells is where the believe may be. Bottom line is we do not have a hard and fast basic science understanding of why HBOT would work in the animal model and so we do not have one in the human model, but there are some theories that are being tested in research.

Let us jump to the area that what I focus on and what this talk is about is clinical trials. Importantly, I am not going to go over all of the animal modeling or the animal trials, but certainly, for moderate to severe TBI, there is evidence of improvement in the animal model for these HBOT. It has also been demonstrated in animals with chronic moderate to severe TBI. We see improvement importantly for chronic, we see improvement in spatial learning and test modeling to some cognitive tasking. There is no specific research in mild TBI in animals to date. Importantly, the research that has been done for acute injury is within minutes to hours of injury and for chronic it is days to weeks post. What is available in the human literature also has been in the acute moderate to severe TBI. There are four systemic reviews of 23 publications. There are also now, which is an update since my last discussion, there are now six clinical trials that are published in mild TBI which is what we are going to focus on. The acute ones have all been related to moderate to severe. These mild ones are chronic. We will focus on those. There is for acute TBI, the quality has been overall low. There was no sham. There was poor randomization. This is again for acute moderate to severe. For the most part, blinding was not used. It is somewhat tough after a moderate to severe to do blinding in a way that will be approved. There are standardized inclusion criteria for acute moderate to severe. There is essentially no significant improvement in functional outcome.

There was a trend. I am not a believer in trends in the world of research. I do not believe there was any positive outcome. If you are a believer in trend, if you believe 0.8 is a trend, I said I would not P values too often, than there was some improvement in ADLs after a year and a half. I am not a believer in trends. I think the only improvement that were shown were folks did die less often with the number to treat being seven. There was some improvement in ICP, intracranial pressure, as well as in pulmonary status time to the be off a ventilator if you look at moderate to severe TBI. It is not an intervention that is being used a lot, if at all, in this country for acute moderate to severe TBI. It is very difficult to use. If you are going to use it, there may be some survivability improvement. It is just that most patients cannot tolerate being in a chamber acutely after injury.

There were very few adverse outcomes even in the moderate to severe group. There were some adverse events in terms of significant ones the numbers were small. The pulmonary symptoms tended to be in individuals that were on ventilators anyway. It was not a significant concern, but it was something to be aware of. The bottom line is after acute moderate to severe TBI, there may be a role, but we are not talking about that today. What we are talking about today is chronic TBI specifically after mild injury and we are going to go over those trials. There are about six trials. We are just going to run through them. Then we are going to summarize.

The first trial was under the auspices of the military. It was by the folks you can see here, Michaelson, York, and Wolf. It was done in San Antonio. It was completed about two and a half years ago. It included individuals predominantly mild. I think there were two folks with moderate TBI in the mix. There were at 48 mild. All folks that were at least three months post injury. These individuals were evaluated using a somewhat state of the art measures. These are acceptable measures. They are not within the NIH toolbox, but they are ones that at the time were competent measures to use. They compared two groups, either those that got a sham exposure to air with some mild compression and those that got full dose of hyperbaric oxygen. This is actually a relatively high amount. It is higher than what is typically used in chambers across the U.S., but again at the time, the goal was to try to give them as much hyperbaric oxygen as possible to give them a more maximal dose. That was fine. They looked at individuals that had both mild traumatic brain injury, as well as those with PTSD. If I recall, about 75 percent of the folks had both TBI and PTSD. This was published in 2012. Wolf was the lead author. They fund no between differences in folks with either mild CBI or mild CBI plus PTSD in either their symptoms or in the objective cognitive batteries that were done. There was not a detailed assessment done in this publication of the FMRI findings from personal communications that I have had with George Wolf and with others in the group, there were no specific findings. From what I recall, they did not actually get FMRI involved with the individuals due to some logistical issues. First study that was published, that had a control in it. The control has been somewhat criticized because someone show has been in a chamber before so someone who is a diver or someone who is has just been treated before could have told that this was in fact not low pressurization. We saw no significant changes between the groups.

Next study, is not a military trial. It is a trial that was in the private sector. Originally, I believe there was some military funding for this. It was led by Dr. Wright and Dr. Harch. Dr. Harch is at LSU. I do not know where Dr. Wright is. He may be there as well. I have always been looking for Dr. Wright. This was in a group of individuals that had both mild and moderate TBI, again, predominantly mild TBI. They could have also had PTSD. From my recollection, they were predominantly individuals that had mild TBI. Originally, this was set at an N of 32, but they published at the halfway point. To my knowledge, they did not finish. They initially did not publish on this study, the complete study, but they did publish on the first 16. They used a computerized neurocognitive assessment, not an assessment tool that is recommended by the NIH, myself, or most researchers. They used SPECT scanning. Again, not a technique that is recommended from my old TBI as an objective assessment. It is certainly used by some. They used a quality of life measure. All individuals were received hyperbaric oxygen. There was no sham group. It was individuals who are coming for treatment, but to my awareness, most of all of the expense was paid for by a small grant that they received. As with the last study, these individuals received 40 sessions, which takes an about two months to receive. They had wanted to treat them longer, but this was not reported in the trial whether they did receive further sessions or whether there were any outcomes that were different. What was reported then in all 16, there were improvements in the symptoms that were initially reported, as well as improvements on the computerized neurocognitive assessment. The quality of life and the SPECT scanning. The improvement in SPECT scanning is enhanced areas of activity. This was published in 2012 in General Trauma just after the Wolf article. Of note, obviously no control group so there is a potential for a bias related to placebo effect. In addition, this was not a randomly assigned group. These were folks that came to Dr. Harch’s center specifically for treatment for this so there was a selection bias as well.

The next trial is one that I was part of. I led off on. This was a trial that was funded by the military. Just as in the first trial by Wolf, we had individuals that were at least three months post their concussion. This was a military related concussion. These were adults. They were randomly put into three groups. One of the groups received a placebo that they were fully compressed, but were receiving room air at the time. One group received one and a half atmospheres of compression, which was the standard treatment in the private and academic community for most things that hyperbaric oxygen treats for including concussion such as in the Harch studies. This is the one that kind of is state of the art. We also gave a larger dose of two atmospheres in an attempt to see if there was not any finding dose finding differences. We were anticipating that this would work at the 1.5 because that is what was claimed. We wanted to see if it would get any better at 2.0. As I noted, we used the same as the Harch and the Wolf battery in that we gave 40 sessions, which took about two months. These folks got a session a day for five days a week and they had time off. The dives or the sessions lasted for one hour. In this protocol there were no different. In our protocol, about 75 percent of the individuals also had PTSD. We saw no between group differences in individuals based on TBI or PTSD in any of these groups. In the two-hour placebo group, which is this group here or in the state of the art standard treatment, which is here. Or in the two atmosphere dive, which is group A. We saw no difference. We did se improvement in all the groups, but we saw no between group differences. There was a placebo effect is we believe was due to and most other authors do was due to but no specific effects of the hyperbaric oxygen. We saw a small incidence, a very minor adverse effects. Here there are multiple references on this one so I could not put it in the table. Here are the references on this project.

The next study was a study out of Israel. It is a group with the University of Tel Aviv. I have had the privilege of meeting directly with this group face to face. I not only read their project, but also discussed it with them. This group was taking individuals who were non-military. These individuals were injured during civilian events. They were predominantly blast events. They were terrorist injuries that occurred in Israel. There were also some non-terrorist civilian injuries and motor vehicle collisions. These were adults. They were all mild. They were all chronic. They used a randomized perspective cross over study designed where individuals either came in with chronic persistent symptoms that were at least in part related to their concussion. They either received hyperbaric oxygen for 40 sessions and then were crossed over to nothing for 40 sessions or for two months or they received nothing for two months or they were getting their standard care. They may have been doing exercises. They may have been taking medications, but nothing was changed. They did that for two months. Then they were crossed over and received 40 sessions over a two-month period. The results, there were no improvements when they were getting nothing. The group two that was just getting standard of care for the first two months saw no improvement, but both groups did improve when they got hyperbaric oxygen. In case one, that would be group one saw improvements during their acute period, during the first 40 session. Those improvements remained during the standard of care. This group two did not improve for the first two months, but did improve afterwards. They used computerized neurocognitive testing, which again I noted is really not the start of the art for research studies. It is not even state of the art for most clinical care. It is really something that is used on the sideline or used for screening technique. It is not a comprehensive evaluation. They used quality of life and they used SPECT, so the same thing Harch used. This was published in 2013 in PLoS One. Again, the criticism dissimilar to the Harch one in that there was a strong potential for a placebo effect. Clearly, there was less of a biased sample because they could have been randomized either way and they did only improve when they were getting hyperbaric, but that would push towards a placebo effect.

The last major study is a study that was published recently JAMA. Scott Miller and others led this along with Lin Weaver. This was a study looking at individuals that had again both PTSD and mTBI. These individuals were all military population. They were all chronic. These individuals were randomized. They were put into either a sham control or a true hyperbaric state. There was also a wait list which was not reported on this study, but which I can report on because I talked to the research, but talked about what was first reported. In terms of the outcome measures, they used the Rivermead post concussive questionnaire, which was very similar to the NSI, the neurobehavioral symptom inventory which we used in our study that they did use the NSI as well. They also used nine other secondary measures of physical functioning, which included some cognitive testing. They used Dynavision to look for reaction time. They use a six-minute walk test to look at a general sense of wellbeing, as well as physical activity. They had a cohort, one which was pure PTSD, chronic cohort two, which was pure mild TBI, and for both cohort one and two, they had no interventions or local care which was the control group, which I apologize they did report on. They had cohort two, which had interventions with hyperbaric oxygen. They had cohort two, which had sham control, which was pressurized air, not at the same level of pressurization, but pressurized air. As with the study of \_\_\_\_\_ [00:36:10] as well as Wolf, there was no differences in the mild TBI group or the PTSD group in terms of their symptoms or their cognitive effect, or for that matter, of their reaction time or their general wellness. There was improvement seen in any group that received hyperbaric oxygen, which was true of the Cifu study, as well as the Wolf study. It had a small incidence of adverse events. I should indicate that both in the Cifu study, as well as the in this Miller-Weaver study, those effects when—folks got better if they received any type of compression whether that was with hyperbaric oxygen or just compressed air equivalent. Of note, they did get better but at the followup period. In our case, at three months post injury, excuse me post dive, these individuals were back to their baseline. Any bump or improvement they had was short lived and was again felt to be due to the placebo effect, which occurred in the group that either got hyperbaric oxygen or did not.

Let us talk about what to do now. What did we find? Clearly, we did not find that hyperbaric oxygen had any demonstrable effect that could be separated from just placebo. This was not unexpected because the symptoms we see after chronic concussion are complex, are multimodal. They certainly may not even be homogenous. We may be, in fact, seeing that there are some individuals who get certain types of concussion due to certain etiologies or due to certain severities that do benefit from different treatment, perhaps even hyperbaric oxygen. We did not find that subset. Maybe the sample was too small. More likely than not, it is multimodal in cause and treatment. If you are going to look at treating someone with 12 different symptoms or with a complex injury such as a concussion, you may need—you are more likely than not to need a multimodal approach. You need to be looking at physical interventions perhaps. You need to be looking at psychological. You need to be looking at factors related to their lifestyles and their personal interactions, their relationships. You need to look at all of those features. Your physical interventions maybe need to be multimodal. They may need to be exercise, as well as a medication to assist with restorative sleep. There may need to be targeted behavioral therapy , which has been shown to improve PTSD and also been shown to improve insomnia, as well as other interventions such as using meditation or using some other alternative modalities. It is important that we do not just lump all the individuals in the same way. By the same token, we cannot assessment someone using a single modality. You cannot just give them a cognitive test. You need to be looking at behavioral symptoms, somatic features. You may need to be looking at sleep as well as balance.

You need to look at multiple features to look at that as well as these other factors. Lastly, and always important, what did the person come to the battlefield with car accident or other sports injury with? What are the subject characteristics? How do those need to be specifically treated? Importantly, the clinical practice guideline for mild TBI which came out in 2008, 2009 from VADOD is just on the precipice of being released. I have seen it. We are just fine tuning it in the next month. It will be out, but it is important. Let us use standardized protocols for these specific treatments. One protocol, we are using a tailored protocol based on symptoms, which this CPG will have, but even if you do not want to use the CPG and use your own one, use standard approaches for folks that have standard complaints. You may have 12 different approaches, but for someone who has got the same symptoms of and is presenting the same way, use the same protocol regardless of the day of the week or how they are feeling. In conclusion, mild TBI is a common injury in civilian and military areas. Persistent post concussive symptoms or symptoms that are in some part related to concussion are common. Those symptoms may result long term in neurologic decline or they may just result long term in persistent symptoms, which may be bad enough. It is important that we be aware of this and that we be addressing these using treatments. Identifying the etiologies of these symptoms may be important to you. It may be important to the patient. They may at some level help some specific patients and you with treatment, but in general, they are in inconclusive. We need to be treating symptoms and bear in mind that those that are multiple etiologies may need multiple modality treatments. At present, hyperbaric oxygen therapy is a misnomer. There is no therapy related to hyperbaric oxygen from mild traumatic brain injury or post concussive, excuse me, PTSD related symptoms. It is not a recommended intervention for purposes and symptoms after mild TBI or PTSD. Lastly, again, I would advocate that you keep your eyes open for the clinical practice guideline for persistent symptoms after mild TBI, which is coming out. At this point, I will stop and thank you for your attendance and for you listening in. I will turn it over to either Ralph or Molly to begin the question and answer session.

Moderator: Thank you so much, Dr. Cifu. This is Molly and I will be doing the Q&A. We have already got some great pending questions, but for those of you that joined us after the top of the hour, I just want to let you know to submit a question or a comment, please go to the Q&A section. I am sorry, David, will you leave your slides up just so we can see your wonderful animation and contact info? Thank you. So as I was saying, if you would like to submit a question or a comment, please use the question section of the Go to Webinar dashboard on the right hand side of your screen. To expand it, just click the plus sign next to the word questions. We will go ahead and get started. This one came into words the beginning of the presentation. If you do not call it post-concussion, than what do you call it?

David Cifu: Well, yes the reason I do not call it post concussive syndrome is because syndrome implies that all of the factors that you are describing are related to a common factor. In this case, they are related to the concussion. It is in some patients, they may be but as I said throughout the talk, it is inconclusive as to which ones came first. Are they all primary or secondary? It is better to just call it persistent post concussive symptoms. I am not really into semantics and splitting hairs, but it is not a syndrome. I think that is a real misnomer. Persistent post concussive syndrome or if you like \_\_\_\_\_ [00:43:11] condition. That would be fine, too, but PPCS I think is what that spells out.

Moderator: Thank you for that response. Do you think that microglial, I am sorry if I mispronounced that, neuroinflammation, plays a role in symptoms after concussion?

David Cifu: That is a 62.2 million dollar question. We are studying that. The answer is acutely yes. I think the microglia are amazingly important in the injury and recovery post injury and probably in perpetuating or facilitating some of the difficulties folks have. The question is does that inflammation persist for beyond six weeks. My friends and colleagues and collaborators at Boston University have recently chastised me as have others that in fact it does persist after six weeks. I defer to their brilliance and their ideas, but I still need to be convinced of that. There are a couple of small studies that are suggesting that. Right now, it is up in the air. I am not a big believer that this is due to ongoing inflammation. One of the reasons I say that is that hyperbaric oxygen specifically has been highlighted to be a treater of ongoing inflammation. It had no effect that we saw as I just outlined. I am not a big believer in that, but certainly the question is still out there for debate.

Moderator: Thank you for that reply. This next question we have, this one came in when you were going over the tables of results. Any chance of the VA doing more research?

David Cifu: I think they mean research in hyperbaric oxygen and TBI. They do lots of research. Right now, the VA and I am not speaking for the VA. I am speaking for me, but certainly I work a lot with Stu Hoffman. Stu, if you are on the call, you can cut me off, but the VA is always looking to do the best research possible. It is open to doing research in hyperbaric oxygen, basic science, as well as clinical, if there is an appropriate hypothesis, and if there is a good study question and if it is put together in a format that is appropriate. The answer is yes. Right now, I am not aware of any that are on the books. Based on these five or six studies, I have highlighted today, I do not see a specific research question that is not answered. We need to better understand the different types of mild TBI, the different types of presenting symptoms, the phenotypes, that we are seeing before we can drill down to a treatment intervention of this type. There are some—it is very expensive to do hyperbaric oxygen. It is very expensive to do the research. So I would say that there is hesitation until we see better research questions, probably even more elucidation of the different types of problem that occur from mild TBI.

Moderator: Thank you. The next question, well, I will just go ahead and read it aloud. You may have already touched on it. Should any more studies be done with larger numbers and long-term followup?

David Cifu: That is an excellent question. Let me answer both of them. Obviously, I said in general no. In terms of long term followup, there is funding that Dr. Miller and Weaver have that is being used to do followup on as many, if not all of these, about 200 or so subjects that were in the three DOD studies. We did do followup in three months roughly in each of these trials. Now, they are looking to do a one-year followup, as well as beyond using existing funds. That is occurring. It does not seem to me to be particularly logical to expect to see long term changes since in three months they were back to baseline, if not worse. I do not think we would see suddenly a rebound if maybe it kicks in after six months or a year, but we are looking at that.

The second question do we need larger numbers? The answer is no. I mean these are well done studies, well controlled. We did power analyses. The power analyses were set up to see results at the numbers that were set up. We did not see them. I am always happy to entertain more research and to look at them, as I said, but I do not think it is just numbers game. I just do not think it is working in general for people with chronic, for symptoms after mild TBI. Maybe there are subsets, but they need to be elucidated.

Moderator: Thank you, just a few couple questions pending. I do see that you have another meeting coming up soon.

David Cifu: I am sorry.

Moderator: No problem.

David Cifu: This takes priority, Molly, you know that.

Moderator: Marvelous, please do not hang up on us. Let us see. The VA has a few centers that are forefront with TBI. Is there a possibility of having HBOT become part of that research?

David Cifu: Yes, there are a number of centers at the VA that are outstanding both clinically as research. As research it is a testament as to how much we care about our vets. Right now, the answer is if there is a good research question, if there is a well-developed protocol and it is submitted and there is funding that can be obtained for that, the VA would be open to looking at that as an option. I, myself, am not going to specifically advocate for that because I do not see right now that research question being out there, but the VA centers that I work with, we have got 14 in our consortium, would be very open to being part of that protocol, as I am sure would others. It is just a matter of finding the right protocol with the right funding.

Moderator: Thank you very much. The next question we have, would you say a few words about your thoughts on exercise as a potential treatment modality for chronic mTBI and for the role of exercise in CPG?

David Cifu: Oh, bless you. The bottom line is return to physical activity, specifically aerobic exercise, but any physical activity, as well as cognitive activity, if there is such thing as behavioral activity, acutely after concussion—I am saying acutely, within a day of the concussion, is state of the art. It is what you are supposed to do. All right, I am not talking about chronic TBI. Certainly, that is always the case. That has been shown to be one of the most effective interventions. I will say that meditation mindfulness are also highly effective. Physical activity and specifically just aerobics, simple aerobic activity, getting your heartrate 65 to 80 percent of age adjusted maximum is state of the art treatment. Acutely after a concussion, you just had a concussion, you are 24 hours into it, you should as best as you can physically get up and move. If you can get back into the gym if you were doing that or outside walking or swimming, do that. You should be protecting your head from another injury or protecting yourself from another fall. You perhaps should not be driving if you cannot see well, whatever thing is. We do not want to do stupid things, but exercise never hurts neurons. Not exercising will cause neurons to not heal well. I return to rapid physical activity is key. I just finished a series of lectures across the country with some other concussion researchers including those from University of Pittsburgh, the folks that came up with the impact study. They fully endorse that as a return to activity for professional sports, amateur athletes, and even bad ones like myself. It is in the CPG and it will be highly recommended for chronic, as well as acute, but I do not feel that strongly about it.

Moderator: Thank you for that response. A quick question about etiology itself. I am sorry, a quick question about concussion itself. Does neural deformation specifically causing depolarization play a role?

David Cifu: Whoa, that is probably above my pay grade. Does neural deformation, certainly if there is a severe enough injury to cause a stretch of an axon that causes abnormality of the axon’s function of there is a shear or tearing of that axon and the next level, if there is a shear and tearing of some of the blood vessels to those axons or the great white junction so that we see even positive CT or MR findings, than yeah there has been neural deformation. There has been deformation of the brain. Has there been depolarization? I would imagine so. I would say that is not something that has been studied in human, but the basic science model that has been demonstrated. So the answer is yes. I do not know what to do with that clinically in terms of treating symptoms, but yeah, that is why these folks are not doing well acutely. Now, the vast majority would do wonderfully at two weeks, three months, one year depending on what stage you look at, but for those that do not, that may be one of the underlying causes. We do not know that, but that is a good hypothesis.

Moderator: Thank you. The next question, where, sorry, let me get this right. Where do they submit the research question? Would it be to his email?

David Cifu: Yeah, I think that is asking—I keep saying we need the right research question, hypotheses. I am talking about if you have got research ideas and hypotheses, than the next step is to identify a funding stream. If you go to the VA research website, Stu Hoffman has a portfolio of available research dollars for brain injury, as well as other areas of neurosciences. Applying to one of those grants indicates that you are going to have a research question. You are going to have a hypothesis. You are going to have research design. Put it all together there. You can send it to me. That is interesting, but I am not a funding source anymore. Stu Hoffman in the VA is. There is money available as we speak. There will continue to be money available. Go to the website. See what grants are available now. Keep checking to see what is going to be available. There is money in the pipeline. You have to have the right research design, research questions. Obviously, they have to have the right research collaborators, I can help you with those, but we need to first identify funding streams. I probably should know the VA research website. It is probably VA.research.gov. Ralph can remind me of that if he can, just so folks know where to check on that.

Moderator: Thank you very much.

Ralph Depoma: You can just go the website. Just go to the ORD website and it will tell you where to apply to which of the funding sources.

David Cifu: Thanks, Ralph.

Moderator: Thank you. Well, that is our final pending question at this time.

David Cifu: That is so sad.

Moderator: I am sorry?

David Cifu: I was just moaning that is so sad. It was just getting into it.

Moderator: That is not to say we have to end it. Ralph, if you have any questions.

David Cifu: Not Ralph’s questions. They are too hard. Ralph’s questions are too hard. Do you have any comments? Forget about questions. Do you have any global comments?

Ralph Depoma: I think this comes as near to settling it once and for all hopefully, as well as we can. We still get a lot of pressure from private sources particularly, as they go through their congressman, but this would be very, very helpful for the future. Thank you very much. It was just terrific.

David Cifu: Thanks, Ralph, thank you, Molly.

Moderator: Yeah, do you want to give any concluding comments, David, or are you all set?

David Cifu: No, I just want to thank folks for being on this. Please continue to manage these individuals. As you will see in the CPG, primary care is where we are recommending the vast majority of management of folks with persistent symptoms after mild TBI. The clinical practice guidelines will help you there. Please do not recommend hyperbaric oxygen at this point. We just do not have an indication for it specific to TBI or PTSD. Continue your great work, but that is about it. Everybody have a wonderful holiday.

Moderator: Thank you so much. I want to thank Dr. Cifu for lending your expertise to the field and for Dr. Depoma for organizing this talk and the entire TBI series, which does happen monthly. Please keep your eyes peeled for further sessions that are coming up. With that, I am going to close out the session now. For attendees, please take just a moment to fill out the feedback survey that is going to pop up on your screen. Thanks, once again, David and Ralph. Have a good day everybody.

David Cifu: Bye bye.

[End of audio]