



COVID-19: IMPACT ON RESEARCH AND CLINICAL TRIALS GLOBALLY AND RISK FOR PEOPLE WITH ALS/MND



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On Thursday, April 9th a webinar with leading ALS/MND Global Clinicians and Researchers took place. COVID-19 and its impacts to the ALS/MND Community have been felt globally. This webinar answered questions about susceptibility and ALS/MND, care, and the impacts to research and clinical trials.

Moderator: David Taylor, Chair, Scientific Advisory Council, International Alliance of ALS/MND Associations

Panelists:

- Dr. Merit Cudkowicz
- Dr. Angela Genge
- Dr. Jonathan Glass
- Dr. Matthew Kiernan
- Dr. Leonard van den Berg

Welcome: Calaneet Balas, Chair, International Alliance of ALS/MND Associations

VISION: A World Free of ALS/MND

PURPOSE: The Alliance is a global network of ALS/MND associations informed by PALS/CALS, that builds capability for its members and connects to external stakeholders.

Note: This document is not a verbatim transcript of the call but a blended Question and Answer format to capture the main themes.



Introduction: ALS doesn't stop, and neither does the research, and this webinar focused on the care and the clinical side, but it should also be acknowledged that from the laboratory side there is still a lot of activity going on. People may be at home but they are actively engaging with their labs, they are spending the time analyzing their data better, finding new ways to understand the disease and make connections around the existing information that there is that they may not have been able to take the time to do...so really taking this as an opportunity to be able to better understand ALS and find new ways to treat it. The labs may be closed but their brains are not and that is the most important part so we wanted to let the audience know that ALS research certainly is continuing and you can take solace in knowing that people are very dedicated around the world to this.



- 1. ALS/MND is a disease that can create an increased susceptibility to potential complications from other illnesses, such as COVID-19, and particularly ones that affect the respiratory system. What would clinical expert messaging be for people with ALS/MND with regard to:
 - a) any potential increased susceptibility for contracting COVID-19, and,**
 - b) potential for risks in managing a situation where someone with ALS/MND contracts COVID-19.****

This pandemic really does pose a serious risk to ALS/MND patients but it's important that they should know that there are things that they can do to minimize those risks. In terms of just a general understanding, we do know that for patients with ALS/MND, any sort of respiratory infection is more serious than the general population and that's due to the fact that the disease is characterized by neuromuscular weakness. Individuals may have difficulties with coughing and many patients are already on non-invasive ventilation, so there is a higher risk that COVID-19 can cause serious problems for our ALS/MND patients. If there are other illnesses such as diabetes, heart problems, or chronic airflow limitations, those risks are then magnified.

We've already seen worldwide that we can try to reduce the risks and problems for patients by doing the simple things that have been suggested. Primarily that includes physical but not social isolation, and it's very important that ALS/MND patients and their carers do that to the best of their ability. Any sort of infection that they get at any stage should be treated very aggressively. Very simple measures like hand hygiene and wearing masks are important for both the patients and their carers.

Another thing that is important is making sure that they have their flu vaccinations. Obviously, the flu vaccination doesn't cover COVID-19, but it covers all of the other respiratory viruses that may be present and what you don't want to do is get two infections at once.

Another process that may be a consideration for patients is respiratory muscle training and certainly in some of the trials that have been done, looking at resistive devices like incentive spirometry which can be purchased over the counter at the chemist/drugstore, there are some promising results. Doing respiratory exercise 2 or 3 times per day may also help to build up a reserve for their respiratory function.

It's very important for people with ALS/MND to stay in close contact with their centres/clinics. Most of the centres are either seeing people virtually, through the phone or in person if they can. They can help to be proactive about your medications, giving you in advance prescriptions for longer. Some clinics are changing how they approve things like non-invasive ventilation and



many things may take more time so reaching out and staying in close contact is really important at this time.

There is no innate increased susceptibility to the infection for ALS/MND patients, it is simply that the consequences of the infection could be more serious if you have significant problems with your breathing. Our main message is prevention, prevention, and prevention. Please try to prevent infection with the virus, stay at home, reduce social contact to zero. That's not only true for patients but also for the other people living in your household. Please try to prevent infection. That's the main message and take it very, very, very seriously because complications can be severe for patients with ALS/MND.

Be careful. There are certain regional hotspots obviously in the world and in different cities in North America and in Europe and so even if you are living in a place that doesn't seem to be heavily infected, don't take that as 'I don't need to take these precautions that have already been described'. This virus is silent until it actually shows itself, we've proved that locally, and I think that has been proven around the world. So be careful no matter where you're living, even if you don't feel that the virus is in your community, it probably is. You need to be cautious until this whole thing is over.

2. How is ALS-MND care is taking place in your centres? We have about 21 different countries represented today on the call, so this provides an opportunity for people to see what is happening in some of the major ALS/MND centres.

The answer to this question very much depends on what's going on locally. In all places, we have to reduce the number of in person visits to the hospitals. In some jurisdictions new patients are seen, with outpatient clinics still open for diagnostic purposes. In some countries, although the numbers have been reduced, new patients are still being seen because they feel that it is very important that people know what they have and what the diagnosis is.

One of the biggest challenges is new diagnoses, because neurologists really do need to see people to make that diagnosis correctly, and in the United States there are state laws restricting diagnostic evaluation in another state. We encourage people to be reaching out to your local ALS/MND Association/chapter so that you know the ALS/MND expert in your city, in your state.

For follow up visits, most of the visits have changed to virtual visits or telemedicine. Please stay in close contact with your multidisciplinary care centres because that is very important. We feel that we can provide care by telephone or telemedicine. Safety comes first and it is still possible to get care in most countries.



Another area that has been impacted in care is feeding tubes for nutrition support. In the past we used to have people stay overnight and that has been changed to a single day in many hospitals. We are also encouraging people to do it much sooner because it is much safer to do when your breathing is better. In particular during COVID-19, waiting too long could be dangerous for patients. We are really encouraging PEG tubes to be done earlier for two reasons. First, there is no downside to it and second, getting somebody scheduled in the hospital for an elective surgical procedure has become very difficult in many areas. The hospitals are full. A lot of surgeons are doing other things so getting them on the schedule early is a very important thing. You've got to maintain your nutrition to prevent loss of weight and nutritional deficiencies. So, I encourage people, if your clinician says it's time to get a PEG tube you should think about it seriously.

Assessing breathing status is an area that has changed during COVID-19. Some clinics are going to old fashioned approaches of assessing people's breathing status, like counting one breath or holding a note. SNIP is another option when they cannot do vital capacity tests (like SVC).

- 3. In the introduction we mentioned that research is still continuing and you've all alluded that. For clinical trials it is happening in modified ways and depending on the region of the particular clinic that is doing the work. I was wondering if we could go around the group to talk about how research is moving forward at your centre with regard to clinical trials and/or any other clinical studies, and maybe a little bit about some specific trials that I know the audience are interested in.**

Dr. Cudkowicz, just yesterday you did a detailed outline of the HEALEY platform and perhaps you could reiterate a little bit about that, about what's happening at your clinic with regard to research, and perhaps a couple of the higher profile trials, like the NurOwn trial. And then with regard to the SVC piece that was just mentioned, some information on the Orion trial where that is a primary outcome measure.

Dr. Cudkowicz: I think I would break it into ongoing and new trials. For ongoing trials we are doing everything possible to keep people in those studies. We are moving things to the home that are safe to do, doing virtual visits, and only bringing in people where the treatment needs to be delivered in the hospital. So for example, the NurOwn trial, people do need to come to the centre to have the administration of the treatment, and we do that in a separate floor. There are no COVID-19 patients on that floor and it is very isolated. We can do it as safely as possible. For treatments that are oral, we are shipping medicines to the home and doing everything remotely. Same for the Orion study, lots of efforts all over the world to move that virtually to the home so that we can get good results. For new studies like the platform trial and some of the other industry new trials, everybody's working as hard as possible to get all the



sites ready, but we are not bringing in new patients yet if there's a stay at home order in that location. We are getting all the sites prepared to start rolling out super quickly as soon as those stay at home orders are lifted.

Moving perhaps to Dr. Genge, what is happening in your clinic and what's happening with the Tofersen (SOD1 ASO) trial? Then perhaps could anyone else that's on that trial indicate whether that's continuing in their centre?

Dr. Genge: The Clinical Research Unit (in Montreal) is open and in fact we are doing the critical ongoing trials for patients who are already enrolled. The unit runs not only ALS/MND trials but brain tumor trials, rare muscle disease trials, and each of the trials for those which patients were already screened and enrolled, they are ongoing. I agree with Merit, that trials like the Orion trial, we are doing everything remotely. However, because the ASO therapies are given intrathecally, these patients are still coming to clinic within their windows, and having their intrathecal injections. This is true for not only the ALS/MND Tofersen trial but the other trials, including the dementia and the Huntington's trials. Patients are receiving their intrathecal therapies as per the schedule. There are some modifications, mostly because we are actually in the luxurious position of having a whole wing of a hospital that is outpatient driven, and the CRU is using that for all of these visits to ensure the safety of the patients. Patients come in, they go to the outpatient unit, they wear a mask, the staff is wearing masks, and the procedures proceed. It is really important in these trials, if at all possible, and I know the shelter in place orders in certain areas of the US is interfering with the treatments there, but for us the patients are actually able to come, they are being dosed regularly, we are assisting a couple of other sites who cannot give their therapies and we are looking at ways that they can get one or two of their injections with us until the original site is open again for the therapies. For new trials our start up, ethics, and contract offices are working normally. In fact, they are working overtime, so a lot like Merit said, we are prepping to begin screening as soon as some of the restrictions are loosened. I think for patients on the line we would expect that in Canada we will be very cautious, and you will see once we are able to bring patients in, we will start screening right away. There are a number of industry trials that are going to be ready for screening as soon as we are able to start. So many of the delays that occur in the normal manner of things are actually being managed right now to just essentially allow every site to be ready to go as soon as the stay at home or the restrictions are eased somewhat. We are not expecting things to be back to normal here in Canada right away, but we are expecting that things like attending clinics and certain other services will be allowed to start being active again once we get through this current period. The most important thing is that patients inform themselves, call the clinics, find out what they could be eligible for, make sure that the coordinators know that they're interested, so that once we are functioning again people can do the screening.



Dr. Glass. At your centre are there any additional pieces that are happening?

Dr. Glass: There are a couple things I'd just like to say. Number one, as you said at the beginning, our research is still going on. This is actually a time when we're not spending a lot of time with patients face-to-face. We are spending a lot of time with data. A lot of interesting research continues both in the labs and at our desks and so we haven't stopped any of that. Number two, again a lot of this is very regional. If you live in a hotspot there may be more restrictions in your hospital than elsewhere. At our place we've had to speak to the administration about whether any specific clinical trial is "essential" and a decision has been made that if you are providing a treatment, especially things like the intrathecal drugs for C9 and for SOD1, then that is essential and we are testing all of our patients for the COVID-19 before they come in. It's not really necessarily for our protection but we do not want to bring patients into a clinical environment carrying the COVID-19 virus, so we are waiting until they are negative to get them in. Luckily, we haven't had any positives so that's good. So again, as Angela said, speak to your local clinic, to the local physicians. We all want to be doing this, you have to understand, we all want to be doing it. It's not our own decisions, but we have to live by the rules locally and some things will continue in some places, and some things won't. I do know that say in New York, in some of the hospitals, all of the clinical trials have stopped, and they are just overwhelmed. They're overwhelmed with patients, and so it depends where you live what's actually going to happen.

Dr. Kiernan, specifically in your clinic in Sydney, as well as some of the more specific trials that are happening in Australia, such as Cu-ATSM and RESCUE-ALS, would you be able to very quickly sort of allude to how those are moving forward?

Dr. Kiernan: Yes, so similarly, ongoing trials are continuing. For RESCUE-ALS, which is a crystalline gold, we are continuing to recruit. We recruited four patients to the study yesterday in Sydney. For the other studies that are ongoing we have to put things through ethics for quick modifications, including the Orion REFALS study to get the medications sent to patients' homes. So, there have been slight modifications that we have had to arrange, and they've been actually done very responsibly by the ethics committee. In terms of observational studies our national registry continues, but the biospecimen approach, the genetic studies and biomarkers, have stopped for the moment. But the clinical phenotyping and progress continue to be recorded.

And Professor van der Berg...

Dr. van der Berg: I'll keep it short so that there is enough time for questions. I just want to say that we are working harder than ever to find a treatment for our patients, so nothing has stopped, we are preparing new trials, recruitment is difficult, and in some countries,



recruitment is still open. For example, I just heard that Italy is still open. It's still recruiting patients for the SOD1 trial and also for the TUDCA. Ireland is also open for TUDCA, but in many other countries, most other countries, recruitment has stopped. The ongoing trials are still moving forward and we try to reduce the number of in person visits to the hospital even for safety, so most visits are changed to virtual visits.

4. How can ALS patients manage in regions where they don't have a multidisciplinary clinic or anyone who specializes in ALS, especially right now at a time where things are very different from the normal situation?

That's actually a great question and it's a question that is appropriate not just for this time during COVID-19 but all the time. What happens to patients who are in a region that doesn't have an ALS clinic? And I think what we are learning here and what this crisis has brought out is that there is a way to do care at a distance. What we are doing right now is extraordinary. The technology is amazing! What can happen is that ALS experts around a country, around a state, even around the world can provide input at least, not necessarily depending on where you live, directly to patients who they haven't met before, but also at least to the physicians who are caring for them. We are learning that as well. Physicians who are not used to taking care of ALS can contact us through this kind of a mechanism and we can actually help them take care of patients. Once we have been introduced by those physicians, we can sometimes connect with patients directly. So, I think in this new world of technology, patients who are not physically near an ALS centre can now benefit from the expertise at an ALS centre through these kinds of web-based systems. I think we are learning that. We are learning it the hard way, but we are learning it, and I think it's going to change the way we care for patients in the future.

This is actually an opportunity for the Alliance because the Alliance chapters may be the strongest presence for ALS support in a particular region and this is an opportunity to create and improve our telemedicine capabilities so that experts who are not necessarily in that region can be linked into the local physician and the patient. I think this is a wonderful silver lining to this pandemic, that we all learn how to do telemedicine. It may be something that we should all look at to support our local neurologists who are taking care of these patients and with some partnerships we can probably help in a number of regions throughout the world.

5. A question that has come up many times is regarding prioritization for ventilation and availability.

It's a difficult discussion, so that's why prevention of infection is so important; that's still the best you can do. It's not only about availability, it's also about the chances that you get off the ventilator and the chances that the condition you'll be in after being ventilated for a long time



could be very, very poor. Availability of ventilators is very, very limited in certain areas so there is a chance that ALS/MND physicians will not even be consulted if there is an emergency and choices have to be made. It is a very, very difficult discussion and for us it is also impossible to interfere, I think, when we are in a crisis. So again, it is not only about availability but it's also about complications and about the susceptibility for severe complications, so I think we are all questioning as ALS/MND physicians, for the patients that already have reduced vital capacity, whether being ventilated is an option for treatment. That is a very difficult choice that has to be made. Sometimes there is not even time for that discussion. So, it is a very difficult issue. Please, please again, be very careful about your social contacts, and not only about your own social contacts but also for all the social contacts for people living in your household. Please be very careful and stay away from people that could be affected.

- 6. Is there a concern that perhaps the shrinking economies, the reduced ability to fund certain things, might reduce the number of companies or trials that are moving forward or companies that are invested in ALS/MND? Will some of them potentially be moving their priorities over to COVID-19 and will that remove the ability for larger companies that have small starting ALS/MND programs, perhaps a Sanofi or a Pfizer, who are interested in ALS/MND? Could they be potentially shrinking away from their direction in this field?**

Biopharmaceuticals are one of the companies that are considered essential, so they are not closed and they're working very hard on COVID-19 but they're still very focused on ALS/MND. There's also a few ALS/MND companies, small companies, who have drugs that are of interest for ALS/MND that also their drugs might be of interest to COVID-19 because of the shared kind of inflammatory reaction and in a way that may actually help those small companies, as they also open studies of COVID-19, to get funding and partnerships. There is hope that this is not going to have a hit on companies interested in ALS/MND but it probably is too soon to really know the answer to that question.

In terms of smaller companies, to follow up on that, is there a good feeling that they would be able to weather this time given that some of them may have less funding to back them up if this were to go on for a while? Is it still an optimistic belief that they will be able to continue with things, such as a Revalesio or companies like that who are starting up trials?

We obviously don't know but hopefully if our governments all also do what they say they are doing to help small businesses it should keep all those companies afloat.

Super small companies, one molecule companies, may struggle, however a number of the companies that have entered into this field are large enough that they have opportunities in



COVID-19 as well as in ALS/MND, which actually allows their ALS/MND programs to keep going. So, I think that although it must be terrifying to think that all of the sudden these tremendous efforts we have in ALS/MND will be diverted, and there is some of that concern at a number of different levels, I think people should be reassured that there is still a tremendous interest and many companies are far enough along to weather this, to take advantage of the various governmental programs that are really about ensuring that companies don't collapse economically as a result of this pandemic. And so, although we may lose a couple, I truly believe that some will come through stronger in fact.

While there is optimism concerning the companies, there is less optimism about the capability for charities to raise enough funding for ALS/MND research. Much of it is based on events and of course most of these events have been cancelled. We hope this crisis will end soon but the longer it takes, it might have an effect on ALS/MND research, so probably after a few weeks we have to really think how we can raise funding again in a better way.

- 7. With regard to the delays in some diagnoses and the given situation, is it possible that this might reduce the eligible pool of trial participants for a while and does anyone think that this might actually cause a rethinking of some of the windows in which people are eligible for trials in the ones that would follow this time?**

In a general sense we are all going to become a lot smarter with our clinical trials and we've already heard that if there is any positives out of this COVID-19 situation it is the advances that we've seen in telehealth and support that were getting from national governments to look after patients in their homes. And with that we are also going to see much better ways to conduct trials, that don't require patients to come to the centres, so I think there will be more equity for patients to become enrolled. Separately we are seeing now that government agencies, including the FDA, are going to become more responsive and the whole process of getting medications through from trials and into the clinic is going to become more streamlined. So, I think these are the positives that I would see out of this terrible period.

Delay in diagnosis will not change the inclusion criteria right away because often criteria is based on the first symptom, not the diagnosis date. It's important for people to get diagnosed, so even in the time of COVID-19, having some of the centres that can see new patients is really important just for the care of patients, so that you don't have that delay.

The difference we are going to see is that we're all going to be ready to screen patients for trials as soon as we're allowed in our institutions. And so traditionally people are screened one a week, two a week, maybe less, one a month, but you will see that once different regions, different clinics, different hospitals are allowed to start recruiting patients to trials again you



will see a lot more activity all at once. I actually think that once this is over, except in very specific centres which Jonathan alluded to - that there are very much regional and even city to city differences - that in general you will see recruitment patterns similar to what happens when a site opens in Europe, where there are a lot of patients recruited very quickly. You will see that more globally, because it will be a situation where people will be aware of patients and patients will be screened as soon as the site is opened as opposed to the more traditional approach to screening and recruitment. If this goes on very long, it will affect recruitment. It really is a question of the timeline and how long it takes different centres to start screening for their clinical trials.

Inclusion and exclusion criteria for trials are based on statistical and scientific methods, and so the idea that we would loosen those inclusion/exclusion criteria I think is probably unlikely because it's very important for doing a good trial.

- 8. Another question is with regard to ongoing trials and the follow up that's being done and the adaptability that's happening. Is there any concern that there could be some potential pieces of follow up data that would prevent any pivotal trials from getting more definitive answers? Is there any concern that you have on those?**

Yes, there is a concern, we are losing data, but as you heard we are all doing our best to reduce the loss of data by virtual visits so we are relatively optimistic that the end result will not change much.

- 9. We've heard that research is moving forward, people are doing everything they can. What about someone at home that wants to know how a person effected by ALS, whether it's a caregiver, whether it's a friend, a family member, or an individual living with ALS, can be doing during this time to help encourage progress and research?**

If financial support is an option for someone, supporting your local foundations who are supporting research at this critical time where they can't do their in-person fundraising is key. I think calling your local clinics and seeing if there are things you can do there to maybe help other patients, ways to keep people, even if we are physically separated, socially connected would be another idea as well.