To introduce sleep smart, Smart is a randomized clinical trial assessing whether treatment of obstructive sleep apnea shortly after an acute ischemic stroke or high risk TE reduces the risk of cardiovascular events and improves functional outcomes representing sleep. Smart today are Doctor Devin Brown and Doctor Sherman. Dr Brown is a professor of neurology at University of Michigan Medical School Doctor Sherman,
who is also a professor for Alaji and a director of Sleep Medicine at University of Michigan Medical school.

Thank you very much for joining us today.

Thank you so much for the invitation and it’s really wonderful to be able to stop by for a visit and talk with you briefly about sleep smart.

As we already said, Ron Sherman is also on the line, and so I’m sure he’s happy to answer any of your most difficult questions will save those for him for at the end.

Sharon’s presentation was very heartwarming at and her house is...
also quite lovely compared to mine, so apologies for the background. And perhaps for the less heartwarming presentation. And so let’s start just by talking a little bit about why in the context of caring for a stroke patient, you would want to even care about obstructive sleep apnea. There are so many other things to consider to worry about to focus on. Why are we obsessed with obstructive sleep apnea, well, obstructive sleep apnea is very common post stroke.
It is approaching the prevalence of hypertension, so it’s up in the 70s.

So when you see a stroke patient, the chances of that person.

Obstructive sleep apnea are extremely common.

We know that obstructive sleep apnea is an independent risk factor for both incident stroke and recurrent stroke, and it’s also an independent risk factor for poor outcomes following ischemic stroke, including both functional and cognitive outcomes.

How does obstructive sleep apnea potentially cause stroke? How does it potentially cause...
poor outcomes after stroke?

Well, there are lots of different.

Sleep apnea causes elaboration of free radicals of khyle 6 E selected.

These things can promote Atherosclerosis.

It promotes deleterious cerebral hemodynamics and through multiple different mechanisms,

including platelet activation and increased EPO,

and decreased fibrinogen increases hypercoagulability and any of these three factors alone or in combination,

can increase the risk of
both incident and recurrent.

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Stroke and then following a
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little bit of a different pathway.
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Sleep apnea again through all
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of the different physiologic
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changes that it can cause.
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May end up producing angiogenesis,
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dendritic and axonal
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sprouting and synaptogenesis,
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and these factors can result
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in poorer stroke recovery.
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So,
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given that we have both of these two
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very important potential outcomes,
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recurrent stroke and stroke recovery,
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which should we target in a
trial looking at treatment of obstructive sleep apnea poststroke? Well, our approach was really that we wanted to have our cake and eat it too, and so this says you can’t have your cake and eat it too. That’s obviously being stated by somebody who doesn’t understand what you’re supposed to do with cake, so we took this approach that we wanted to. Test both of our hypotheses that CPAP could improve prevention and it could improve recovery and within sleep. Smart participants are enrolled as if it
is a single trial they’ve taken through.
The protocol is if it’s a single trial,
but then at the time of analysis,
which hopefully will come at some point in several years.
It then breaks down into really two separate trials,
each where all participants are contributing their data to the prevention outcome,
and those include both the high risk Tia.
Of which there are very few,
and the ischemic stroke patients,
and they have to be enrolled within 14 days of symptom onset.
But then to answer the recovery aim,
we use only a subset of
the enrolled participants. Those who had an ischemic stroke within seven days of consent, and those who also have to have had an NIH stroke scale of at least one at the time of enrollment, because, otherwise, how are you going to be able to note that there has been an improvement in their recovery? So the design of sleep smart is that it is a late phase multicenter trial. The control group is usual care, so it’s usual care. Plus automatically adjusting.
CPAP versus usual care alone.

We could have designed this to have an active control will not active control,

but a placebo control using sham CPAP and it’s something with which we have experienced.

But it really would have complicated our design substantially and the possibility of are using a run at night, which is a key part of our protocol design,

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we used a probe design where the outcome assessors are masked to randomization assignment and
then again as I said before, this is really a secondary prevention trial with an embedded recovery trial. This shows how a participant goes through the protocol. So after consent and baseline data collection, the first night is allocated to sleep apnea testing with an ox T3 sleep apnea device and then to have qualifying obstructive sleep apnea. The Respiratory Event index has to be at least 10 and half of those events cannot be no greater than half of them can be central events.
and then the person moves on to the second night where he or she.

Essentially gets a taste of C. Pap gets to try it out in the run and night, and if that subject uses C PAP for release cumulatively 4 hours during that night and also does not exceed 10 for the central apnea index read off of the device. So meaning therefore the person did not have treatment induced central sleep apnea and the participant is willing after that one night of exposure to see PAP to have a 50:50 chance of intervention versus control group, then that person.
Is eligible for randomization and receives again either automatically adjusting CPAP plus best medical therapy versus just best medical therapy alone and then we follow the subjects for three months for the recovery outcomes and then six months for the prevention outcomes. We were asked to cover a couple of different topics during this brief talk, and so I’m going to move on to enrollment criteria and how we we conceptualize those. And we’re going to try to highlight some of the questions that were asked of us. So the enrollment criteria really
We're trying to have a generalizable trial. We're trying to have a treatment that potentially can help the most number of participants. So there the inclusion criteria are really, very broad. If you've had an ischemic stroke or high risk TA in the prior 14 days in year, very broad. If you’ve had an ischemic stroke or high risk TA in the prior 14 days in year, at least 18, and you're asleep smart site, you're essentially eligible from the inclusion side of things we have. For what I'm going to describe is 4 categories of exclusion criteria. The first are really the general ones, so if you have somebody who's a...
00:07:41.504 --> 00:07:42.890 pregnant woman incarcerated and
00:07:42.890 --> 00:07:44.385 can’t sign our own consent,
00:07:44.390 --> 00:07:45.562 that somebody who you’re
00:07:45.562 --> 00:07:47.027 going to want to exclude,
00:07:47.030 --> 00:07:48.566 and if it’s somebody who could
00:07:48.566 --> 00:07:50.218 not perform all of his or her.
00:07:50.220 --> 00:07:51.864 Activities of daily living
00:07:51.864 --> 00:07:53.508 prior to the stroke.
00:07:53.510 --> 00:07:55.374 Then that’s also someone
00:07:55.374 --> 00:07:57.238 who would be excluded.
00:07:57.240 --> 00:07:59.060 The next category are the
00:07:59.060 --> 00:08:00.516 CPAP specific related issues.
00:08:00.520 --> 00:08:03.336 So if you are on currently on mechanical
00:08:03.336 --> 00:08:05.839 ventilation or if you have a tracheostomy,
00:08:05.840 --> 00:08:07.376 you’re not going to benefit from
00:08:07.376 --> 00:08:07.379
C P AP and so you’re excluded. And then if you’ve used C P AP in the last month, we have a concern that if your randomized so the control group you’re going to go home and use your P AP and therefore crossover, so you’re excluded for that as well. The third category are things that we think potentially could make CPAP riskier. It’s very low. Risk treatment, but there there are some factors that may increase risks and so those include things such as bullous lung disease, pneumothorax having hypo tension.
that’s so significant that you’re requiring pressers at that time.
If you’ve had massive epistaxis.
If you have a possible CSF leak or Numa cephalus,
or if you’ve had any kind of bone off procedure where the bone has not been replaced on the head,
then C Pap maybe a little bit more risky.
In those participants,
and therefore they are excluded.
We also have a category for the site P.
I feeling like there’s some other entity that increases the risk of C PAP and so we allow for of
course the judgment of the local teams to decide this is not a good idea for our patient.

And then the 4th category really is something that makes it really unfeasible. For instance, if the participant or if the sort of the patient is using oxygen supplementations greater than four liters per minute, you can’t believe. That into our CPAP machines, and therefore it’s really unfeasible and then if that person is on some type of precautions, contact precaution, respiratory precautions, we don’t want to cross contaminate.
00:09:39.641 --> 00:09:41.636 with our equipment and infect

00:09:41.636 --> 00:09:43.631 another participant so it really

00:09:43.697 --> 00:09:44.919 becomes unfeasible.

00:09:44.920 --> 00:09:46.820 Switching gears a little bit,

00:09:46.820 --> 00:09:49.158 we were asked to talk a little

00:09:49.158 --> 00:09:51.033 bit about the stroke physicians

00:09:51.033 --> 00:09:53.038 versus the sleep positions and

00:09:53.038 --> 00:09:55.140 how those interactions occur.

00:09:55.140 --> 00:09:58.857 We’ve had some comments from potential

00:09:58.857 --> 00:10:01.496 sites where they have said is CPAP

00:10:01.496 --> 00:10:03.669 So I’m concerned that if my person

00:10:03.670 --> 00:10:05.252 if my patient is enrolled and then

00:10:05.252 --> 00:10:07.245 randomize the intervention group,

00:10:07.245 --> 00:10:11.034 that CPAP could potentially cause harm
that is most commonly said by a sleep.

I started a stroke.

Position if it is,

if it said and on the flip side,

there are some sites where they’ll

come back to us and say how

can you withhold CPAP after you

know that the patient has been

diagnosed with obstructive sleep

apnea by randomizing that person

to the control group that is more

to the control group that is more

commonly said by a sleep physician.

And so overall,

we really feel that we are in a

we really feel that we are in a

position of clinical equipoised with

CPAP for stroke patients.
We don’t know whether CPAP will help harm or essentially do neither for our stroke patients. There have been no definitive randomized controlled trials for stroke outcomes that have shown anything is improved by CPAP. So we feel comfortable with holding it from the control group, and there’s precedence for this. There have been numerous randomized controlled trials that have enrolled either patients with cardiovascular disease, such as Save Rick Ads or SIRKAS.
or that have enrolled lots of participants with severe sleep apnea, such as apples where patients are randomized to a control group or, in the case of apples, to a sham control. So other investigative teams, other funding agencies, other peer review panels have found this to be completely ethical and not have any concern. There’s also the 2017 U.S Preventive Taskforce report that helped inform our decision making at the time that we were designing sleep smart and proposing it for the first time that states that
there is no established benefit of C PAP for any health outcome. This is just. In the general population, not even specific to stroke aside from the modest improvement in sleep related quality of life, and the more recent U. S preventive taskforce doesn’t say anything that would compel us not to randomize participants to a control group. We were also asked to talk a little bit about crossover so crossovers where you have a control person who’s randomized to the control.
00:12:19.334 --> 00:12:21.402 group who then wants to use CPAP.
NOTE Confidence: 0.907452343636363

00:12:21.402 --> 00:12:23.110 So when that does occur and it’s
NOTE Confidence: 0.907452343636363

00:12:23.174 --> 00:12:24.714 not something that we thought
NOTE Confidence: 0.907452343636363

00:12:24.714 --> 00:12:25.946 would be very common.
NOTE Confidence: 0.907452343636363

00:12:25.950 --> 00:12:27.755 Based on our preliminary work
NOTE Confidence: 0.907452343636363

00:12:27.755 --> 00:12:30.110 and based on prior CPAP trials,
NOTE Confidence: 0.907452343636363

00:12:30.110 --> 00:12:32.462 pilot trials among stroke
NOTE Confidence: 0.907452343636363

00:12:32.462 --> 00:12:34.482 patients if that does occur,
NOTE Confidence: 0.907452343636363

00:12:34.482 --> 00:12:36.630 then the clinical team should absolutely
NOTE Confidence: 0.907452343636363

00:12:36.691 --> 00:12:38.767 feel free to refer the participant
NOTE Confidence: 0.907452343636363

00:12:38.767 --> 00:12:40.809 for sleep apnea testing for sleep.
NOTE Confidence: 0.907452343636363

00:12:40.810 --> 00:12:43.258 Get me a treatment in the clinical realm,
NOTE Confidence: 0.907452343636363

00:12:43.260 --> 00:12:45.332 it usually takes some time for that
NOTE Confidence: 0.907452343636363

00:12:45.332 --> 00:12:47.389 to be available to the participant,
NOTE Confidence: 0.907452343636363

00:12:47.390 --> 00:12:49.890 so it may actually.
NOTE Confidence: 0.863257626

00:12:49.890 --> 00:12:52.046 Push the see PAP treatment for clinical
00:12:52.046 --> 00:12:54.486 care outside of the even six month window.

00:12:54.490 --> 00:12:56.436 By the time the person is able

00:12:56.436 --> 00:12:58.055 to get tested and treated and

00:12:58.055 --> 00:13:00.369 have a C Pap in his or her home,

00:13:00.370 --> 00:13:02.904 but the research team, we would suggest

00:13:02.904 --> 00:13:04.850 not help facilitate that process.

00:13:04.850 --> 00:13:06.999 It is a protocol violation for a

00:13:06.999 --> 00:13:08.449 control participant to start using

00:13:08.449 --> 00:13:10.321 C PAP so it has to be reported

00:13:10.385 --> 00:13:11.945 as such and in the analysis,

00:13:11.950 --> 00:13:13.812 at least in the intent to treat

00:13:13.812 --> 00:13:15.779 component which is our primary analysis.

00:13:15.780 --> 00:13:17.760 The control participant who starts

00:13:17.760 --> 00:13:20.480 using C PAP will be analyzed.

00:13:20.480 --> 00:13:23.288 As a control participant.
Crossovers from control.

NOTE Confidence: 0.863257626

Two intervention or to to CPAP use

NOTE Confidence: 0.863257626

have been very uncommon in in sleep

NOTE Confidence: 0.863257626

smart so far it’s been around 2%.

NOTE Confidence: 0.962847176

So what about anticipated challenges?

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Well, we knew that recruitment

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would be an issue.

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Recruitment is an issue for every

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randomized controlled trial.

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CPAP adherence is an issue

NOTE Confidence: 0.962847176

for every CPAP related trial,

NOTE Confidence: 0.962847176

but some of the things that we did

NOTE Confidence: 0.962847176

not anticipate having difficulty

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with included a global pandemic.

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We did not presage that,

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and having difficulty achieving
in window outcome assessments

Then we had anticipated we have

more missing data at the three

TIMEPOINT for the modified

Rankin which is our primary for

that aim than we had anticipated.

We did try in the design of sleep smart

to prepare for some of these challenges.

So for instance we built in telephone

outcome assessments from the onset

that was always allowable and sleep

smart even pre COVID and most of our

outcomes can be assessed by telephone.

There are only a few secondary outcomes.
Exploratory outcomes that cannot, but most of them can. We really tried to be very careful and intentional about the selection of our outcome assessments to make them as short as possible and when possible, to allow something to be conducted by phone. We also created a lot of tools for site teams to be able to reach out to participants in case there were any issues trying to achieve outcome assessments. So we built in a place in the back of the consent form. For instance, where lots of contact information, alternative contact information
for the subject, alternative contact information for partners, friends, family members could be documented and then referred to. We created several letter templates for sites to use to reach out to subjects about scheduled appointments. Missed appointments unable to reach those types of things we’ve developed. A slide set that sites can use to help educate teams. Clinical teams, including nurses about sleep smart and we created a document.
that provides our sort of answers to potential difficult patient questions at the time of enrollment, and we also of course built in Tele Med telemedicine approach to outpatient. Management of CPAP, which in COVID has been very advantageous. But despite the challenges, there remain lots of hope. There’s hope because the of the vaccine, which hopefully will assist teams and getting back to their usual state when it comes to coordinator coverage. Respiratory therapy support, but mostly our hope comes from
our sites and the sites have been doing a fantastic job despite the pandemic in the face of a pandemic, we are really grateful to every site. There are some sites, as you see who are randomized. In the 50s and the 60s, number of participants, which is fantastic. I would like to give a little shout out to two of your sites. North Shore with 16 and Yale with nine Randomizations. We’re very grateful to you for all of your work.
You also have Hartford and Staten Island, and we are grateful for those sites as well.

And then just looking at by RCC and you see that some are CC’s are just going gangbusters. Some are not participating in sleep smart that is very few of them. And then I’ve outlined Yale doing very well here somewhere in the middle.

And so I thank you very much for again, the invitation and for your attention. And again, Ron is is available to answer any difficult question that you have. Thank you very much for that Devin.

Uhm, I just had a question about a trial powering.
Whether it was parked for both the cardiovascular events as well as the recovery outcomes.

Yeah, no, that's a good question. So we did look at power calculations for both and we anticipate that a certain percentage of the total will be available for the recovery outcome. And it turns out that we are we have a higher proportion than we had anticipated, so we think that those two are kind of going to ride along together and by the end we should have a sufficient number in both groups. Fantastic in such an innovative approach.
innovative trial design. Thank you.

Alright, I think those are the questions.

Well, thank you so much for joy.