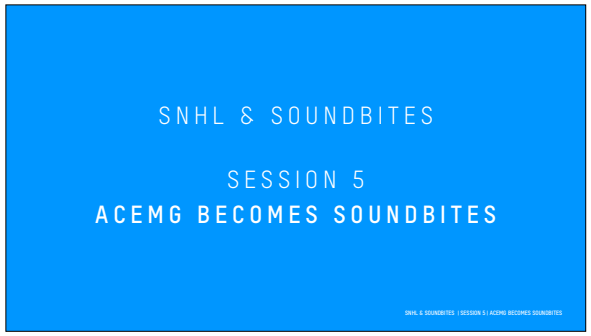

1

Hi, and welcome to Session 5, ACEMg becomes Soundbites. This session covers two topics.

2

First, I'll review the translational medical research process

---

3

Then I'll explain ACEMg's sixteen-year journey through it. If you've watched the previous videos you know how the story ends: ACEMg became known as Soundbites, clinically proven to preserve or improve hearing.

4

Let’s start by outlining the translational medical research process

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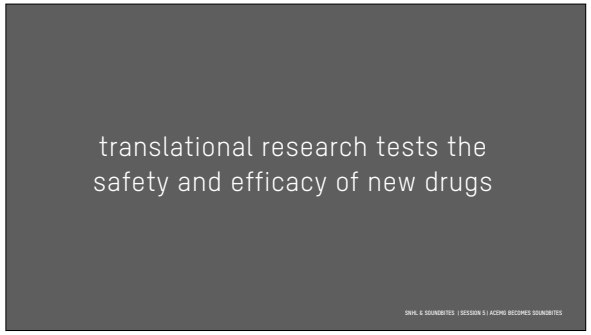
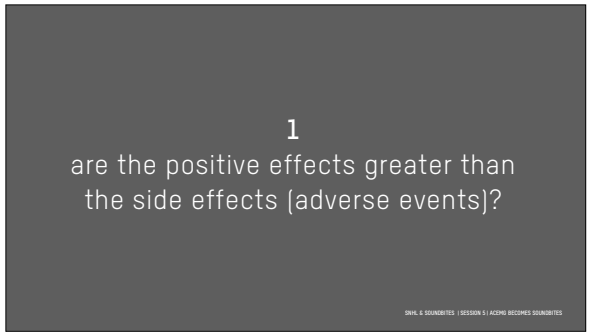


5

The goal of translational medical research is to test the safety and efficacy of new drugs.

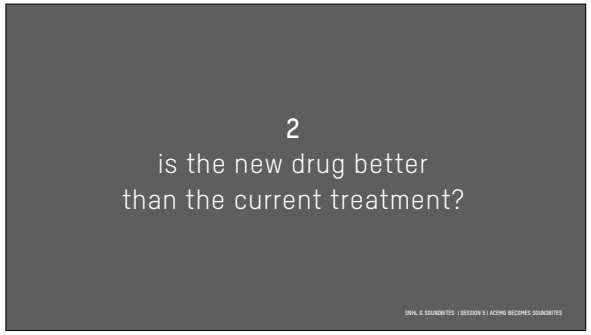
6

In the U.S., the process is overseen by the Drug division of the Food and Drug Administration. The European Medicines Agency does this for Europe.



7

The process has two tests. The first test must prove that the new drug's positive effects outweigh its harmful effects, called side effects or adverse events.



8

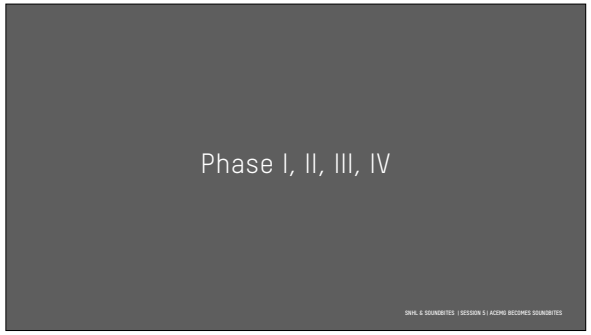
If a drug candidate passes that test, the second test answers the question, "Is the new drug better than the current treatment?"

9

If the clinical data says yes, the FDA authorizes the new drug to be prescribed to patients by licensed medical professionals who must monitor its efficacy and side effects.

10

Most people know translational research by its terms Phase I, Phase II and especially Phase III, the final clinical trial phase in humans.



11

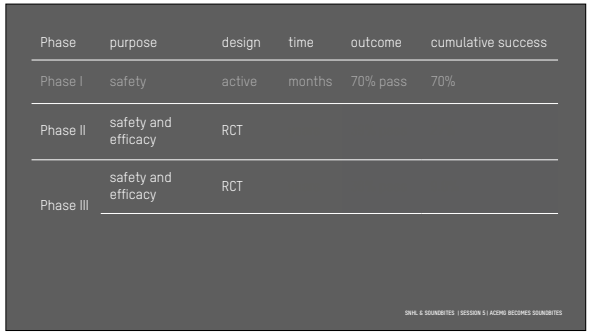
Phase IV studies follow people after a treatment is approved to gather more data about long-term benefits or side effects that may not have surfaced during Phase III trials. The data help physicians prescribing the drug and patients receiving it.

12

The process starts with Phase I safety trials conducted on small numbers of patients to determine dose range, aiming for the highest dose that doesn’t produce unacceptable side effects.

13

About 70% of new drug candidates survive Phase I. About 30% fail, mainly because their toxicity can't be moderated. By the way, all the numbers I'm sharing are aggregated approximations of historical data.

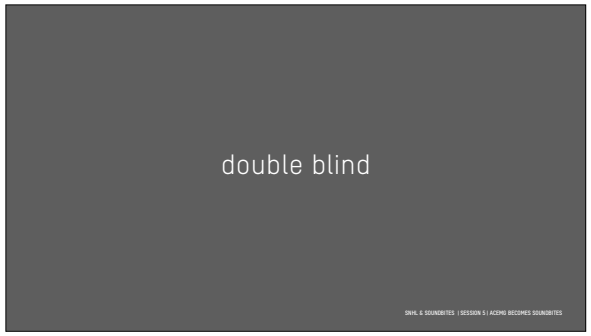


14

Surviving drug candidates proceed to Phase II and III to random control trials, or RCT to test whether the new drug is better than the current treatments.

15

In RCTs, people with the disease get either the new drug or a harmless placebo, the no-treatment control.

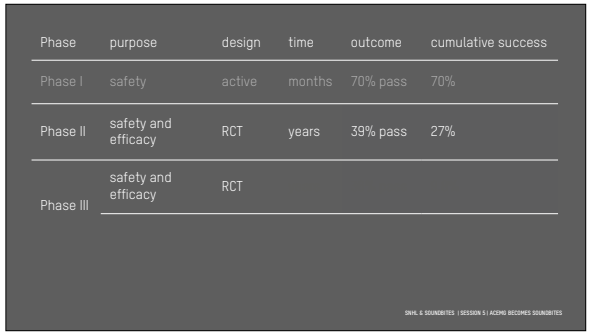


16

RCTs are double blind, meaning neither the people conducting the trial or the patients know who gets what. The drug and placebo are made to seem identical. The odds of getting the treatment are 50/50.

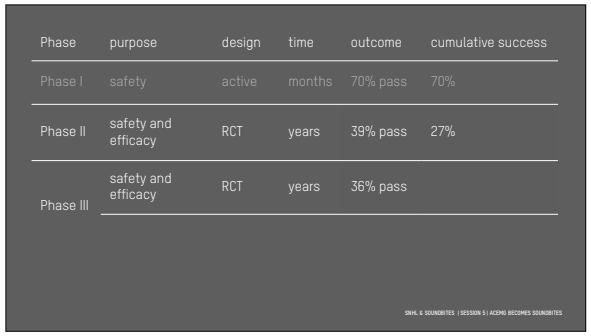
17

The benefit among treated patients compared with untreated patients is expressed as efficacy. Efficacy is weighed against side effects and is debated in the approval process. For example, the Alzheimer's drug Aduhelm was approved under protest and ultimately withdrawn from the market.



18

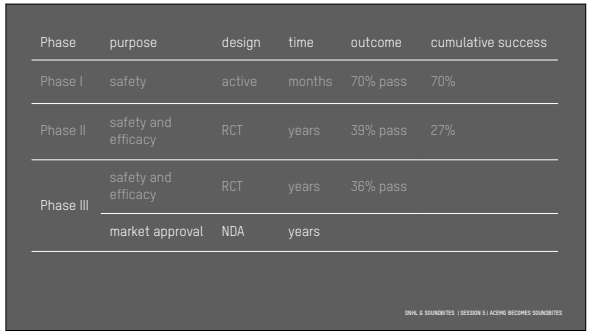
RCT trials take years. Phase II trials are conducted on small groups of patients typically a few hundred. Historically, about 40% of drug candidates pass Phase II, so less than 30% of new drugs go on to Phase III.



Phase	purpose	design	time	outcome	cumulative success
Phase I	safety	active	months	70% pass	70%
Phase II	safety and efficacy	RCT	years	39% pass	27%
Phase III	safety and efficacy	RCT	years	36% pass	

19

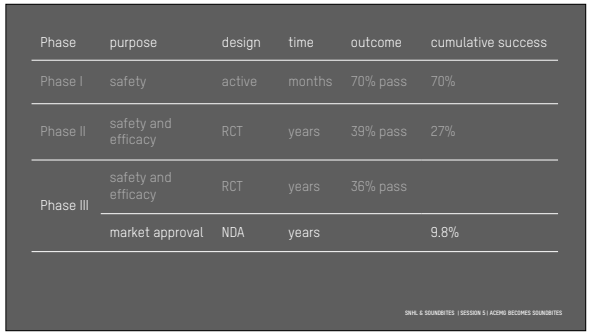
Phase III RCT studies are typically conducted on thousands of patients.



Phase	purpose	design	time	outcome	cumulative success
Phase I	safety	active	months	70% pass	70%
Phase II	safety and efficacy	RCT	years	39% pass	27%
Phase III	safety and efficacy	RCT	years	36% pass	
	market approval	NDA	years		

20

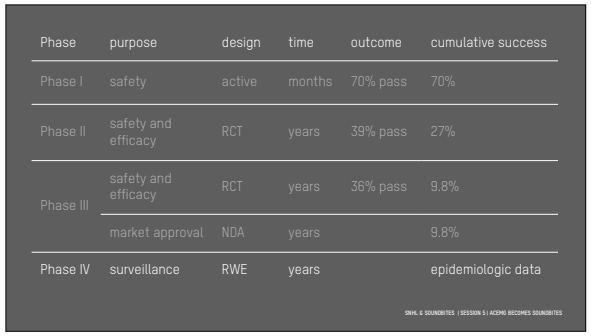
Drug candidates that survive Phase III file an FDA New Drug Application. Review can take several years.



Phase	purpose	design	time	outcome	cumulative success
Phase I	safety	active	months	70% pass	70%
Phase II	safety and efficacy	RCT	years	39% pass	27%
Phase III	safety and efficacy	RCT	years	36% pass	
	market approval	NDA	years		9.8%

21

In the the end, fewer than 10% of new drug candidates survive translational research to become approved prescription drugs.

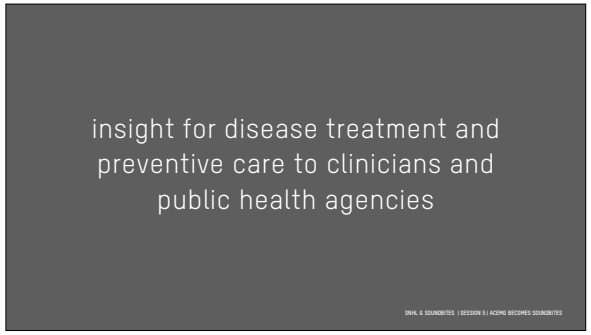


Phase	purpose	design	time	outcome	cumulative success
Phase I	safety	active	months	70% pass	70%
Phase II	safety and efficacy	RCT	years	39% pass	27%
Phase III	safety and efficacy	RCT	years	36% pass	9.8%
	market approval	NDA	years		9.8%
Phase IV	surveillance	RWE	years		epidemiologic data

SNHL & SOUNDBITES | SESSION 5 | ACEMG BECOMES SOUNDBITES

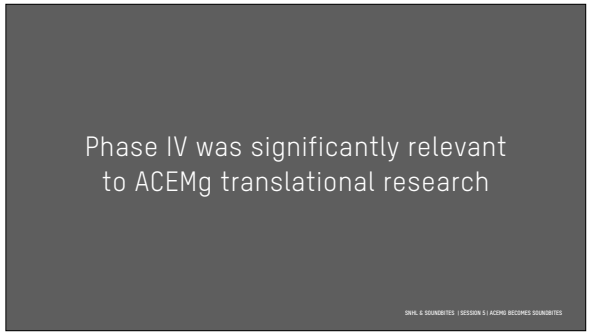
22

I said earlier that Phase IV surveillance studies, called real-world evidence or RWE studies, are long-term studies that gather real-world data about long-term benefits or side effects from people taking the medication that may not have surfaced during Phase III trials.



23

Real-world data from real-world evidence studies offers insight for disease treatment and preventive care to clinicians and public health agencies.

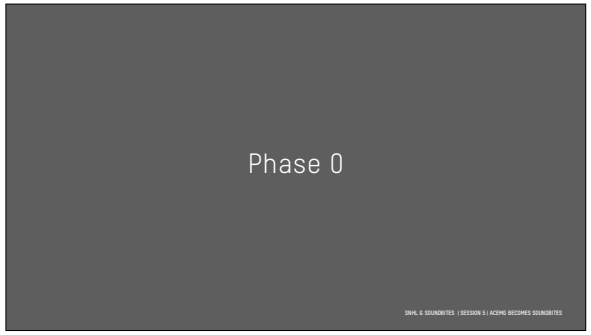


24

As we’ve seen, Phase IV real-world evidence became significantly relevant to ACEMg translational research.

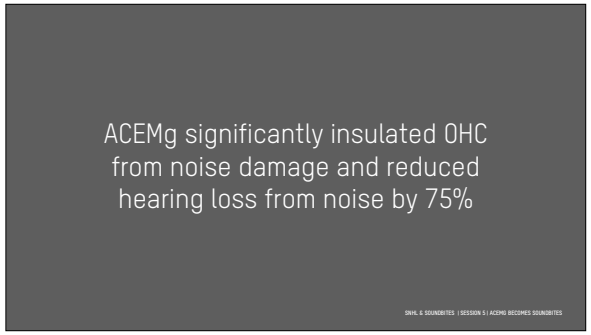
25

Now let's look at ACEMg's journey through translational medical research.



26

Successful lab research is the gating step to translational research.



27

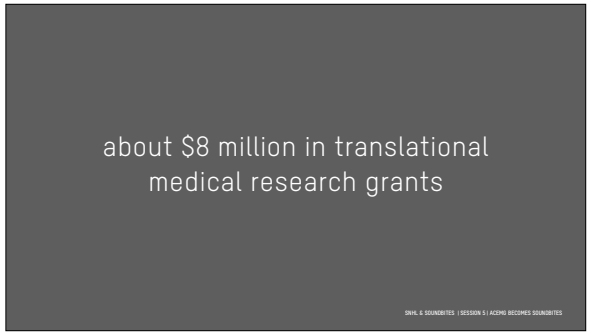
The 2007 ACEMg lab findings are an example. Peer-reviewed data from lab studies confirmed ACEMg significantly insulated outer hair cells from noise damage and reduced hearing loss from noise by 75%.

28

The next step was to collect statistically significant clinical data from translational medical research. We decided to pursue translational research because we believed RCT studies would deliver the data we were after.

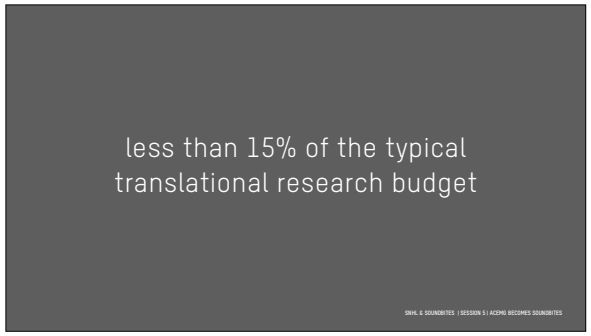
29

We believed ACEMg was a good candidate for government grants to support those costs, and we were right about that.



30

ACEMg received about $8 million in translational medical research grants from the U.S. NIH and the European government.

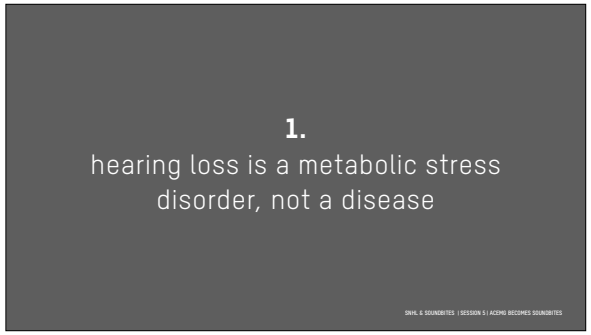


31

But the the process typically costs about $55 million, so we had less than 15% of the budget we needed.

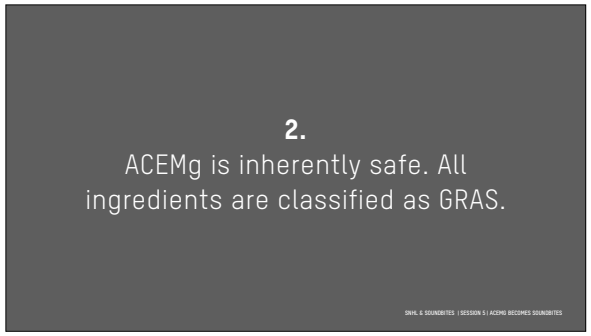
32

Moreover, translational medical research isn't required for safe biomedicines like ACEMg for two reasons.



33

First, hearing loss is a metabolic stress disorder, not a disease. ACEMg was designed to maintain or help improve the normal structure or function of the human body.

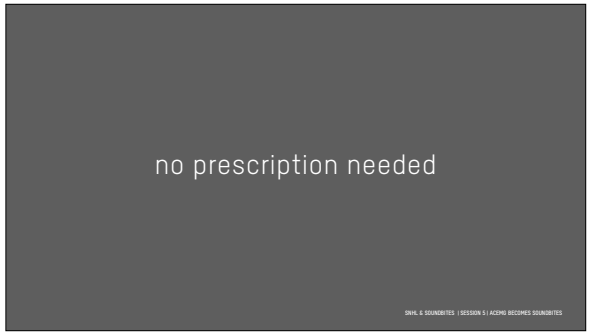


34

Second, ACEMg is inherently safe. all the ingredients in ACEMg are classified as Generally Regarded as Safe by the FDA and the U.S. Pharmacopoeia.

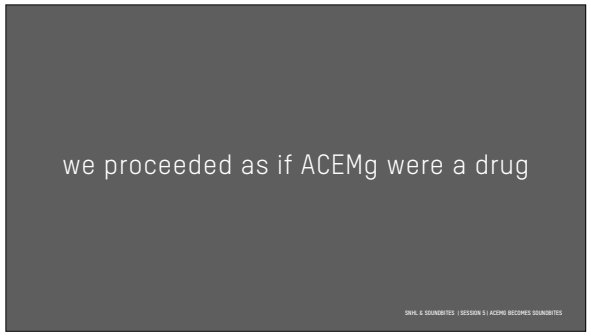
35

Presuming we could make the ACEMg formula into a product for RCT studies and demonstrate it's effectiveness, ACEMg would be regulated as a dietary supplement the food division of the FDA.



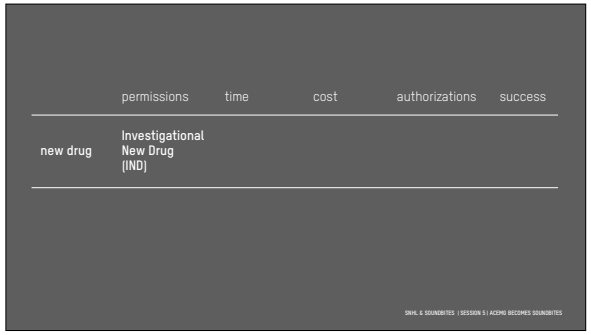
36

ACEMg would be available to the general public without a prescription.



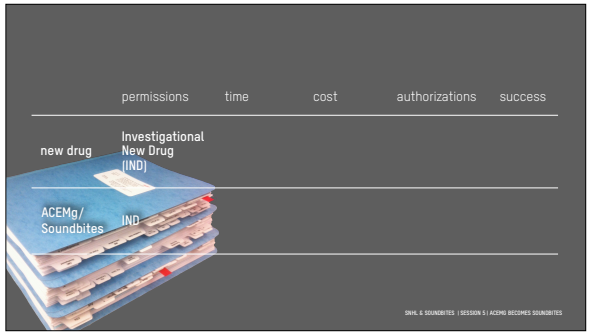
37

Nevertheless, we proceeded as if ACEMg were a drug.



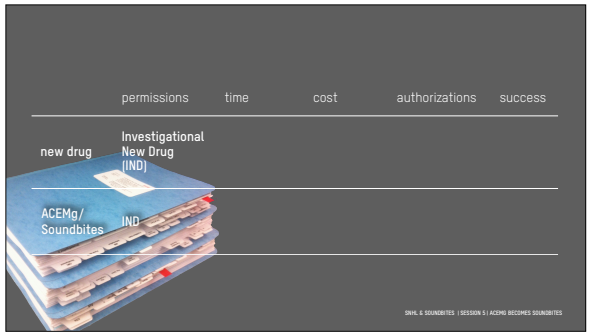
38

An Investigational New Drug application is required before starting of translational research. The application describes the research plan and the drug in great detail.



39

The ACEMg IND was 600 pages, compiled with assistance from the University of Michigan Institute for Clinical and Health Research, or MICHR, submitted to the FDA in hard copy and pdf.



40

IND regulations mandate pharmaceutical quality manufacturing, described in the IND section called Chemistry, Manufacturing and Controls, or CMC. IND regulations require pharmaceutical quality manufacturing for the active administered to the treatment group and for the identical placebo administered to the control group.

41

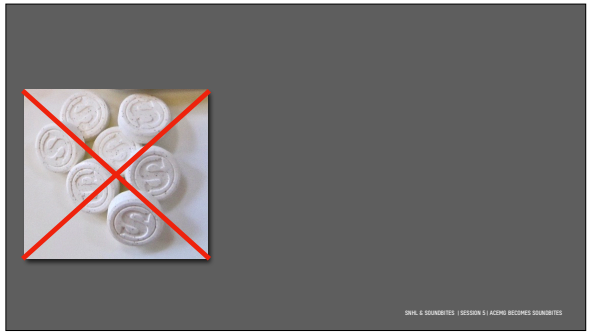
Here’s how we made ACEMg into a product

42

Even though it wasn’t required by the FDA, Soundbites committed to making a pharmaceutical grade product in compliance with current good manufacturing practices, or cGMP, partnering with Patheon Pharmaceuticals for its development and manufacturing.

43

The first format was a chewable mint, produced by Patheon Pharmaceuticals in Cincinnati, Ohio. Think Altoids for your ears. The mints inspired the Soundbites name, which stuck.



44

But the mints failed as a medicinal product.

45

Next, Patheon in France tried a sachet, which is a powder mixed into liquid.

46

That format was abandoned because the active didn’t mix very well, and it wasn’t possible to formulate an identical placebo.

47

Liquid was next, developed by Patheon in England. Think a 2-ounce energy drink for your ears.

48

The formulation technology wasn’t sufficiently advanced to achieve reasonable shelf life with guaranteed stability at room temperature, but that technology now exists, and we are developing Soundbites Shots, a 2-ounce energy drink for music professionals and fans who attend loud live events.

49

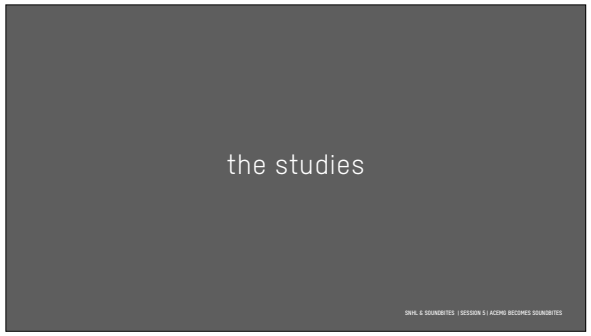
Finally, Patheon Netherlands succeeded with softgel capsules and an identical placebo.

50

The softgels ticked all the boxes. Convenient. Affordable. Easy to swallow. Identical placebo. The Soundbites softgels you can buy today are the same as used in clinical research.

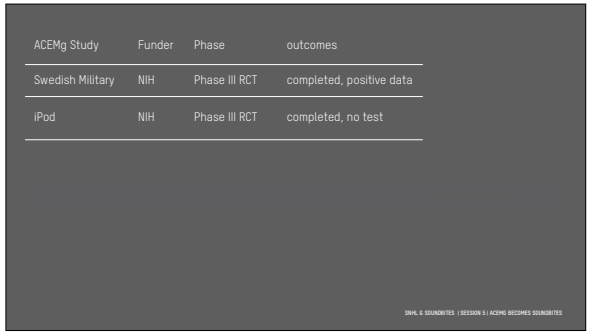
51

That accomplishment required filing a second IND with the Federal Institute for Drugs and Medical Devices, the German medical regulatory body, because our final RCT was conducted at the Hannover Medical School, funded by the European grant.



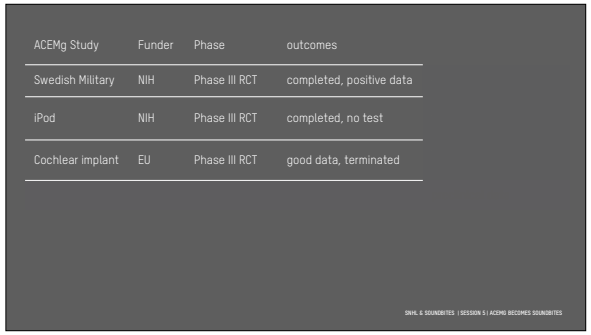
52

Next, I'll summarize the translational research studies



53

The Swedish Military Study and the iPod study at the University of Florida funded by the NIH were designed to test ACEMg to prevent acute, short-term hearing loss from noise. But it is unethical to expose all subjects in a study to a known harm and only treat half of them, so noise exposure was controlled. Despite that, the Swedish Military Study returned some promising data. The iPod study was a no test, no there was no meaningful statistical difference in the data between the control and treated groups.



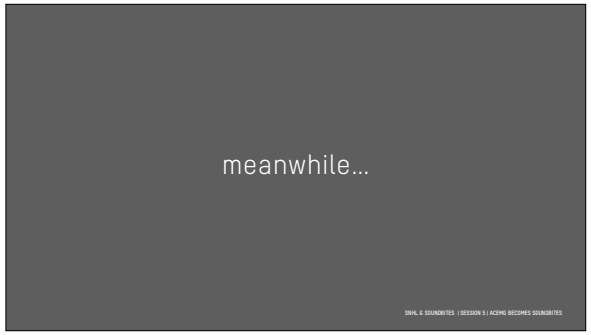
54

The cochlear implant study at the Hannover Medical School in Germany also focused on addressing acute trauma, this time surgical trauma associated with inserting electrodes into the cochleas of patients receiving cochlear implants. These patients were already functionally deaf. The study's aim was to assess the potential that pre-treatment with ACEMg could help the few remaining hair cells survive the trauma. It did. Patients receiving ACEMg recovered about 8 dB of OHC auditory function. However, the trial suffered clinical investigator mismanagement of patient recruiting. The trial was terminated with about 17% of patients

recruited.

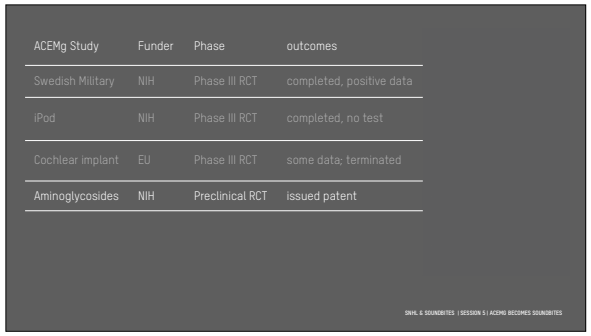
55

Eight years of ACEMg RCT studies didn’t produce sufficient clinical data for adequate analysis.



56

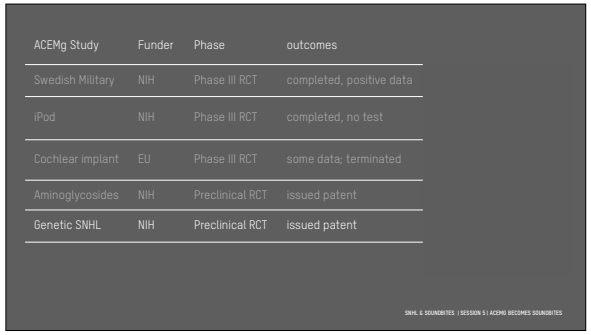
Meanwhile, ongoing lab research had yielded new insights.



ACEMg Study	Funder	Phase	outcomes
Swedish Military	NIH	Phase III RCT	completed, positive data
iPod	NIH	Phase III RCT	completed, no test
Cochlear implant	EU	Phase III RCT	some data; terminated
Aminoglycosides	NIH	Preclinical RCT	issued patent

57

A University of Michigan study demonstrated ACEMg mitigated SNHL from aminoglycoside antibiotics, a class of drugs used to treat gram-negative bacterial infections that upregulates free radicals as a side effect.



ACEMg Study	Funder	Phase	outcomes
Swedish Military	NIH	Phase III RCT	completed, positive data
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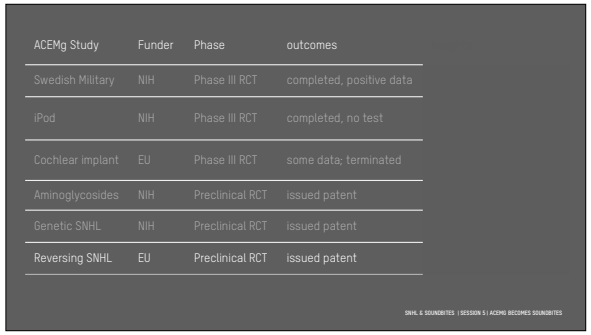
Cochlear implant	EU	Phase III RCT	some data; terminated
Aminoglycosides	NIH	Preclinical RCT	issued patent
Genetic SNHL	NIH	Preclinical RCT	issued patent

58

Another University of Michigan study demonstrated ACEMg mitigated SNHL from genetic mutations that account for the majority of hearing loss in children.



ACEMg Study	Funder	Phase	outcomes
Swedish Military	NIH	Phase III RCT	completed, positive data
iPod	NIH	Phase III RCT	completed, no test
Cochlear implant	EU	Phase III RCT	some data; terminated
Aminoglycosides	NIH	Preclinical RCT	issued patent
Genetic SNHL	NIH	Preclinical RCT	issued patent
Reversing SNHL	EU	Preclinical RCT	issued patent

59

Important basic research at a university in Spain demonstrated ACEMg mitigates the apoptotic action of proteins regulating apoptosis, programmed cell death, helping explain the findings from the ACEMg real-world study.

60

All was not lost. My daughter gave me a change purse with the motto that defines persistence.

---

four insights helped define
the research we needed

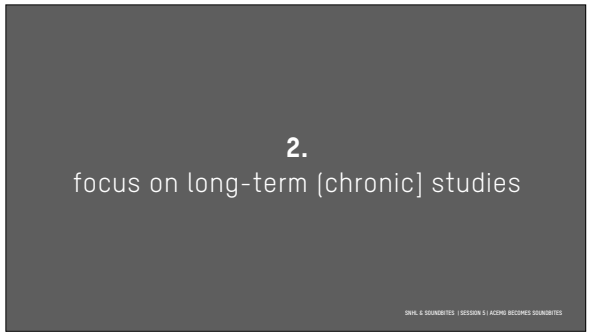
61

We had gained four insights that helped define the research we needed to reach our goal of making ACEMg available to anyone who wanted it, backed by statistically significant clinical data.

1.
avoid short-term (acute) studies

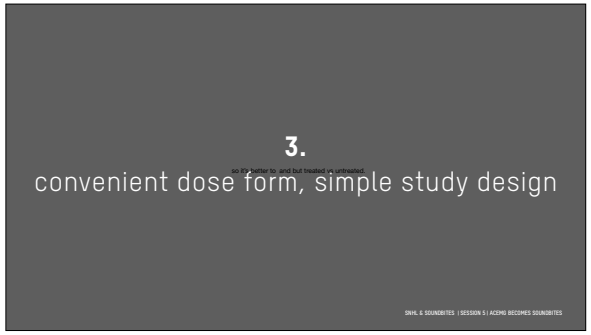
62

First, we learned to avoid short-term studies of acute noise exposure mainly because it’s medically unethical to purposefully expose humans to damagingly high levels of noise and only treat half of them.



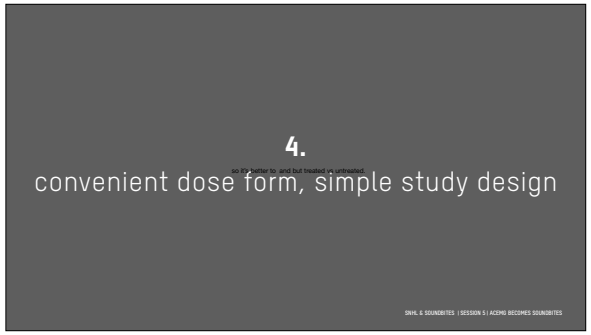
63

Second, persistent noise exposure is commonly understood to be an important contributor to progressive hearing loss, but the variety and conditions of exposure are vast. Instead of RCT, it's better to focus on uncontrolled long-term clinical surveillance studies comparing treated and untreated patients.



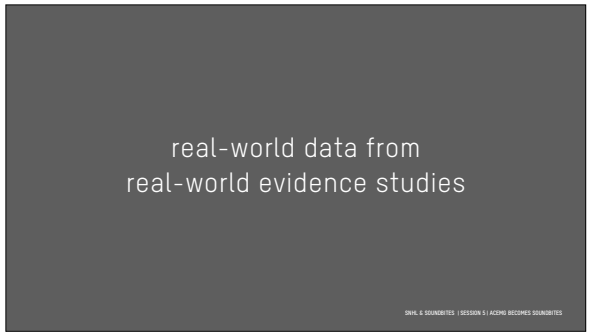
64

Third, the ACEMg intervention must be administered in a convenient format and the clinical study design for clinicians and patients must be simple and easy to follow.



65

Fourth, the scope of real-world evidence research to include a broader range of SNHL etiologies, and include children, which would require a special dose form, which we knew how to do.

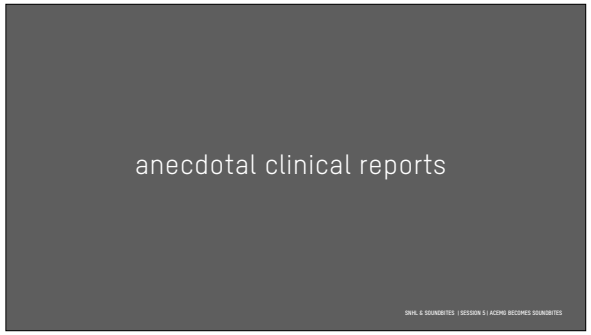


66

Everything we learned convinced us that we needed to collect real world evidence data in Phase IV real-world evidence real-world data studies. The fact that ACEMg could be purchased without a prescription made these studies possible.

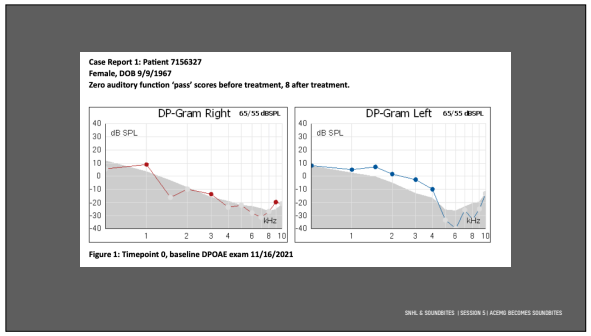
67

You know from the previous sessions that the ACEMg project moved back to Ann Arbor, Michigan and limited direct distribution of Soundbites started in late 2019.



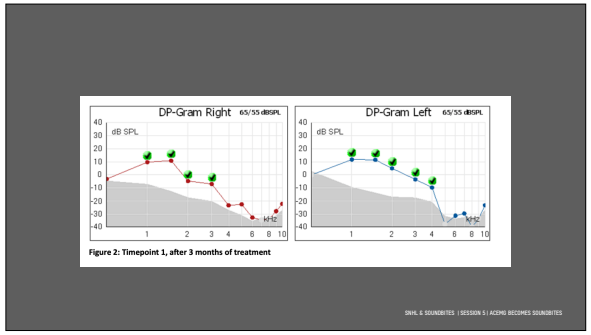
68

Chicago-area audiologist Dr. Lori Halvorson ordered Soundbites, urged her patients to start using it, and started sharing data from otoacoustic emissions examinations demonstrating consistent objective improvement in inner ear function. Let me show you de-identified data from one patient.



69

This is the patient's initial OAE examination data from both ears before starting Soundbites. Frequency responses go from low to high, left to right.



70

This is the same patient at the three-month timepoint. Hearing cells that didn't register as functional on initial OAE exams were coming back to life in subsequent exams, noted by green checkmarks on the OAE test monitor. This isn't supposed to be possible, and it was happening consistently and with several patients. The findings led to the formal study that yielded statistically significant real-world data.

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The next step is a scale-free study using OAE examinations to generate a larger dataset for ongoing analysis and reporting to clinicians and public health agencies.

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You can stay updated about that on keephearing.org.

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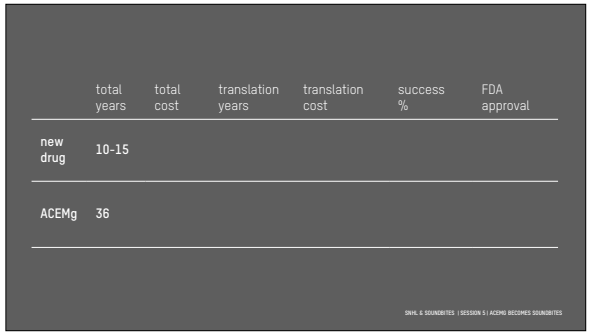
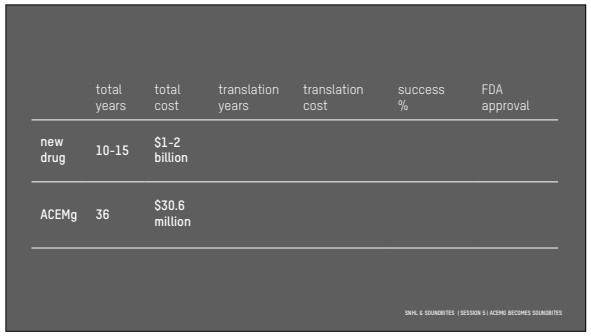
I’d like to conclude by comparing the ACEMg project with drug discovery and development.



74

Drug discovery and development typically takes 10 to 15 years. It took ACEMg 36 years.



	total years	total cost	translation years	translation cost	success %	FDA approval
new drug	10-15	$1-2 billion				
ACEMg	36	$30.6 million				

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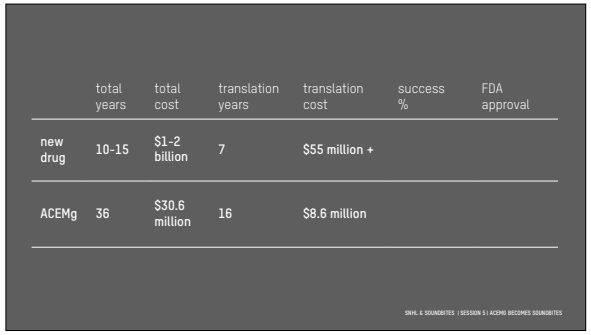
Drug discovery and development typically costs between 1 and 2 billion dollars. ACEMg total costs were about $30.6 million, about 1.5 to 3% of the cost for a new drug.



	total years	total cost	translation years	translation cost	success %	FDA approval
new drug	10-15	$1-2 billion	7	$55 million +		
ACEMg	36	$30.6 million	16	$8.6 million		

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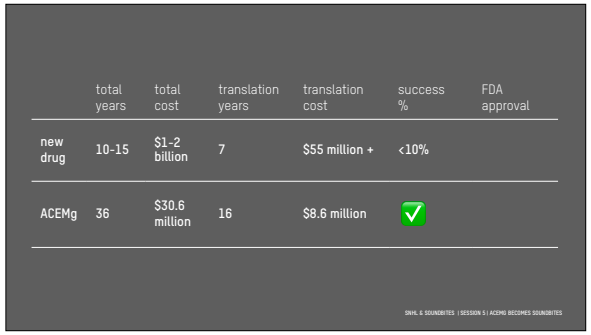
Pharmaceutical translational research typically takes about 7 years and costs about 55 million dollars. It took ACEMg a total of 16 years, more than twice as long as for a new drug, but cost about 8.6 million dollars, about six times less than drug translational research.



	total years	total cost	translation years	translation cost	success %	FDA approval
new drug	10-15	$1-2 billion	7	$55 million +	<10%	
ACEMg	36	$30.6 million	16	$8.6 million	✅	

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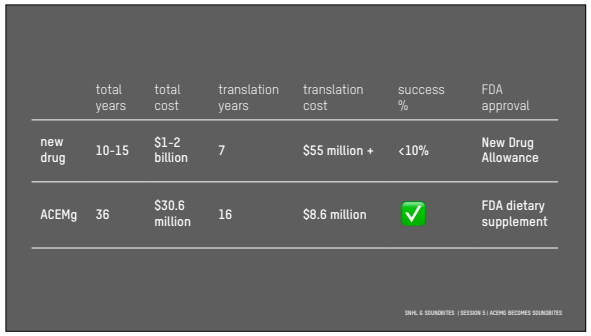
The odds of success for a new drug are a little less than 10%. ACEMg is the first hearing preservation therapeutic we're aware of that has attained the clinical validation milestone.



	total years	total cost	translation years	translation cost	success %	FDA approval
new drug	10-15	$1-2 billion	7	$55 million +	<10%	New Drug Allowance
ACEMg	36	$30.6 million	16	$8.6 million	✅	FDA dietary supplement

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Approved drugs receive a ten-digit National Drug Code enabling prescriptions. ACEMg – Soundbites – is pre-approved for sale to the general public without a prescription.

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Thank you for completing the course!
