Role of Naloxone in Opioid Overdose Fatality Prevention

Thursday, April 12, 2012
8:30 a.m. to 5:30 p.m.

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Welcome and Opening Remarks

DR. LURIE: Good morning, everybody. My name is Peter Lurie. I'm a senior advisor here in the Office of Policy and Planning here at FDA, the Office of the Commissioner. And I'm pleased to welcome you this morning to our meeting on the Role of Naloxone in Opioid Overdose Fatality Prevention.

We put on a lot of meetings here at FDA. I think this one is cut from a different cloth. And I think for all of us, it is a very exciting opportunity for us to engage in conversation with you about this interesting and important topic.

This meeting is put on collectively by the FDA, by the National Institute of Drug Abuse, by the Centers for Disease Control and Prevention, and by the Office of the Assistant Secretary for Health in the Department of Health and Human Services.

The problem before us, as everybody in this audience knows, is an enormous one. We have enormous increase in the use of opioid analgesics,
about 20 percent, in the last decade or so. Opioid analgesic deaths have risen along with this. Prescription drug overdose deaths have increased about threefold since 1999. And ever since 2003, the number of overdose deaths from opioid analgesics have actually exceeded the number of such deaths from cocaine and heroin combined, a fact that I think a lot of people in the public don't fully appreciate. So we're really dealing with a huge problem here, and the question is: what can be done about it?

You'll hear a lot about a number of efforts that have been taken on by people in the federal government and elsewhere to address the problem of prescription overdose deaths. But today our focus is simply on one of those things, and that is naloxone.

As I think everybody in this room knows, and you will hear I'm sure in greater detail, naloxone is an opioid receptor antagonist, which is currently approved for use by injection only for the reversal of opioid depression, for the
diagnosis of opioid overdose, and for adjunct use in the treatment of septic shock.

Currently, it's only being used by trained medical professionals, primarily in the emergency rooms and in ambulances. But the question before us is might there be potential new patient groups that might be brought. And, of course, there are a lot of important programs that are in place and a number of programs across the country that have pushed in this direction, including described in a recent MMWR article about which we're sure to hear.

So the question is, what can be done to further the use of this product, if appropriate, among illicit drug users and for those who are on long-term narcotics, for example, those with chronic cancer pain.

To put this in context, I just want to point to a couple of things. One is on the international level. I want to point to the UN Commission on Narcotic Drugs, which in 2012 released the following statement: the Commission "encourages all member states to include effective elements for the
prevention and treatment of drug overdose, in particular opioid overdose, in national drug policies where appropriate, and to share best practices and information on the prevention and treatment of drug overdose, in particular opioid overdose, including the use of opioid receptor antagonists such as naloxone," one of the longest sentences I think I've ever had to read.

(Laughter.)

DR. LURIE: Domestically, we have had parallel reaction, I think, and so I wanted to talk a little bit about the Office of National Drug Control Policy, ONDCP, colloquially known as the drug czar's office.

The drug czar's office has its own prescription drug abuse plan, and that prescription drug abuse plan says -- and I'm quoting again -- that we should, "hold a public workshop to discuss medical and social issues related to naloxone use by nonmedical personnel," here we are, "and provide guidance to researchers, community groups, and the pharmaceutical industry on
potential routes to marketing approval for novel naloxone formulations." So in a lot of ways, this meeting is putting into effect something in the ONDCP plan.

We had invited the ONDCP to come today, and unfortunately they were unable to. But in their stead, Gil Kerlikowske, who is the director of ONDCP, sent the following statement for me to read verbatim to you. And so here I go.

"On behalf of the White House Office of National Drug Control Policy, I would like to welcome you to this important public workshop. In 2010, the Obama administration's first drug strategy was released. This strategy, as well as subsequent strategies, recognizes the important role naloxone can play in overcoming drug overdoses.

"With more people dying from unintentional drug overdoses than car accidents, it is vitally important that we do what is necessary to prevent drug abuse while also preventing drug overdoses and getting people the treatment they need."
"Thank you for taking time to discuss this issue, and I look forward to continuing this important conversation."

So that's from Director Kerlikowske.

So with that, what are our goals for this meeting? Well, the main purpose is to initiate a public discussion about whether naloxone should be made more widely available outside of conventional medical settings to reduce opioid overdose fatalities.

We have a morning and an afternoon. The morning is really a scene setting kind of exercise. We'll discuss who's at risk for opioid overdose, what the epidemiology of overdose is. We'll describe attempts by public health groups to address overdoses in general. And then we'll talk about naloxone and its particular characteristics and how they affect the material that comes up really in the afternoon session. And we'll have a series of presentations that describe the experience of different groups using naloxone in nonmedical settings.
In the afternoon, we'll get to what, in a way, is the meat and potatoes of the meeting. We're going to talk about regulatory issues, what it would take to get an intranasal form of naloxone approved, what it would take to get a product switched from prescription to over-the-counter status. We'll have an industry perspective on why they might or might not want to enter the market, and we'll discuss the ethical issues that are involved in the studying of these products.

Then we're going to have a very packed open public hearing, which we're looking forward to greatly. Twenty-eight people have signed up. And we're sorry for the short time that that affords everybody, but we also need everybody to be heard. So it's a very, very packed open public hearing session.

After that, we'll have a final session on social and legal concerns, which will begin with lessons from other public health interventions, where the question of behavioral disinhibition, if you will, has been raised. And we'll hear about
the experience with the HPV vaccine, Gardasil. And then we'll have a panel discussion, which we look forward to being lively, in which all of these issues will be batted back and forth for all of our edification.

I should say that the discussion with all of you in the audience is not confined to the open public hearing session. Each of the sessions that I've outlined has a time for question and answer. And I'll ask you to please identify yourself at the microphone, directly in the middle over here, before you speak at those question-and-answer sessions.

Let me just mention a couple of logistical details before closing. As I've mentioned, we have a very full agenda, so we ask you to make it back in time so that we can cover everything in an expeditious way and so that I can get out of here to pick up my kids.

(Laughter.)

DR. LURIE: We do have ample breaks built in. Kiosks will be set up outside the meeting room...
where refreshments will be sold during breaks and at lunch. There will be salads, sandwiches, other refreshments when we break for lunch. The bathrooms are out this door and to the right.

Only those with FDA badges will be able to venture past this immediate area without going through security measures. In solidarity with you, I left my badge behind today so that I'm stuck here as well. As to logistics, we ask you to turn your cell phones off while you're in this room because signal transmission can interfere with the transcriber who is recording this meeting.

So I wanted to, before closing, make sure to thank the people who are responsible for pulling this meeting together for us. And I know that many of you have dealt with them in person before coming here. Matt Petcovic and Jan Shelton were instrumental in pulling everything together. But more than anybody, I think, Mary Gross is the person who deserves a lot of credit for how well we believe this meeting is going to flow.

So in conclusion, I just want to say that
this effort today is part of many things that the
U.S. Government is doing about prescription drug
abuse and about overdoses in particular. And this
meeting will allow a discussion of various
potential uses of naloxone.

The purpose of the meeting is really twofold
and bidirectional. One is for us to hear from you
about the possibilities for naloxone by use outside
of conventional medical settings as well as the
potential risks, and for you to hear from us about
the available regulatory pathways for naloxone.

We want to show you what it would take for
over-the-counter, what it would take to develop a
intranasal form on the assumption that not
everybody who has worked in the naloxone field may
be as familiar with those rather intricate
processes as might be the case. And we hope to
show you, therefore, a roadmap to help us
collectively make the best use of naloxone for the
public health.

Okay. That concludes my opening remarks.

Doug, you're next.
DR. RAPPAPORT: Good morning. I'm Bob Rappaport. I'm the director of the Division of Anesthesia, Analgesia and Addiction Products in the Center for Drug Evaluation and Research here at FDA. And I'm the moderator for the first panel today, and I'm pleased to see that there's so much interest in this important topic.

The increasing numbers of unnecessary deaths due to opioid overdose in the U.S. is clearly a true public health crisis, and I know we're all here with the same agenda. And that is to establish whether allowing naloxone to become more widely available for use by nonmedical personnel in treating these overdoses is one mechanism that should be considered as a potential intervention.

In order to make that assessment, it's important that we all start out on the same page in regard to what is actually known about naloxone and about the population that this drug would be administered to. And it's also important for us to acknowledge and understand the earlier and ongoing
public health strategies that have been employed to
address this problem.

To that end, we have three outstanding
speakers for the first panel today. We'll begin
with Dr. Len Paulozzi from CDC -- I'm sorry,
Paulozzi. I do that to you every single time. I
apologize -- who will provide us with data on the
populations at risk for opioid overdose.

Len will be followed by Mr. Nick Reuter from
SAMHSA, who will tell us about other public health
strategies that are addressing the opioid overdose
problem. And last but certainly not least,
Dr. Gregory Terman from the University of
Washington will discuss the pharmacokinetics, the
clinical benefits, and the potential toxicities of
naloxone.

We're on a very tight schedule today, as
Dr. Lurie said, with a packed agenda. So each of
the moderators, including myself, will be
attempting to keep the speakers to their allotted
times, and the question-and-answer session will be
limited to 10 minutes. So I apologize if I have to
cut you off. We'll try to find time for questions, if possible, that weren't fitting into the allotted times.

So let's begin, and I'm very pleased to introduce you to Dr. Paulozzi.

Presentation – Len Paulozzi

DR. PAULOZZI: Good morning, everyone. My job is to lay out some of the epidemiology of populations at risk from opioid overdose. I'm going to talk about the opioid analgesic epidemiology as well as heroin. And I'm going to cover some trends and then move on to risk factors.

This is really why we're gathered here today, this figure which each year we add another year of data to this, and the numbers seem to keep going up. This shows data through 2009, national mortality data based on death certificates. We are up to about 15,000 deaths involving opioid analgesics in the United States with growing numbers in the last two or three years for heroin.

As was already mentioned, for a number of years now, deaths involving opioid analgesics have
outnumbered deaths involving either heroin or cocaine in the United States.

You can break down the opioid analgesic deaths into three subtypes by the available codes in the international classification of diseases. And there are basically these three groups shown here: the group of the codones, hydrocodone, oxycodone, morphine, codeine and so on, shown on the top line; methadone; and finally, the other synthetic narcotics, including fentanyl, merperidine, formerly propoxyphene, buprenorphine, et al.

I show this in part to emphasize the relative importance of these three groups, in particular methadone, where we are seeing some improvements and some flattening of the trends there. But methadone is really just 2 percent of all opioid analgesic prescriptions in the United States, yet it is involved in about one out of three opioid analgesic deaths in recent years.

Moving on to risk factors, men are the largest risk group for opioid overdose in the
United States, whether, it's the analgesics or heroin. The analgesic bar is the center bar shown in orange. Heroin is in yellow. The male rate is twice that of the female, roughly, for the opioids and about four times greater among men for heroin.

Age group, this is the group of all drug overdose death rates, so it's all drugs, not just opioids. And this slide is really just to demonstrate that if you look at the unintentional group in yellow or suicides involving drugs, or the group that is called "undetermined intent," undetermined mostly whether it was a suicide or unintentional, the peak rates are in the 45 to 54 year age group. So this really is mostly a middle-age problem.

Rates really start to jump up in the 15 to 19 age group, particularly at age 18 is when kids leave the home, go off to college, and we see the largest increase when you look at it by single years of age. There's something of a bulge growing now in the people in their 20s, and after age 60, rates drop off dramatically. When you get into
ages 65 plus, whether it's -- including suicides, the rates are relatively low compared to people in their 40s.

This is the same thing: rates by age group. But here I'm looking at drug overdose death rates by drug type. And basically, you see the same kind of pyramid, whether you're looking at cocaine or methadone or other opioids. The only real difference there is the heroin bar in yellow where the peak age is 25 to 34 years of age. For the other age groups, 45 to 54 remains the peak age in terms of rates.

I show this slide really just to contrast it with the overdose curve by age group. These are opioid prescriptions per person by age group in the U.S. in 2009 -- this is data that was published in JAMA from Dr. Volkow of NIDA -- and really looked at this way, people over age 60 get more prescriptions per person than people in middle age. So it's in contrast to, the peak in middle age, it's really not a similar pattern in terms of usage measured this way.
Rounding out the demographic variables, this is race, ethnicity data from 2008 in the United States, again, cocaine, opioid analgesics, and heroin. For the opioid analgesics, the highest rates are in non-Hispanic whites closely followed by American Indians and Alaska natives. Hispanic whites, blacks, Asian Pacific Islanders are much lower. For heroin shown in yellow, the non-Hispanic whites still have the highest rates with Hispanic and blacks being slightly lower; American Indians also having rates comparable to Hispanics and blacks.

This is an attempt to look at urbanization by drug type. So in order to do this in what I thought was the fairest fashion, I just looked at states that have centralized medical examiner systems because the degree of specification of drugs on death certificates seems to vary a lot between coroner and medical examiner systems.

So if you look at these 16 states and you restrict it just to U.S. whites, which that restriction is because of the confounding between
race and urban residence, you can see that the highest rates for drug overdose deaths are in non-core, non-metro, the most rural counties over the right side of the figure, for opioid analgesics. It's not a stair step phenomenon, but, in general, the non-metropolitan counties have higher rates for opioid analgesics. In contrast, the heroin rates are significantly higher in large, central, metro counties and get progressively lower as you proceed to non-metropolitan counties.

This slide does two things. It shows that the drug overdose death rates in 2008 are concentrated in Appalachian states, Florida, Louisiana, states in the southwest. I borrowed this figure from a recent MMWR article, which focused on naloxone prevention programs in 2010 in the United States, some of the authors of which are here today. And I do this to emphasize the contrast between the location of the current programs and the drug overdose mortality rates.

These are drug overdose deaths. See, these are all drugs, but the bulk of them are going to be
related to either heroin or opioid analgesics. And this is maybe related to the rural nature of the states, maybe related to income factors. It's unclear as to why we have these geographic patterns.

Moving on to other personal characteristics of people who die of drug overdoses, a lot of this information has to come from sources other than death certificates. So you'll see me citing frequently studies based on state medical examiner data. And this is a study we did a few years ago looking at unintentional pharmaceutical overdose deaths in West Virginia in one year, 295 some deaths, using medical examiner records.

We found that about 80 percent of the people had some history of substance abuse, whether alcohol or drugs. Forty-three percent had some other kind of mental illness, other meaning not substance abuse. And about one out of five people used a nonmedical route of administration, meaning that they injected the drugs or ground up the drugs and snorted them. And about one in six people had
a history of a previous overdose.

Another study done later in 2008-2009 in Utah, a very different setting from West Virginia, but they found that about 60 percent of people had a history of substance abuse, about half had what they called signs of nonmedical use, which in this case was defined as use without a prescription or using nonmedical routes of administration.

Most people had a history of some kind of chronic pain. And, again, most people had some kind of mental illness other than substance abuse diagnosed by a provider, was the definition that they used in that study.

So those medical examiner studies typically are numerator data. They don't have comparisons. You're just looking at people who died, so you don't have the ability to see whether it's really a risk factor. There are a few studies, however, that do have some comparison groups.

In West Virginia, actually, we were able to compare the people who died or look at the rates by residence in counties based on their poverty level.
to basically look to see whether counties that had higher percentages under the poverty level had higher rates. And residents in counties with 22 to 39 percent of the population living in poverty, which was the highest poverty level, had a relatively high risk of 2.1 compared to residents in a West Virginia county with the lowest level of poverty, 9 to 16 percent.

Also, related to income is Medicaid eligibility. In Washington state, Medicaid-enrolled Washington residents were studied compared to non-Medicaid-enrolled Washington residents. The Medicaid group had almost six times a risk of a fatal prescription opioid overdose in that study.

Similarly, there are some studies that are able to generate relative risks or hazard ratios, and I have combined some of them here looking at substance abuse and mental health problems.

A study of group health by Dunn in 2010 showed a substance abuse diagnosis in patients on chronic opioid therapy had 2.6 relative risk.
These are developed by just combining the rates in the study. They did not do the statistical testing.

Another study by Bohnert in 2011 saw that a substance abuse disorder among chronic pain patients was associated with a risk of opioid overdose, a significant relative risk of 2.5.

Depression diagnosis, again in patients on chronic opioid therapy in the group health study, was associated with a a threefold increase in risk. And psychiatric disorders other than substance abuse in the Bohnert VA study had a relative risk of 1.9, which was statistically significant.

Finishing up these other personal characteristics, lack of a prescription for the involved drugs among overdose deaths has been a common feature of a number of state studies. In West Virginia, 63 percent did not have a prescription in the state prescription drug monitoring program for one or more of the pharmaceuticals involved in their deaths. In Ohio, 25 percent did not have a prescription in the
previous three years in the state prescription
monitoring program. In Utah, unintentional opioid
deaths, 37 percent, again based on the state
prescription monitoring program.

If you look particularly at methadone in a
couple of the states, North Carolina and Ohio,
about three-quarters of the people did not have a
prescription in their state prescription monitoring
programs for the methadone that was involved in
their deaths.

And lastly, prescription history, there have
been a few studies in recent years looking at
prescription history of individuals oftentimes
using state prescription monitoring program data.
Again, the Ohio study found that one out of six
people who died of a prescription overdose had
filled prescriptions from an average of five
prescribers per year over the previous three years.
In the study we did in West Virginia, it was
similar, about 21 percent had filled prescriptions
from five or more prescribers in the preceding
year.
In a study we did more recently in the state of New Mexico, these are crude odds ratios, just to show that as the mean number of prescribers goes up -- and multiple prescribers is what people often use as the definition of, "doctor shopping." there was a fairly steady increase in risk. And when you get into people with 10, 15 or 20 or 30, you're approaching 10 times the odds ratio or 10 times the risk of dying of a drug overdose.

This is from the same study. It looks at prescriptions rather than numbers of prescribers, so multiple prescriptions for controlled substances of any kind. Again, associated risk of unintentional drug overdose in New Mexico. And when you get into numbers like 30 to 35 prescriptions, the odds ratios are 68 for people in that category.

As a last measure, in a growing number of studies about dosage, daily dosage usually converted to morphine equivalence as a daily dosage, measured in different ways and different cut points. The first study probably was the study
by Dunn looking at people with chronic pain in the Group Health Cooperative. They looked at people with more than 100, a 100 or more morphine milligram equivalence per day daily dosage, compared them to people with no recent use of opioids and found a relative risk of 8.8.

Braden looked at people with a dose of over 120 compared to people below the median dose, found a small increase in risk, although it was statistically significant of 1.08.

The Bohnert VA study, similarly, over 100, was associated with a relative risk of 7. And Gomes' study in Canada, dosage over 400, elevated risk, and our study in New Mexico, dosage over 120 compared with less than 120, was associated with an odds ratio of 7.6.

Another figure from the New Mexico study again showing a steady increase with risk as you increase in dosage. Although when you get up to the very high dosage levels, there seem to be an attenuation or a flattening of risk. It may be that dosages over 500 milligrams per day of
morphine equivalent, people are not actually taking
all the drugs themselves. And they may be
distributing them to others. And perhaps that
explains why their risk is not going up at levels
of 1,000 or 2,000 morphine milligram equivalence
per day.

To summarize, we looked at the demographic
variables, saw that male sex was a risk for opioid
analgesics and heroin. Age, middle age, risk for
opioid analgesics, 25 to 34 for heroin;
non-Hispanic white race. Ethnicity is a risk
factor for heroin as well as opioid analgesics.
Non-metro counties for opioid were a risk whereas
metro counties were a risk for heroin. Low income
or Medicaid populations were at risk for opioids.
State of residence with regional patterns seems to
be connected.

Personal characteristics included substance
abuse, history thereof; other mental health
diagnoses; nonmedical use of the prescription,
which might include nonmedical routes or use
without a prescription; and route of
administration. Prescription history risks are multiple prescriptions, multiple prescribers and high daily dosage.

I call these potential markers. I mean, some of these analyses are adjusted; others aren't. These may be indicators and markers. They largely correlate with one another. So they may identify high-risk populations. But probably the best label for them is markers rather than risk factors, given the nature of the analyses, oftentimes descriptive analyses that generated this list.

Thank you.

(Applause.)

DR. RAPPAPORT: Thank you, Len.

Anybody interested in this field is familiar with Len's work, but you may not be familiar with his background. And since I neglected to give a little bit of it before I introduced him, let me just tell you. Len is a medical epidemiologist in the Division of Unintentional Injury Prevention of the National Center for Injury Prevention and Control. And his area of concentration, as we all
know, is drug overdoses, especially those due to prescription drugs.

He received his bachelor's degree from Yale and his medical degree from Ohio State, and a master's degree in public health from the University of Washington. He's board certified in preventative medicine, and he began his career in CDC in the epidemic intelligence service in 1983. He joined CDC's injury center in 2000, and he's had a leading role in the design and startup of the National Violent Death Reporting System and other surveillance systems.

He's been concentrating on the drug overdose problem since 2005, so I think his expertise speaks for itself.

Okay. Our next speaker is Nick Reuter. Nick is a senior public health advisor in the Center for Substance Abuse Services, the Division of Pharmacological Therapy at SAMHSA. He is a graduate of the University of Maryland and the Johns Hopkins University School of Public Health. Previously, Mr. Reuter served as a consumer
safety officer here at the FDA in the Office of Health Affairs. And in these positions, he's been responsible for coordinating and developing agency positions in many areas, including those related to drug abuse and drug control, as well as the oversight of narcotic treatment programs.

Nick was active in the implementation of the Drug Addiction Treatment Act of 2000, which enables office-based opioid treatment. And, in addition, he has coordinated the department's implementation of the National All Schedules Prescription Electronic Report Act of 2005.

**Presentation – Nicholas Reuter**

MR. REUTER: Good morning, everyone. It's a pleasure to be here, and I want to thank CDC and FDA for permitting SAMHSA to be a part of this. This is our 20th anniversary. We're a relatively young federal agency. And it's timely that the substance abuse mental health issues that affect our country can be discussed in the context of this morning's proceedings as well.

It fits nicely with SAMHSA's missions and
SAMHSA's objectives, preventing substance abuse and mental health issues. We think that treatment is effective, and obviously, people can recover from their substance abuse, and in this morning's context, their opioid-overdose-related issues. It fits nicely.

So what FDA asked me to talk about this morning was a little bit of the background on opioid overdose outbreaks throughout the U.S., focusing on one in 2005 and 2006, a little bit about some of the public health interventions. I think it's important in this context to remember the different kind of state responses because there are regional and state differences in the way opioid overdoses are prevented and reversed; a little bit about education on opioid overdose risk reduction; a little bit about the toolkit.

So I'm just going to paint a broad picture. You'll hear later today some of the more specific information about the various toolkits that are out there and intervention techniques in more detail; a little bit about naloxone distribution.
Since I work for the Center for Substance Abuse Treatment within SAMHSA, I'm going to talk a little bit about how treatment can fit into this opioid overdose reduction initiative.

In 2005 and 2007, there was a genuine outbreak of non-pharmaceutical fentanyl-associated deaths. And if you look at Dr. Paulozzi's slide, you could see in 2006, there was a blip on the bottom lowest line there. And that reflects this outbreak of non-pharmaceutical fentanyl-associated deaths.

Around 1,000 deaths were reported between 2005 and 2007. Although it wasn't national in nature, it was evident in 13 states. This epidemic peaked in 2006 with the maximum number of cases of 150 cases, and it declined down in 2007. Most of the issue was fentanyl sold on the street that was being offered as either heroin or cocaine, and just about all of it was being injected.

There was a clearly public health response to this epidemic, and it was coupled with a law enforcement reduction initiative as well. The
public health part of it included epidemiological
task forces that were formed in different states
and regions. And what these groups did was develop
alerts to providers, alerts to law enforcement
people. Information was provided to drug users.
And there was an intensified outreach to drug users
as part of this initiative.

The outreach activities themselves included
training drug users and others on CPR
resuscitation, rescue breathing, how to prevent
overdoses, and in some areas providing take home or
parenteral intranasal naloxone as an opioid
antagonist used to reverse an overdose.

Now, these programs and the naloxone
distribution were in place before this epidemic
hit, but I'd like to think that it received
additional emphasis as a result of this acute
exposure here.

The response also included a law enforcement
sort of supply reduction component where
non-pharmaceutical fentanyl was seized and
destroyed. Fentanyl clandestine labs were
identified by law enforcement and disrupted. DEA published an immediate rule that controlled one of the precursors used to make this illicit non-pharmaceutical fentanyl.

There was a creation of a standing informal biweekly group of -- a very informal opioid surveillance conference call group, where individuals throughout the U.S. try to look to see if there are any emerging outbreaks on the horizon and then bring the people together to try to address those through a prevention activity. And it was thought that this was justified. There was genuine concern that future epidemics of opioid overdoses may occur -- and there was a genuine risk that that could happen -- and the impact from that would be substantial.

So it's an informal monitoring system that is there to informally but reasonably, effectively look to poison control centers and people and field offices to see if there are emerging opioid overdose issues.

There are some recommendations from that
initiative -- it was all summarized nicely in a MMWR article not too long ago -- about what to do about some of this risk associated with opioid overdoses. And essentially, the primary recommendation was to expand public health programs for drug users and others to help them obtain addiction treatment, educate them about the risks of overdose, educate those who continue to use drugs how to avoid and respond to overdoses, how to prevent and reverse overdoses, the kind of thing we're looking at.

It was mentioned earlier -- Dr. Paulozzi talked about a recent MMWR article that chronicled the naloxone distribution programs throughout the U.S. And as of October 2010, there were 188 such programs identified. And between 1996 and 2010, these programs in 15 states provided naloxone to 53,000 people, resulting in over 10,000 drug overdose reversals using naloxone.

The article also pointed out that many states with high drug overdose rates do not have overdose prevention programs that distribute
naloxone. And Dr. Paulozzi's slide showed this very nicely. One of the highest rates of opioid overdose in the U.S. is in the state of West Virginia. And I didn't see a dot in there for a naloxone distribution program in that state.

Now, there are many different programs out there, and we'll hear more about them later today. But I'd like to just focus on one to give you a flavor of a typical naloxone distribution overdose prevention program. This one was in the city of San Francisco. It's called the DOPE Project Intervention.

Just to summarize it, since 2003, they've had a program to train and distribute naloxone. And it's interesting the entities where they distribute the naloxone: in needle exchange programs, reentry programs for law enforcement, which is a very interesting place to distribute naloxone, when inmates are released and reducing the risk of overdose, which is a little bit higher than the general population. Some materials are distributed at pain management clinics. I think
that's consistent with a lot of the overdose prevention programs you'll hear about. Similarly, methadone maintenance programs are a source of distributing these overdose prevention materials.

Buprenorphine treatment programs, those are physicians who are authorized to prescribe buprenorphine for addiction treatment, but in different settings that actually constitute programs, and in the Tenderloin District of San Francisco, where they're called single-room occupancy hotels.

So just an example of the DOPE Program Intervention, the trainings focus on overdose symptom identification, revival strategies, notifying first responders and EMS right away, and administering naloxone. Specifically, the naloxone that is administered -- and this is consistent through many of the programs -- is .4 milligram vials or prefilled syringes together with a breathing mask and other materials.

In San Francisco, almost 2,000 providers were trained and prescribed naloxone as part of
their prevention initiative. Eleven percent of the participants used naloxone during an overdose event, and 83 percent of those overdose responses reported that naloxone successfully reversed the overdose in those cases. So the message there is that if you can conduct these trainings, naloxone can be distributed, it can be used. It can reverse opioid overdoses.

Now, I just pulled out the San Francisco program, but there are other programs. For example, the state of Illinois, I don't know if we have anyone here from Illinois or not, they have a very -- much more specific and detailed program where individuals are trained. The division of alcohol and substance abuse services certifies the trainers. People who receive training on overdose prevention, education and naloxone distribution receive certificates. They're updated periodically. So it's a much more formal kind of program in Illinois.

Also, in San Francisco, they did make an attempt to look at, in addition to outcome, some of
the adverse events that were encountered with the
naloxone distribution. Serious adverse events were
rare, but there were in the publications some
reports of seizures, something we'll talk about a
little bit later.

Vomiting was the most commonly reported
negative effect. And universally, what you can
anticipate in arousing somebody from an opioid
overdosed state, is anger and discomfort. I think
that's pretty much consistent with all of these
reversal cases.

I wanted to talk a little bit about
prescription opioid pain relievers. We heard the
statistics. The three classes with the highest
rates tripled from 1999 to 2006. I just wanted to
talk about methadone and single out methadone for
just a second, because methadone deaths rose more
rapidly than any other opioid analgesic between
1999 and 2006. But as Dr. Paulozzi reported, they
actually started to decrease and taper down or
trend down in 2008 and 2009. And this leads me to
just discuss some of the federal interventions that
went into place to address specific kinds of opioid overdose issues.

We trained the opioid treatment program providers on risk management, induction procedures, co-occurring disorders and polydrug abuse because during that induction period, we see the highest rates of opioid overdoses in methadone treatment programs.

And just for the record, we've done many analyses, and the trend in methadone-associated deaths increases is correlated much more closely with increases in methadone prescribed for pain and not very much correlated with any kind of increase in methadone distributed or an increase in methadone patients in opioid treatment programs treated for addiction.

So in the second bullet, that leads us to physician continuing medical education. This is something SAMHSA has supported for four or five years now. We go into states and provide CME education to physicians on appropriate prescribing practices for opioids for pain relief, spend a lot
of time talking about methadone because of the
higher risks associated with methadone for pain
treatment. We also have a prescription drug
monitoring expansion initiative using the NASPER
program and the Harold Rogers grant program, all
components of the ONDCP strategy.

So other federal initiatives to address and
prevent prescription drug opioid overdoses include
surveillance. We have the poison control systems,
the biweekly conference calls, forming some kind of
passive surveillance system. We're trying to
revise medical exam or case definitions because
there is some inconsistency there in the way deaths
are attributed to one opioid or another, whether
polydrug abuse and other factors contribute to
these overdoses.

Something that affected, I think, the way
methadone is distributed for pain in this country
is DEA’s successful effort to get the 40-milligram
methadone diskettes, which are labeled just for
addiction treatment but which were being
distributed extensively in pharmacies to be filled
by prescriptions for pain treatment -- actually not
distributed through pharmacies to be used in pain
treatment and dispensed by pharmacies in
prescription.

We spent a lot of time developing consumer
education on methadone safety. We've worked with
FDA and developed some educational materials that
elaborate on the risk of methadone, how to use it
safety, what to look out for, not to change your
dose level, when to contact a health professional,
and things like that.

Methadone is part of the FDA opioid REMS
system, and methadone as a prescription drug also
fits into the ONDCP prescription drug abuse
prevention program.

So all those things taken together, a little
bit of a drop in methadone distribution, and you
see a decrease in methadone-associated mortality.
So that might be some things to think about when it
comes to preventing prescription drug overdose
deaths.

A couple years ago, we convened a group of
state officials, and the idea was to look at the
states that had the highest rates of opioid
overdoses and bring in states that had lower rates
of opioid overdoses, and try to find out on a state
level what may be the differences and why some
states have higher rates of overdose and some
states have lower rates of opioid overdose.

So we brought in the people who fund
substance abuse treatment, and the other kind of
state entities that oversee opioid use and
substance abuse treatment, and found that some of
the issues that emerged in states that had the
highest rates of overdoses included continuing
stigma against methadone treatment; funding and
resource shortages, both for prevention efforts and
for treatment interventions.

They emphasized the need to interface with
the criminal justice system. They also said there
was an important need to integrate treatment
interventions and referrals into overdose
prevention activities. Special attention to
adolescents and young adults were important factors

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in these differences. And they cited -- and this was important to the states -- a lack of evidence and research to guide states on the effectiveness of opioid overdose strategies. Those were the differences between states with effective risk reduction programs and those that had the highest rates of overdose.

So to try to address that, we worked with the Association of State and Territorial Health Officers to develop an opioid treatment overdose toolkit. As far as I know, this would be the first opioid overdose reduction toolkit issued by a federal government entity. And we targeted opioid treatment programs.

These programs are regulated by SAMHSA, and we have been working with them for quite a while on methadone safety. We've prepared DVDs with health professionals, with patients, and others in opioid treatment programs to explain some of the risks about methadone treatment.

We also believe that OTPs have experiences with opioid overdoses. If not directly in the
program itself, the patients know about them. The patients have friends not in treatment, and they have people in the community that they interact with who are at risk for opioid overdoses. So taken together, we thought that was the best approach for getting an educational toolkit available.

Similar to many of the other toolkits that are out there today, overdose reduction toolkits, there's content in the toolkit for providers; a separate piece of information on patients; a section in the toolkit that talks about dos and don'ts, what to do, what not to do; steps to take; and information to recognize an opioid overdose.

It talks about rescue breathing. This is consistent with many of the other toolkits that are out there, a big section on understanding how naloxone works and how to administer naloxone. The toolkit, as we're developing and issuing, is not going to provide naloxone. Instead, it's going to provide resources and information where people can get naloxone.
We expect to have that toolkit released maybe this afternoon for public review and comment, maybe tomorrow, but soon. And we'd like to invite the people in the group to take a look at it and provide more input and comment. A few of the people here in the front row helped us work on that toolkit, and I think it's a very, very fine product.

I wanted to spend a few minutes talking about treatment interventions. We can reduce opioid overdoses. We can intervene. We can prevent. We can lower the risk. We can distribute naloxone. I think it's important to have as part of these procedures a treatment intervention component, and some of them do.

When we met with the states, they thought this was a substantial shortcoming, that treatment interventions' availability should be included in these overdose reduction interventions. In the U.S., we have methadone maintenance programs that use the full opioid agonist, methadone. It is safe and effective in both reducing withdrawal symptoms.
It's effective in blocking opioids' effects as well.

Currently, there are around 300,000 patients in the 1250 opioid treatment programs in the U.S. That capacity has quadrupled in the last four years. So in the wake of this opioid overdose epidemic, there has been an increase in methadone maintenance treatment available as well.

We now have programs in every state except for North Dakota and Wyoming. And as I said, we emphasize the higher risk of overdose during the induction period in all our regulatory guidance and education components that we apply to opioid treatment programs.

The partial agonist buprenorphine is available in office-based treatment settings. It's been available since 2006. Currently, there are 22,000 physicians authorized in the U.S. to begin this treatment. Those physicians are in emergency departments. They're in public health treatment programs. They are in every state of the country. So that treatment capacity exists.
In 2010, 800,000 people received buprenorphine prescriptions for addiction treatment from physicians who had that authorization in all those different settings. I would estimate that there is around 500,000 people currently receiving buprenorphine treatment through the office-based physician program. There's a mono formulation of buprenorphine, and there's a combination formulation that contains naloxone, naloxone in place to reduce the risk of intravenous abuse of that formulation.

Finally, the treatment medication Vivitrol in 2010 had its label modified to reflect its use in preventing opioid relapse. It includes the narcotic antagonist naltrexone in sustained release 30-day formulation.

So to sum things up, from our perspective at SAMHSA, we clearly think that overdose risk reduction programs have increased over the last several decades. And they're in place, and they have demonstrated substantial effectiveness in reversing opioid overdoses. We think the public
health prevention approach has resulted in
thousands of overdose rescues.

Our questions from SAMHSA, and I think for
the rest of today's discussion, should be how these
prevention initiatives can be integrated into
treatment and recovery programs that further reduce
the overdose risk.

One question I have in developing our opioid
risk reduction toolkit -- we brought in folks who
talked about their rescues with naloxone, and it's
never entirely clear what happens after an
intervention with naloxone to reverse the overdose
and whether that has changed the patient's
perspective, whether they now are at a lower risk
of overdose, whether they want to avoid those
situations again.

I think from our panel, it was a little bit
mixed, that the naloxone was in place. It was a
successful rescue intervention. But what happened
next? Were there further -- was there more
intervention to reduce that risk further? And I'd
like to see those two things tied together.
Finally, I think we need to discuss today a little bit more about future research needs: How can this be safety and effectively be used? What about the adverse effects associated with the use of these products? Is that something that needs to be the subject of future research so we can have an informed decision about the way the naloxone distribution programs advance from this day forward?

Thank you.

(Applause.)

DR. RAPPAPORT: Thank you, Nick.

Our next speaker is Dr. Greg Terman. Greg's a professor in the Department of Anesthesiology and Pain Medicine and the graduate program in neurobiology and behavior at the University of Washington in Seattle. He is a Mayday fellow in pain and society and is currently on the board of directors of the American Pain Society.

Dr. Terman received a Ph.D. in behavioral neuroscience from UCLA and studied mechanisms of endogenous pain inhibitory systems, including
interactions with tolerance to endogenous and exogenous opioids.

After receiving his medical degree from the University of Miami and completing an anesthesiology residency and a fellowship in pain management at the University of Washington, before joining the faculty there in 1991 -- and since that time he's continued his basic and clinical research on opioid pharmacology as well as working clinically both in the operating room and on the acute pain service.

So I think we've got a great person to teach us about naloxone.

**Presentation – Gregory Terman**

DR. TERMAN: Thank you, Bob, for that nice introduction. I thought the reason why you asked me was you couldn't find anyone who had been involved in giving naloxone to more species than I have.

(Laughter.)

DR. TERMAN: I was asked to give a slide on conflicts of interest that I have. And you should
know right up front that I have no known financial
interest in the drug naloxone nor companies that
make naloxone, nor companies that produce devices
to administer it. On the other hand, I've spent
more than 30 years performing behavioral
pharmacology research on opiates, and many of those
studies would not have been possible without
naloxone.

Further, I've spent more than 25 years
trying to safely take care of people with
postoperative pain. Some of those people received
opiate overdoses for one reason or another and may
owe their lives to naloxone.

Finally, two faculty colleagues in my
department have had children die from prescription
overdoses in the past few years. So, clearly, I'm
very interested in what wider use of naloxone
might -- how that might affect these tragedies.

So I'm going to talk about the nuts and
bolts of naloxone. I'm going to divide it up into
three areas: specificity, toxicology and problems
with naloxone, which I will argue are largely an
unmasking of ongoing disease processes in the
group that are receiving it or people who are
receiving it.

As many of you know, opiates work by binding
to proteins in the cell membrane called receptors,
and the crystal structure of the opiate receptor
has actually just been published in the last month.
That receptor binds morphine or its pro-drug,
heroin, or a related drug, oxycodone, for instance,
like a key into a lock.

Now, back in the '60s long before crystal
structure was known and even opiate receptors were
known, it was found that a modification of a
metabolite of oxycodone, oxymorphone, could turn
the agonist properties into an antagonist,
essentially reversing all the effects of the
agonist.

Whether or not people understood the
importance of that finding at the time is a little
before I can comment. But the latest version of
the book, pharmacology book, Goodman & Gilman,
talks about naloxone as a pure opioid antagonist,
talks about that you can get effects in giving it IV, IM, subcutaneously, through an endotracheal tube, so into the lung, and also intranasally.

Oral naloxone doesn't work very well, not because it's not absorbed from the gut but because it has such a high metabolism, first pass metabolism, in the liver once it's been absorbed in the bloodstream there, which may be why it has a relatively short duration of access -- duration of effect similar to its one-hour half-life.

Now, the idea of pure opioid antagonist was certainly novel in the '60s and still today. What I mean by that is that it is devoid of agonist activity and is thought of as the drug of choice for opioid-induced respiratory depression or other side effects from the opiates.

In another related area of medical investigation, when I was looking around to try and decide about graduate school in the mid to late '70s, I was enthralled by this Hughes and Kosterlitz identification of two peptides in the brain that had opioid agonist activity. These were
later called endorphins. But Leslie Iversen, in a commentary that accompanied the publication of these endorphins, said that a crucial item of evidence was that the effects of morphine and of the morphine-like compound in brain extracts could be blocked by low concentrations of specific morphine antagonists such as naloxone.

This amazing specificity was something that I used later in my graduate work in the early '80s, where the reversal of phenomenon, behaviors, by naloxone was essentially a synonym for endorphin activity.

So if this drug is specific, what about its toxicology? Well, so in rats, I didn't look too far, but what I did see was a similar reversal of, in this case, opiate-mediated stress analgesia with 100-fold change in the dose with no apparent toxicities.

In people, the drug is packaged .4 milligrams per milliliter, and the indicated dose is .4 to .8 milligrams IV. In our hospital, we use about 10 times less than that because in
post-op pain patients, it decreases the amount of
time when they don't have any pain relief. But if
you use 700 times as much as the indicated dose,
you will not see any adverse effects in
opiate-naive subjects who are not having pain.

And that may explain why Goodman and Gilman
has a kind of a short list of contraindications and
adverse reactions. Now, that's in contrast to a
dangerous drug like ibuprofen.

(Laughter.)

DR. TERMAN: Which we don't have time to
talk about today.

Now, that's not to say that there haven't
been reports of adverse events following naloxone
treatment. And I'm going to spend the rest of the
time trying to convince you that many of those
adverse events are related to an unmasking of
disease in those animals or people who have
received the naloxone.

So one of the things that's mostly likely to
happen -- and we've talked about it before -- is
acute withdrawal. If you unmask dependence with
naloxone, you will get withdrawal symptoms. Now, it's important to realize that unlike, say, benzodiazepine withdrawal, opiate withdrawal is not a medical emergency. In fact, Farrell describes withdrawal as moderate to severe flu-like illness, subjectively severe but objectively mild.

I don't know if you would agree with that. Certainly, people in withdrawal might not. But in my rats or in people, the symptoms are not medical emergencies, particularly in otherwise healthy or younger patients. And most of the adverse events are probably -- that have been reported are probably -- related to opiate withdrawal.

But let me just take a step back and admit that if there's wider distribution of naloxone, then more people who are older and may be sicker are likely to get that drug. And that leads me to talk about cardiovascular effects.

Now, the concern in cardiovascular effects probably again have to do with withdrawal, catecholamine release, which actually probably causes a number of the symptoms that we looked at.
with withdrawal, including sweating and other things. But tachycardia or other arrhythmias is the concerning one. And this could synergize with other drugs in the system, for example, cocaine with cardiovascular sequelae, or even people with preexisting cardiac disease may not be able to tolerate a tachycardia and may develop myocardial ischemia as a result.

Probably most concerning about the catecholamine release is that it increases or it adds to the irritability that's there from hypoxia or hypercarbia, both of which can contribute to arrhythmias.

But I would argue that this isn't really an effect of naloxone, arrhythmias due to hypoxia and hypercarbia. The hypoxia and the hypercarbia are more likely the reason why the patient is getting the naloxone rather than an effect of the naloxone itself. But it's still something that has been reported.

In fact, it's also been reported that naloxone has anti-arrhythmogenic effects. That has
been suggested as something that should be given for arrhythmias in the emergency room, although I'm not sure the level of evidence there is at the moment for that.

In addition to tachycardia, catecholamine release with withdrawal can produce hypertension. Now, increases in blood pressure could be dangerous in someone who has an aneurysm, for instance. Or in someone who has a congestive heart failure, an increase in blood pressure may make that worse, perhaps causing pulmonary edema.

In fact, naloxone-induced pulmonary edema has been reported widely, and particularly in the anesthesia literature. Review of the literature probably suggests that the pulmonary edema is due to negative pressure caused by acute airway obstruction increasing the intrapulmonary pressures and essentially sucking liquid into the alveoli and causing pulmonary edema through that way. And certainly, negative pressure pulmonary edema occurs independent of whether opiates -- certainly naloxone or even opiates are involved.
So I would suggest that most pulmonary edema episodes are not so much the result of hypertension but, in fact, are due to airway obstruction, again a likely cause for giving the naloxone in the first place.

Having talked about withdrawal adverse events, let me talk about an adverse effect that's unlikely to be due to withdrawal. Seizures. And, in fact, another study of adverse effects after naloxone found that several of the patients that received naloxone had generalized convulsions or seizures.

The seizure concerns are around the theoretical idea that naloxone may lower seizure thresholds for patients with prior seizure disorders or immediately after their seizures when they're in the postictal period. And, in fact, in the room next to me during my graduate school days at UCLA, while I was working on the implications of endorphins for pain, Hanan Frenk and others were -- Yehuda Shavit -- were looking at the effects of endorphins in modulating seizure
activity and finding that with seizures, endorphins were released that kind of put a lid on the excitability of the system to try and decrease further seizures.

Theoretically, giving naloxone could inhibit that effect and reintroduce seizure activity, although I'm not sure there's a lot of evidence for that in the literature in people.

Certainly, naloxone almost certainly can unmask seizures from other drugs that have been co-ingested from again; for example, cocaine. And they may unmask seizures that are due to hypoxia or hypercarbia. High CO2 or low oxygen can both cause seizures. But again, this association between naloxone and the seizures may not be relevant to the naloxone itself but unmask a process that's already there. You just don't see it because of the severe overdose that's taking place.

Finally, there's been some concern that renarcotization might take place. The naloxone is an hour half-life drug, as I mentioned. That's shorter than most opiates, and including heroin,
where two to three hours tends to be the half-life. The concern is if you give the naloxone and patients are doing fine, will they run into problems later when people aren't noticing because the naloxone goes away.

This has actually been studied out of hospital situations. And, in general, these studies show that there's really no or few to no deaths. All the people who refused transport to the hospital, for instance, after being awakened by the naloxone, were not actually able to be found to make sure that they were still alive. But the majority of evidence suggests that this is a not a major problem, out of hospital.

However, this study from emergency rooms makes the cautionary statement that longer-acting drugs, overdoses from longer-acting drugs, were more likely. So long-acting drugs like methadone or Oxycontin or others with longer half-lives, much longer than naloxone rather than just a little bit longer, may be a concern.

So, in summary, naloxone -- despite having
amazing specificity and forgiving toxicology, it does have a concern in terms of unmasking disease processes that may be ongoing in patients or people that receive this drug. Most of those are around opiate withdrawal, but certainly, the co-ingested substances or hypoxia or hypercarbia can produce effects that will cause adverse effects associated with naloxone.

Similarly, airway obstruction can do the same thing. And healthcare providers need to be aware that renarcotization, particularly with longer-duration opiates, may also be something that they need to be willing to treat or aware of and anticipate treating. Similarly, pain, if people are taking these drugs for pain, is likely to be quite severe. However, anyone who has taken CPR training knows that the first two approaches to CPR are airway and breathing. The idea is save the patients so that they'll have pain you can treat tomorrow.

(Laughter.)

DR. TERMAN: Now, realizing a picture is
worth a thousand words, I thought I would give you
a picture about naloxone. Here, we're giving nasal
naloxone to a rat who has, after animal care
approval, gotten an overdose of morphine
subcutaneously. And it's important for you to know
that you shouldn't really do this at home –

(Laughter.)

DR. TERMAN: -- that nasal naloxone in a rat
is not that easy to do. But I was fortunate in
knowing John Hoekman, who got his Ph.D. in pharmacy
from University of Washington and is now at a
company in the Seattle area, Impel NeuroPharma, who
has actually spent much of the last 10 years giving
drugs of one sort or another nasally in rats.

And so he came and helped us inject 10
microliters of naloxone into this rat with the
lethal dose of morphine, using that thing down on
the bottom, which is really kind of an inhaler sort
of apparatus attached to the needle. And after a
little less than two minutes, the naloxone had its
effect.

In just a second, he's going to smile at us
here.

(Laughter.)

DR. TERMAN: Well, actually, I only had one other slide, and that was an acknowledgement slide. I want to thank you very much for your attention.

(Applause.)

Questions and Answers

DR. RAPPAPORT: Thank you.

Okay. We have 10 minutes for questions for the three panelists. If you have a question, please come up to the microphone and please introduce yourself and your affiliation.

Do we have anybody on the panel who would like to ask a question first?

DR. THROCKMORTON: Len, this is -- I'm Dr. Throckmorton. I'm from the FDA. Len, I have a question for you from your slides.

One of your slides about demographics of risk seem to suggest that the Indian, white population had high risk as well. Have we seen that in more than one place? Is that a consistent finding? That seems a population that we might try
to focus efforts on?

DR. PAULOZZI: Sure, it's been consistent over a number of years. We haven't broken it down by region of the country. But overall in the country, there are very high drug overdose rates, and a very high proportion of the deaths are pharmaceuticals among Native Americans.

DR. RAPPAPORT: Any other questions from the panel?

Okay. At the microphones?

DR. JONES: My name is Steve Jones. I worked at the CDC on HIV prevention among injection drug users, and I'd like to advocate for the importance of ethnographic research, particularly among the prescription opioid users.

In the case of HIV among injection drug users, ethnographic studies were able to identify key points for intervention. And I don't think we understand fully what's going on in prescription opioid users and people who overdose, and how we can best reach them, and how to intervene. And I think ethnographic research would be very valuable.
DR. RAPPAPORT: Any comments on that?

(No response.)

DR. RAPPAPORT: Thank you.

Yes, sir?

DR. WERMELING: Dan Wermeling. I'm from the University of Kentucky for Dr. Terman.

Two points. Does the rate of administration of naloxone in which the brain has a certain rate of exposure from IV versus other routes, does that affect the incidence or the severity of the side effects that you were mentioning? Does the rate of exposure to naloxone affect those events?

DR. TERMAN: So let me see if I understand that question. You're asking does the rate of exposure of the naloxone affect the --

DR. WERMELING: If you gave an IV bolus over the space of 10 seconds versus if you do other things, where you have a more gentle administration, does that affect the incidence or severity of these concerns that you've raised?

DR. TERMAN: So all I can talk about is from my own experience, where I've given naloxone
subcutaneous, now intranasally, IV. The answer is that it all works pretty quick.

If you look at the Goodman and Gilman slide about IV, it still takes a minute or two to start working or to finish working, and so these are pretty quick effects. And I'm not sure it would be easy to get that data, whether over 30 seconds versus over two minutes, wouldn't make much of a difference in terms -- either way, I've seen these effects regardless of whether it was over 30 seconds or over two minutes.

DR. WERMELING: Okay. And the second part of the question, do you believe that it's important to reverse the hypoxia and hypercarbia before you give the naloxone? So if you have control of the airway and can do this, would that also help reduce the incidence or severity of these problems that you've described?

DR. TERMAN: You said do you have to --

DR. WERMELING: Is it useful?

DR. TERMAN: -- and the answer is no, definitely not. You don't have to. But there is
some evidence -- I think, or at least
anecdote -- that if you ventilate the patient, you
will decrease the number of seizures and
particularly arrhythmias. And that's likely -- I
mean, that makes a lot of sense if you think of
you're trying to reverse other causes that may add
together to cause a naloxone-associated adverse
event.

MS. SZALAVITZ: Hi, I'm Maia Szalavitz. I'm
a journalist. I write for Time.com. And I'm
actually also a former IV drug user. And I'm not
allowed -- I don't know if I can ask this question,
but I'm going to try, which is I'd like to ask all
three of the panelists whether they support making
naloxone over-the-counter.

DR. PAULOZZI: Well, I'd have to say that's
the reason we're here today is to discuss the issue
and to learn more about it. So I would say that we
don't have an official position on the issue as
yet.

MS. WHEELER: Hi, my name is Eliza
Wheeler --
DR. TERNAN: Let me -- so get back to me at the end of the day, okay?

(Laughter.)

DR. TERNAN: Because I'm not an expert in -- I'm an expert in opiate pharmacology, but I come with an open mind as to what the pros and cons are. I can tell you what the medical evidence is. I just did. But in terms of what the public health implications are, that's not my specialty. And so I'll be interested in the continuing discussion through the day.

MR. REUTER: And I would just say I can't take a position on it. I want to wait and hear the evidence. But as I said during the presentation, my view is that it shouldn't just be the naloxone administration. There should always be a public health component to intervene and to get people into treatment, reduce the overall risk.

DR. RAPPAPORT: Yes?

MS. WHEELER: Just a question for Dr. Terman. So considering the potential risk of unmasking these disease concerns that you talked
about after administering naloxone, would you ever recommend not administering naloxone because of the potential risk of those problems?

    DR. Terman: That, I can answer. No, absolutely not.

    Ms. Wheeler: Thank you.

    Dr. Terman: These are not risks that would keep me from saving this patient.

    Ms. Wheeler: Thank you.

    Dr. Sommerville: Hi, Ken Sommerville from Pfizer.

    Dr. Terman, I guess we're all picking on you today. The question is: is there a ceiling on how much of a bolus dose you can give of the naloxone?

    Dr. Terman: So is there a ceiling in terms of the lowest dose you can use?

    Dr. Sommerville: No, the highest.

    Dr. Terman: In terms of the highest dose. So as I showed, the toxicology is pretty forgiving. There are reports of 700 times the recommended dose with no adverse effects. So I would say that -- you don't need to give that, though, and
that's why we give ten times less in the hospital setting. But in that setting, we have people around who are starting to control the airway, who are able to inject another dose if that's necessary. But the ceiling that you can give is much higher than any need to give, as far as I can tell, much higher.

DR. SOMMERVILLE: So with the .4 milligram dose, if someone accidentally gave an extra dose, it probably shouldn't have much effect, one would think?

DR. TERMAN: Based on the anecdotes and the literature, you could give 700 times that dose without adverse effects.

DR. SOMMERVILLE: Right. Thanks.

DR. BELETSKY: Hi, I'm Leo Beletsky. I'm at Northeastern Law School and College of Health Sciences. I wanted to also ask Dr. Terman if you can comment on the sort of population level incidence of these side effects that you have identified.

DR. TERMAN: The population level. So it's
going to depend on what population you give it to. The effects we see in the postoperative period are pain, severe pain. And they're not talking about nausea. They're not talking about headache or confusion. But the best place to look for the incidence of these is in that paper that I showed where the percentages are -- of any adverse effects, at least in the one study, it was more than 1,000 patients. And there were six patients that had what they considered severe adverse effects. That was the one where there were three that had seizures, and one that had an arrhythmia, and one that had pulmonary edema. I can't remember what the sixth one was.

So that gives you an idea of at least the most severe adverse effects and the incidence.

DR. BELETSKY: Would you characterize that as common or rare, or somewhere in the middle?

DR. TERMAN: I don't know. I don't know what that means. If it happens to one person, it's common for that person.

So the question is, what happens if they
don't get that drug and die, not -- I mean, I can't -- the question of rare or common, that's not something that I deal with. I have to be ready for the effects, knowledgeable about the effects, ready to treat those effects. And whether it's rare -- I mean, as an anesthesiologist, all I do is worry about rare effects, okay? That's what I do. I tell patients, I'm going to worry so you don't have to. So I don't -- rare is not meaningful to me. It's not meaningful to us.

DR. BELETSKY: Thank you.

DR. RAPPAPORT: We're going to need to break now. Sorry. We'll be coming back in 10 minutes exactly, so that is -- I'm sorry, 20 minutes exactly. That's 10:30.

(Whereupon, a recess was taken.)

Panel 2 - Moderator Wilson Compton

DR. COMPTON: I'm taken aback by the rock and roll radio station announcer who just asked everyone to please take their seats.

It's a pleasure to be with you this morning. I am Wilson Compton. I'm with the National
Institute on Drug Abuse. And before I introduce
our panel, I want to take a moment to say a few
words on behalf of NIDA.

We are very pleased to be cosponsoring this
meeting with FDA and CDC. I want to particularly
thank Dr. Peter Lurie for showing such leadership
in introducing this topic and keeping us on track
as we planned this meeting over the last nine
months to a year now. It's been quite awhile while
we've had this underway.

The topic is certainly one of interest to
all of the agencies, but this ability to join
forces between three federal agencies is actually
much more daunting than any of you might realize
and is unusual. It really speaks to the leadership
within the Department of Health and Human Services.

Dr. Lurie and Dr. Nora Volkow of NIDA are
co-chairs of a committee that's a subcommittee
looking at the issue of prescription drug abuse and
coordinating efforts across the department. And
this meeting in some ways is a reflection of that
collaboration and certainly reflects the
coordination that that subcommittee has provided to
all of our efforts.

Prescription drug abuse is a major theme and
topic for NIDA. We've been addressing these issues
through multiple mechanisms over the past at least
10 years since I've been at NIDA. And under
Dr. Volkow's leadership, we've had a particular
emphasis on this topic.

You can see it in our portfolio in multiple
ways. It is reflected in our basic science
portfolio, in issues such as trying to develop less
abusable forms of analgesics or non-narcotic
analgesics to completely eliminate at least the
overdose potential and the addiction potential.

We certainly see it in terms of our
treatment development program, and you'll be
hearing some of our researchers later today in
terms of the work to develop an intranasal
formulation of naloxone, for example, as well as in
our prevention and communications portfolio.

I would highlight for you some of our work
to change the way we educate physicians and other
healthcare providers in the United States to provide a more balanced and nuanced approach to treating pain. We think this may be one of the ways to reduce the tremendous reliance, and in some ways over-reliance, on narcotics as the approach to treating pain, and in some ways we hope address this epidemic of opioid overdoses by reducing the pipeline of availability of prescription opioids.

Now, what's NIDA specifically doing in this area of prescription drug overdose, and what are we doing in the area of naloxone as a potential approach to addressing this? Well, I've already mentioned one grant you'll be hearing quite a bit about this afternoon in terms of the development of an intranasal formulation of naloxone, which is certainly much easier to administer and maybe able to be more widely available.

In addition to that, we have two funded randomized clinical trials that are looking at use of naloxone for overdose prevention. You'll be hearing in just a few minutes from Dr. El-Bassel who has a randomized trial in an international
setting. And I'd also highlight Dr. Jody Rich's study of prisoners who are being released in Rhode Island, to look at the potential use of naloxone to prevent overdose in that extremely high-risk population.

We've other studies under consideration. And I look to you-all, to this audience and to those you may know, to submit your excellent scientific ideas to us to develop this area further. It turns out that the actual data on use of naloxone for overdose prevention is quite thin. And that's what we do at NIDA, which is to try to improve the amount of knowledge and information to guide clinical practice and guide policy.

I'm particularly excited today to learn from each of the presenters. The first three panelists were terrific, and I look forward to the group I'm going to be introducing and then the rest of the day to help guide our research program and our research portfolio in this area, so that together we can do a better job of addressing the public health and individual needs of patients in the
populations we serve.

I think that's the main information that I wanted to do by way of a general introduction. And so it's now my pleasure to introduce the first of our three speakers.

Dr. Ingrid Binswanger is joining us today. She's an assistant professor in the Department of General Internal Medicine at the University of Colorado and also a visiting fellow at the Bureau of Justice Statistics in Department of Justice, who are very interested in this topic. Some of the work looking at prescription drug misuse and problems are funded by Department of Justice, so this affects both health and criminal justice issues.

Dr. Binswanger.

Presentation – Ingrid Binswanger

DR. BINSWANGER: Hi. So I'll be talking today. I have really three main goals. I want to give an overview of naloxone for bystander use that will help set up some of the other presentations that come right after this one. And then I'll talk
about some of the work that we've done on high-risk
times for overdose mortality, particularly in
criminal justice settings.

I'll discuss the results of some work that we've done on the risk of overdose death after
release from prisons as well as some about jails. I'll also talk about some work that we've done from
interviews with former inmates about the acceptability of naloxone for bystander use in that population.

Then finally, I'll just briefly mention some of the other high-risk times, populations and settings that have been guided by the epidemiologic data.

So this is a picture of an intranasal kit that actually Dr. Walley uses in their program in Massachusetts and that is also the way that naloxone is used by paramedics in the Denver area, where I'm from.

So the rationale for naloxone for bystander administration is that it helps prevent complications of overdose through earlier
treatment, so before the paramedics get there, or
when fear of police inhibits calling 911 at all.
And we know from some of the qualitative work that
this is common, especially in heroin users and in
criminal justice populations.

The complications that we're trying to avert
with naloxone for bystander administration are not
only mortality but also morbidity, high cost
healthcare utilization in emergency departments,
intensive care units in hospitals, and things like
anoxic brain injury and aspiration pneumonia that
can come from a prolonged period without breathing.

It's generally distributed with the
education component that's on identifying
overdoses, administration, the need to call 911,
and rescue breathing. And I think it's very
important that the distribution of naloxone takes
place in conjunction with policy changes at the
state level to allow for 911 Good Samaritan laws.
This provides some immunity to bystanders who
witness an overdose and then call emergency
services so that they don't get arrested for having
paraphernalia or other -- prescription medications without a prescription around.

So there have been some evaluations of the existing programs that have taken place, and basically what these evaluations have generally shown, although a lot more data is needed, is that they are feasible programs. They're associated with increased knowledge and skills among the people who are trained.

They also do not seem to result in an increase in use by the people who have been trained to treat overdoses, bystanders, and they may be associated with an increased entrance into drug treatment because they provide additional education and contact with drug users. And finally, it looks like they're associated with a reduction in overdose fatalities in some communities, and you'll be hearing more about that.

I think it's important to stress that naloxone should be part of a comprehensive strategy, and we've already heard some of the components of such a strategy to help prevent
overdose. And these include prescription drug monitoring programs; prescription drug take-back events, where we reduce the amount of prescriptions that are in the home and potentially accessible to youth, especially teenagers; safe opiate prescribing education for physicians; expansion of opiate agonist treatment like methadone and buprenorphine; safe injection facilities. These have been used in other countries successfully where people can go inject heroin in an environment where somebody may be able to recognize an overdose and respond to it. And then also safe storage of prescription opiates in the home, again to prevent diversion to people in the family, such as teenagers.

So there are certain times. We've already heard about some of the populations that might have higher risk of overdose, but there's also certain specific times that are key for naloxone distribution.

So there's been international studies and also a recent meta-analysis looking at the risk of
death among former inmates. And these have all 
pretty much shown the same findings. The risk of 
death among former inmates from drug-related causes 
is high compared to the general population, and 
it's also high in the first two weeks after release 
from prison.

So I'll just show you some data from one of 
our studies in Washington state. This was a 
retrospective cohort conducted from 1999 to 2003. 
Actually, we're updating with NIDA funding the 
study from 2004 to 2009, and I'll just make a 
comment. I'm not going to show data from that 
study because we're still cleaning the data, but we 
have probably fourfold the number of overdoses in 
this updated cohort than we had in the first. So 
this problem has definitely not diminished, and 
it's probably expanded since 1999 to 2003.

The risk factor data comes from a nested 
case control study within the cohort study, and 
I'll just discuss a few findings from that. So the 
population was basically all released inmates 
during a four-and-a-half-year period from
Washington State Department of Corrections with a sample size of over 30,000 people. We linked data to the National Death Index to establish the deaths and the causes of death, and we had comparison data from CDC Wonder for the general population estimates.

Essentially, our findings were that the risk of death from all-cause mortality, not just drug overdose, but all-cause mortality was three and a half times higher than in the general Washington state population overall.

So the adjusted Washington state population death rate adjusted for age, gender, and race is with the red line. The columns represent the death rates in the former inmates. And then in the first two weeks after release from prison, the death rate from all causes was 12.7 times higher than the general population. Then it diminished somewhat to a baseline that was around three and a half times higher. For overdose deaths, this would actually be much more dramatic with 127-fold increased risk in the first two weeks.
So drug overdoses represented just under a quarter of the deaths, so 103 deaths out of 433 deaths. I'll just note that the mean age of death in this cohort was 41, so this is a very young population, dying basically.

The relative risk compared to the general population was 12.2 overall during the whole follow-up period for the drug overdose deaths. I put this in context of some of the other leading causes of death, some of which are also injury related, and two of the suicides in our cohort were also related to opiates.

So these are some of the substances involved in the deaths in our cohort. I just note that this is in the Pacific Northwest where there's a lot of methamphetamine and cocaine use. So it may be a little bit more skewed towards those substances than we might see in other parts of the country, but opiates represented were involved in about 44 percent of all the deaths. And 27 of the deaths, so about a quarter, had more than one drug involved.
In terms of risk factors for overdose deaths after release from prison, we found that so far in our case control study that a documented history of injection drug use in the prison medical chart or the substance abuse chart was associated with a substantial increased risk of both all-cause mortality and overdose mortality.

So 48 percent of the cases or the people who died had a documented history of injection drug use and 34 percent of the control, the adjusted odds ratio for the overdose deaths, was 7.2, and that was statistically significant.

We also looked at whether people had received opiate prescriptions, thinking that maybe this happened in some people who were on opiates for pain while they were incarcerated; so if they had been receiving opiate prescriptions for the 60 days before their release. And basically, we found no association for that group. This may change over time again. These data are from prior to 2003, and this might change since then.

So I then want to just comment about the
scope of the criminal justice system in the U.S. because I think these results have wider implications than you might realize. So the year-end population of state and federal prisoners in 2009 was 1.5 million with about 2.3 million people going in and out of the system, so they handled many more people than just the year-end population.

For jails, this is tremendously larger. So the number of people in jails at the year-end was .8, but 13 million people interact with the jail system, so are incarcerated and then released. So this risk of death after release from incarceration is particularly important for jails because it affects so many people.

A recent study with some colleagues at the New York City Department of Public Health showed that also this risk of death from drug-related causes after release also applies to the release from jail.

So this I think is pretty significant. The blue bars here represent the rate of death per
100,000 person years. The first set is from drug-related causes, the second set from homicide and the third set from suicide. And the other bars basically show that the risk of drug-related deaths in former jail inmates is also higher than among other New York City residents and among residents in the poorest New York City neighborhoods. So there's really something about this transition in incarceration that's particularly significant.

So now I'm just going to turn to talk about some data that we collected much more recently in a prospective cohort study of former inmates recruited immediately post-release, so basically within 7 to 21 days of their release from prison into the Denver area.

This is just to show you that this was a very balanced group of individuals in terms of race, ethnicity and gender. We had 25 percent women. Normally, the incarcerated population is about 13 percent female. The mean age was 41.

We had 32 percent reporting a history of an emergency department visit for an overdose. This
reflects a tremendous amount of health service utilization that is costly that's associated with these overdoses. Forty-four percent reported a history of injection drug use, and 10 percent had HIV.

When we asked people about whether they had witnessed a heroin overdose and whether the person lived or not, 46 percent said, yes, they had witnessed a heroin overdose. At the last witnessed overdose, did somebody, you or somebody else, call 911? Unfortunately, only 54 percent of the cases did somebody call 911. This is why intranasal or any other form of naloxone for bystander use is very important because such a large proportion of the cases, nobody calls 911.

Whether they were willing to receive training to use Narcan for a witnessed overdose, 86 percent said yes. Whether they were willing to give it if somebody they injected with overdosed, 90 percent of people said yes, they were willing to give it. So they were more willing to give naloxone than to call 911. People leaving jails
and prisons should be given Narcan, 76 percent of the people said yes.

So now I'm also just going to share one quote that reflects a couple of the themes that I've mentioned or touched on from some qualitative or ethnographic interviews we did with former inmates who were in this high-risk vulnerable time. These were people recruited within two months of release from prison.

And this gentleman shared with us that, "The last time I OD'ed, I was on parole. I did too much. I went back to my normal dosage, what I was doing before I went in, and that didn't work. I wound up in intensive care three days later from a coma. I know that when you come out of DOC your body is clean, so you need to be careful and know what you're doing, and you never know what you get."

And what's very unfortunate about this case is it took him several overdoses to understand this concept of tolerance and then the associated risk. This is why I think education that comes along with
naloxone distribution would be very helpful.

The other thing is that he had three days in the intensive care unit, which obviously cost probably more than $100,000. And he was uninsured, so obviously that's a tremendous amount of cost. It suggests that we should engage healthcare systems who may be paying for the care of these patients in helping with some of the costs associated with the prevention efforts.

I'll just mention a couple other efforts with criminal justice population. One of them is the N-ALIVE trial that was funded in the United Kingdom. It's a planned RCT to prevent deaths through distribution of naloxone in prison inmates. Unfortunately, I'm not quite sure what to think, but basically Scotland just started implementing naloxone distribution for former inmates. And so it's kind of had some effects on their ability to randomize people to naloxone. So there's some interesting ethical and research issues involved in this.

The other thing is the PONI program in Rhode
Island is also anticipating enrolling former inmates or actually people hopefully before they leave prison. And then also, the DOPE Project that we've heard a little bit about has worked in reentry centers. I think it is going to be complicated to give naloxone to people before they leave the prison, but that's probably the best time to do it.

So now I'm just going to touch on a few things. I think some of this has already actually been addressed. But some of the high-risk times to think about for naloxone distribution are not only this release from prison to the community setting but discharge, for whatever reason, from drug treatment and detoxification is a very dangerous time. That would be a great time to give people naloxone.

I think also the induction of treatment with longer-acting opiates is also high risk, both for methadone and buprenorphine and other long-acting opiates. I think that this is an issue probably in drug treatment and in pain management.
The reason that I think that this is important is this data out of the United Kingdom. This was a large study of people in opioid substitution treatment in primary care. So obviously, overall, being on treatment saved lives or was associated with a lower risk of death, but the first two weeks of treatment had somewhat of a bump. That's the first arrow you see there in terms of the risk of death. And then the first two weeks off of treatment was also associated with an increased risk, but considerably higher.

These are deaths per hundred person years, which is a really horrible death rate, very, very high. So if you imagine, almost five for people off of treatment per 100 person years is tremendously high.

So I've just made some recommendations about some of the populations. We've already discussed a few of these: drug treatment clients, people with prior overdoses, and so on. In prescription opiate users, it might make sense to target naloxone to people on high dose, people who are opiate naive,
so at the initiation of treatment, people on concurrent sedating medication such as benzodiazepines, people who use alcohol or who have comorbid liver and respiratory disease. And I should also just mention it's worth thinking about people who have trouble accessing medical care, very rural people or for other reasons can't access care quickly.

These are many of the settings we've already seen from the DOPE Project that had been targeted. I want to just mention about medical settings provision of naloxone to patients with a prescription, or if it's OTC, fine, that'd be great. Emergency departments and primary care settings are probably good settings to think about.

The reason I mention primary care specifically is because I work in a community health center in Denver where we see many of these patients who are at high risk for overdose. So I pretty much see people in all of these risk groups there. And I think if it was more available to me to prescribe to my patients, I could probably get
access to some special populations that we've already identified. I could also reach people who don't themselves identify as drug users, so may not go to a community-based organization to get services but nonetheless are at risk.

Insurance billing would overcome some of the cost issues, especially for community-based organizations that don't have a lot of funds necessarily to pay for naloxone. It would also be very analogous to other prescriptions I write, such as epinephrine for individuals with a history of anaphylaxis or glucagon for diabetics. It's basically giving a prescription to someone who may use it on someone else who needs it. And then it would encourage physician patient discussion about the true risks of overdose, and I think that might be the most useful part of having the naloxone to give in primary care.

So I'll just conclude with a couple statements about that I think former inmates are definitely an appropriate target population for overdose education and increased access to
naloxone. It's definitely acceptable to the population who is most likely to have it used on them or to use it on other people. I think that's very important and may get to some of the ethical issues that we may discuss later today.

Epidemiologic data can certainly guide the selection of key times, populations and settings for increased access. And I think we definitely need more further research about some of the implementation issues, especially in criminal justice and some of these special settings.

So thank you.

(Applause.)

DR. COMPTON: Thank you very much, Dr. Binswanger.

I'm pleased to introduce our next speaker, who will be Dr. Alex Walley from Boston University. Dr. Walley is an assistant professor of internal medicine at Boston University and will be telling us about the naloxone distribution program in Massachusetts, which I would suggest will show us how the public health community in some ways is way
ahead of the research community and the regulatory officials. So we wanted to learn from what's happening in real-world settings, and Dr. Walley is here to teach us about the Massachusetts story.

**Presentation – Alex Walley**

DR. WALLEY: Thank you, Wilson. And thank you to the FDA, CDC and NIDA for giving me this opportunity to both come and listen and learn and also to tell you about what we're doing in Massachusetts.

So I'm going to start with a form. This is an enrollment form from our overdose education and naloxone distribution program. And you can see the date on the form is March 15, 2011. Location there is 5, which stands for detox. So this is a person who got overdose education and a naloxone distribution in a detox.

So this person had witnessed 20 overdoses in his lifetime at the time that he was trained. And in the last 30 days before he was trained, he used heroin on 30 of those days. He used benzodiazepines, a prescription pill likely without
a prescription, for 15 days, and he used cocaine or
crack for 15 days.

In October of the same year, so seven months
later, he returned to the detox for another detox
treatment. And at that time, he requested a refill
for his naloxone. So he'd already been trained,
and he requested a refill. And the reason he
requested a refill was because he used his naloxone
during an overdose. And so we collected
information on that overdose as we do when people
report an overdose.

So the person who overdosed was a friend of
his, a male friend, who had used both
benzodiazepines and heroin. And this occurred in a
private setting. The person lived. 911 was
called. The firefighters or EMTs came, and in this
case, there was a negative interaction with the
firefighters and the EMTs.

He stayed with the person until medical
attention arrived. And in addition to delivering
naloxone treatment, he delivered a sternal lip rub.
He did rescue breathing, and he did this without a
barrier.

So that's just an example of what we're seeing in Massachusetts as far as training and overdose rescue reports.

For the talk I'm going to give, I have two take home points. Our experience in Massachusetts is that opiate overdose death rates have been reduced where overdose education and naloxone distribution has been implemented. And I'm going to show you a study that we're conducting that I think shows some evidence of that. And then also, that the nonmedical community health workers provide effective overdose education and naloxone distribution with low rates of adverse events.

So this is a map of the 351 towns in Massachusetts that are shaded by the number of deaths that occurred between 2004 and 2006. So the darker the shade, the more deaths in those towns.

The initial OEND programs started in Boston and Cambridge in the years 2006 through 2007. You can see them marked in pink. In 2007-2008, the Massachusetts Department of Public Health expanded
this effort to the additional towns there. And you can see that most of those towns are dark shaded.

Then there was further expansion in 2009. And then here you're going to see, in a second, the cities that are marked here with yellow circles. Those are cities that had more than five opioid overdose-related deaths in each of the calendar years 2004, 2005, 2006, where we did not implement programs up through 2009.

So the diamonds are the towns where we did implement programs, and the yellow circles are the towns where we did not implement programs that had high rates of opioid-related overdose deaths.

So based on this difference between towns where we implemented and towns where we did not implement, we conducted this study called the INPEDE OD study. And the objective there was to determine the impact of opioid overdose education with intranasal naloxone distribution programs on fatal and nonfatal opioid overdose rates in Massachusetts. And this study was funded by the Center for Disease Control and Prevention.
So it's a quasi-experimental interrupted time series, again, 19 Massachusetts cities and towns with five or more opioid-related unintentional or undetermined poison deaths in each year from 2004 through 2006. And the setting was these OEND programs that were implemented in some of those towns. The outcome was fatal opioid overdose per town population per year using registry of vital records and statistics, basically death certificates. And then our second outcome was opioid-related emergency department or hospital discharges per town population per year.

Our analysis approach was Poisson regression which compared annual opioid-related overdose rates among the cities and towns by OEND implementation. This regression gives us natural interpretations as rate ratios. We adjusted these models for city and town population rates of age, gender, race, ethnicity, poverty level, inpatient detox treatment slots, the number of methadone treatment slots, the number of state-funded buprenorphine treatment slots. So Massachusetts has a relatively
aggressive program of funding buprenorphine
treatment in the community. And then prescription
to doctor shoppers, we used the prescription
monitoring program in Massachusetts to calculate a
rate of doctor shopping per town, and then adjusted
for that. And then the year to adjust for the
temporal trends in overdose rates, opioid overdose
rates.

So these are the results from our final
model that we did, and you can see the first row,
no enrollment is the reference group. And these
are the town/year strata, so the town/year strata
where there was no enrollment in the towns, those
yellow circles that you saw in the map before, and
also, the diamonds in the years before they had
enrollment.

So that's our reference group. And compared
to that, we looked at two other categories, so
those towns that had relatively low cumulative
enrollment, 1 to 150 people per 100,000 people in
uptown population and greater than 150 people
enrolled and trained per town population.
And you can see that in the adjusted analyses, there was a substantial and statistically significant reduction in the adjusted rate ratio. So that's that .73 there for the enrollers with lower enrollment, so that's a 27 percent reduction in the overdose death rate in those towns. And then in those with high rates, greater than 150 enrollments per 100,000, .5 was the rate ratio, which is a 50 percent reduction in the rate in the towns with high enrollment.

We ran similar models looking at -- instead of opioid-related overdose death, we looked at opioid-related ED visits and hospitalization rates. And you can see with these models, in both the adjusted and unadjusted models, there is really no statistically significant or substantial difference in the utilization of ED visits or hospitalizations at the different levels of implementation.

So the summary I wanted to stress here for the INPEDE study is that fatal overdose rates were decreased in Massachusetts cities and towns where OEND was implemented, and the more enrollment or
the more implementation, the lower the reduction in overdose rates. We did not see any clear impact on acute care utilization such as ED or hospitalization rates.

So I'm going to explain a little bit more about what we do in Massachusetts, what is this program, how does it look. I'm going to talk specifically about our standing order model as well as a little bit on intranasal naloxone.

So the Massachusetts overdose OEND pilot is a standing order model. We conduct this pilot under state drug control program regulations. It allows the medical director to issue a standing order for the distribution to potential bystanders.

What this means is the traditional doctor or prescriber patient interaction is not necessary. A community health worker can distribute -- or do the overdose education and distribute naloxone under a standing order from the medical director. This allows us to access populations at highest risk, we think.

The components of our OEND program are very
similar to the DOPE program and to other programs that came before us and have come after us across the country. So community program staff enroll, train, and distribute naloxone. The kit that we use includes two doses as well as instructions in the kit. The curriculum delivers education on overdose prevention, recognition, and response, not just on naloxone. And all of the programs that do OEND have access and refer to addiction treatment as it's available and when it's appropriate. We receive reports on overdose rescues when people come back for their refills, and each overdose report is reviewed by a data committee.

The staff members who do this training of the bystanders, they complete a four-hour didactic training, and they complete after that a knowledge test. And they have at least two supervised bystander training sessions before they do training sessions on their own. Each of the sites participate in quarterly all site face-to-face meetings, and we have monthly adverse events phone conferences with each of the sites where we discuss...
events that come up.

I want to talk a minute about intranasal administration from our perspective. It has pros and cons. The pros are that it's the first line for some local EMS, and it really has transformed the way the Boston EMS deals with overdoses, I think, making it more efficient.

There are randomized controlled trials that show that there's a slower onset of action of intranasal naloxone compared to intramuscular but milder withdrawal symptoms. It's acceptable to nonusers who are important stakeholders in our efforts to address overdose in Massachusetts. There's no needle stick risk for intranasal, and the disposal concerns are much less.

The downsides are that this delivery method is not FDA approved. There's been no large randomized controlled trial. There's assembly that's required for our kit, and it's subject to breakage. It's a high cost for each kit, not relative to an EpiPen, by the way. It's actually much cheaper than that. But for a program that
doesn't have a lot of external funding or doesn't have insurance coverage, it's $30 per kit.

The naloxone maker is currently not participating in the Medicaid rebate program for outpatient medications, and so this means that insurance is no longer covering it. They were actually covering it as of four months ago, but that's changed. And there's a current national shortage, which I think is a big issue. I'm sure FDA is dealing with this in a lot of drugs, but now it's occurred with naloxone.

So I'm going to give you an idea of the scope of what we're doing in Massachusetts. So the study that I showed you took us up to 2009. But now we're in 2012, and you can see that some of those towns where we had not implemented before, we now have implemented the program. So that's Worcester, Lowell, and Lawrence, which are high overdose towns.

We have almost 13,000 individuals in Massachusetts who have been enrolled and trained, and we're enrolling at a rate of 300 per month, so
that's 10 people per day. We documented 1300 rescues since the beginning of the program, and our current rate of rescue documentation is 30 per month or 1 per day.

We enroll in a lot of different places, and that's really due to the creativity of the individual programs, these community-based public health programs. So detox, addiction treatment, is one of the places where we're enrolling the most people right now. We continue to enroll at the four syringe access programs that exist in Massachusetts as well as drop-in centers, community meetings, other substance abuse treatment locations, including as well as methadone clinics, medical facilities. And some of the sites are doing home visits. They're going to homeless shelters, and they're doing street outreach.

So I just want to highlight here the difference between the light blue and the neon green here. The light blue are the people who are either actively using drugs or they're in treatment, whereas the neon green are the nonusers.
They're usually families or parents or staff members who work with people who are at risk for opioid overdose. And you can see at the community meetings, the vast majority -- and this is one of our fastest growing sites. The vast majority of the people we enrolled are actually nonusers. These are parents, family, and friends.

Our enrollee characteristics, you can see here that approximately a third of the people we've enrolled are nonusers. That's the far right column. And in that group, even though they're nonusers, they witness overdoses at almost -- well, over 40 percent of them have witnessed overdoses. And among the users, three-quarters of them have witnessed overdoses. Half of them have had an overdose.

Among the half that have had an overdose, 44 percent have received naloxone themselves before they were trained. High-risk times like inpatient detox or being incarcerated are common. And among all the people that we train, if you're in the user group, 7 and a half percent of them return to us
and report that they use the naloxone for an overdose. That's a number needed to treat 15. Among the nonusers, mostly parents and family, two percent of them return to us and report an overdose. And so we have the nonusers actually using naloxone to reverse overdoses.

What drugs are people using among the users? What substances are they using at the time when we enroll them? Well, I just think we can't stress enough that polysubstance use is occurring in the community, and I think it's one of the major drivers of overdose. And we see that in the people that we're enrolling.

Heroin has been and continues to be the major issue in Massachusetts, and prescription pills like benzodiazepine and barbiturates are behind that. We do a lot of enrollment at methadone clinics, so we see a lot of methadone. There's also cocaine, alcohol, and buprenorphine.

So when people come back, this is to report their overdose, what do they say happened? Not their overdose, the overdose that they reversed
using naloxone, their overdose rescue. What else had they done besides deliver naloxone?

Well, among the users, about 30 percent of the time, they've called 911 and got public safety to help them. This number, about 30 percent, is similar to many of the other studies of these programs, and also the studies of drug users that are witnessing overdoses without naloxone. The nonusers are more likely to seek help, although not universally seeking help, even though that's what we train them to do. Rescue breathing occurs about a third of the time, and almost all the time, bystanders stay with the person until they're alert or help arrives.

What about adverse events? So among the 1300 overdose reports that we've documented, seven of them were deaths. And I can tell you that having reviewed each one of these, in each case, these were people who were dead when the response came about. So the person was already dead. They didn't have any response to the naloxone because their heart wasn't beating any more.
Overdose requiring three or more doses, so this does happen. And so this scenario is really when -- because we only give two doses in the kit. It's usually the person gives two doses, and then they've called 911, and the ambulance comes, and they give more naloxone. So that does happen.

Recurrent overdose. This is, I think, Dr. Terman referred to this. This is when somebody is usually on a long-acting opioid or has severe liver disease, and their overdose is reversed and then it recurs after the naloxone wears off. And so we have one report of that.

Precipitated withdrawal I think happens more commonly than what we see, but this is what has been reported on our reports, very low rate of .3 percent.

Difficulty with the device. We recognize this is an issue. The device either breaks when it's assembled, or it's already broken. But it happens very uncommonly, about .7 percent of the time.

Then negative interactions with public
safety. So about a quarter of the time, the interaction when you call 911 is a negative one. That means three-quarters of the time it's either neutral or positive.

Confiscations are also a consideration if we're going to be distributing this to bystanders. What if we distribute it to them and it gets confiscated either by police, or by a homeless shelter, or by a drug treatment program?

So I just want to reiterate my take home points. Opioid overdose death rates in Massachusetts were reduced where OEND was implemented. Nonmedical community health workers can provide effective OEND with low rates of adverse events.

I think just to address the purpose of today's conference, the implication for me is that naloxone should be made more widely available to trained laypersons in an effort to reduce deaths due to opioid overdose. And then I have just three considerations.

So I think from our experience here in
Massachusetts, we can say that intranasal works in the real world, and it's popular. We've really been able to draw in a diverse group of stakeholders to be invested in this. It could be improved, however, with a one-step affordable FDA-approved intranasal delivery device.

The nonmedical community health workers provide effective OEND. I think this is a lesson really from other programs that we join in: broad dissemination to high-risk groups and their networks, family, friends and staff.

It's facilitated in our case -- this is one place where Massachusetts is somewhat unique in the standing order model. Most of the other programs do not have that, and that's really facilitated for us getting to thousands of people in a relatively short period of time. And if there's any way we can figure out how to make that easier for other places, I really think that would be a step forward.

Prescription status is a barrier when you're talking about wide distribution outside of medical
Fear of police is a barrier to help seeking, and that's been demonstrated in multiple studies. And we don't have a good Samaritan law in Massachusetts. And I think while that is not the only answer, that I think is helpful in getting better interaction with the emergency medical system.

There are a lot of people to thank, but thank you.

(Applause.)

DR. COMPTON: Thank you, Dr. Walley.

Our third speaker is Dr. Nabila El-Bassel. Dr. El-Bassel is a professor in the School of Social Work and Public Health at Columbia University and is a current member of NIDA's advisory council.

Dr. El-Bassel will be presenting to us on an unusual project taking place in Central Asia to show that these kind of projects can benefit from information gleaned from international settings as well as the United States.
DR. EL-BASSEL: Good morning. It is a great pleasure and honor to be here and to talk about the topic that I'm very, very committed to. I spent the last seven years in Central Asia doing prevention science in HIV and overdose prevention. And the title of my talk is Project Renaissance: An Overdose Prevention Among Injection Drug Users in Kazakhstan.

What I'll do in the coming 20 minutes, first, I'll talk about policies on availability and distribution of naloxone in Central Asia. Second, I want to share with you findings from Project Renaissance. It's a randomized control clinical trial and coupled with HIV prevention that incorporates overdose prevention. The study is funded by NIDA, and I want to say that the study is underway, has not been completed. So what I'll share with you is data from the baseline and six months' follow-up.

I'll talk to you about overdose rates, use of naloxone, and overdose reversals among couples
and their social networks. I'll talk about mortality rates among participating couples in the study, and also to look at the relationship between access to naloxone and its impact on use of heroin and overdose.

For you, having been in the region, as you see, Kazakhstan is Central Asia. It has borders with Russia, China, Iran, and Afghanistan. And I will highlight Afghanistan given that Afghanistan is the largest producer of opium and 35 percent of the opium production or hemp production from Afghanistan, it goes through Central Asia. Kazakhstan by itself, if you look at the red lines, has 10 drug trafficking routes of heroin to other countries from Afghanistan. So the access to drug use and drugs from Afghanistan to this region increase clearly drug use and also increase the cost -- reduce the cost of drugs which increase overdose.

This is a map that published recently by the Lancet, showing that there are 250,000 registered IDUs in Central Asia. And I am saying registered
because there are many more that are not registered.

In terms of the rate of fatal and nonfatal overdose among IV use in Kazakhstan or Central Asia, it is unknown because there are no centralized systems for data collection or reporting in all these countries. However, there are reports from people who are sitting in this room showing that more than two-thirds of injection drug users overdose at least once.

As I mentioned earlier, the geographic proximity to Afghanistan increases the drug use but also decreases the purity of drugs, which increase overdose. What we see in Kazakhstan, based on several reports, the IDUs mix heroin with other drugs and alcohol, which increase the overdose. There is a high rate of incarceration and discrimination among drug users, which also increase the risk of experiencing, overdose which we have seen also in the United States. The issue of high risk of HIV and HCV also compromises the immune system of the drug users, which increase the
Discrimination against drug users in the region is huge. Fear of the police prevent drug users from calling the police during an event of overdose. Also, it prevents their social network to call the police. And in many cases, when they call the ambulance, the ambulance brings the police. And in many cases, the drug users and the people who witness the overdose, they are arrested and put in jail. And also in many cases, drug users are taken into detox and put in detox for maybe a few months. And then they go out, and again, they go through the same process. So this leads -- not only the drug users but all people who witness drug use will not call the emergency services to deal with these issues. Also, there is lack of naloxone in ambulances and in hospitals.

Another problem among drug users that increases overdose is the ineffective methods that the drug users use, injecting saline solution, taking a shower, or shaking the person. These are
strategies the drug users use to deal with overdose. Again, I want to highlight that there is low quality of medical care related to overdose in emergency services. And in many cases, the medical services provide primarily CardiaMin to treat overdose.

To give you a little background on the policies of overdose in Central Asia, in Kazakhstan, the overdose is registered since 2004. It is only on the list of life-saving medicine. However, it's available in one city, in Almaty. It's not available in pharmacies. And, in fact, the sad story, in 2011, the government did not include naloxone on the centralized purchase list of medications, and therefore there is no naloxone in the country.

In Kyrgyzstan, I want to thank the Open Society Foundation for providing us and working together with funding to advocate for registration of naloxone. And in 2012, naloxone became registered in Kyrgyzstan. However, it's not available in many places, and there is limited
distribution of naloxone.

In Tajikistan, a very poor country, very, very close to Afghanistan, a huge drug problem. Naloxone was registered in 2007. It is available in ambulances. It is distributed somewhat in a limited way by the Global Fund and by the Open Society Foundations. It also has limited distribution, peer distribution.

Uzbekistan is a country that is very hard to get into it. We're trying to work in this country, and we have limited data about the country. But naloxone, not registered, is not on the list of life-saving medicine. And there are NGOs working there, the Global Fund and the Open Society Foundations, to supply some naloxone into emergency services but no peer distribution.

This is a map that was published by the Open Society Foundations recently showing the peer-based naloxone administration. And you see the dot lines, there are very countries, low and middle countries, that have access to naloxone, unfortunately.
So the second part of my talk is Project Renaissance, which I'm very, very excited to talk about it. This is a randomized control trial. It's the first trial that has been done in the region. The intervention, it incorporates HIV prevention with naloxone prevention. And I want to tell you that it's very important to integrate HIV and naloxone because in some regions in Central Asia, the prevalence rate of HIV range between 20 to 25 percent.

So the purpose of the study and the primary outcomes is the reduced incidence of overdose and mortality rate, to reduce incidence of HIV and other STIs and also reduce the drug risk behavior. The secondary outcomes are very important, is to improve access to harm reduction programs and HIV treatment and care.

Why we combine again HIV with overdose, we know that overdose is the leading cause of death among injection drug users living with HIV. HIV infections increases where there is drug overdose, and access to naloxone, in fact, is found to
increase engagement in HIV treatment and care.

This is the clinical trial we used. As you see here, we screened people. We screened around 966 individuals. And we did the baseline and overall randomized at 300 couples, 600 injection drug users in two arms. We have data about the 600, but I will talk today about the 600 IDUs.

After the baseline, we randomized the couples into two arms. The first arm is providing four sessions of couple approach using overdose and HIV prevention, and the second arm which is called placebo arm, where we provided naloxone, but the intervention is not HIV. It's health promotion intervention. And we follow the couples at six months and 12 months.

These are the lists of the core components of the intervention that primarily related to overdose, and we're going to talk about intervention on HIV. As you see here, we did a educational piece, education about causes of opiate overdose, how to avoid overdose. And what I'd like to highlight in these core components is that we
talk a lot about how you can work with your social
network, how you can work with your family to help
you to live and how to use naloxone.

In another piece we do, we end the
intervention itself for both arms. We give a
naloxone kit where the IDUs, or the couples
together, or one of the couple members, go to the
primary care setting and receive naloxone. We
could not give ourselves the naloxone to the
participants, but we give them a prescription to go
and get the naloxone kit.

If you look at here the description of the
population, they are young, 35 average age. The
majority are Russian, which is typical in the
region, and the majority are married. The history
of incarceration is quite high. And if you see
here, in terms of the HIV prevalence rate,
26 percent, but if you only look at the IDUs, the
prevalence increases to 28 percent. HCV is a huge
problem among this population.

Injecting heroin. And here, as you see,
76 percent injected heroin, and they are using
other type of drugs. And we are seeing increase in methamphetamines, and binge drinking is a huge problem in the region.

Because we're dealing with couples, we have data about women and men. And as you see from this figure, men use more than women, all the types of drugs, but still women are using. And if we look at the proportion of injection drug using women in our sample, 64 percent of the females are using, injecting drugs, and 95 percent of the men.

We asked questions among the heroin users. And here, I'm moving to heroin users. In our sample, we had 458 heroin users, and we asked them how many inject drugs. As you see here, 92 percent ever injected drugs; share needles, 50 percent. And when we asked the question where do they use drugs in Central Asia, typically the drug is used at home, at a friend's place, and less in public places, as you see in this figure.

We also asked them what do they do when they use drugs, and many of the heroin users say they use alcohol while they're high on heroin, which
increases the overdose. And they mix drugs with heroin more than a third of the time. And here, as you see, when we ask what do you mix with heroin, many of them say that they mix Demerol or Benadryl.

We asked if they ever overdose, and 74 percent of the population, the 458, said they ever overdose. And in the past six months -- we are not asking historically, but in the past six months, we see 23 percent overdosed. And we ask the question if they knew people, if they overdosed, and more than 50 percent said yes. And if they knew people who died from overdose in the past six months, 26 percent of them, they said they know people who died from overdose.

We asked them what do you do when this happened, and here in the past six months, it's current behaviors. And 23 percent, they said they called the ambulance, and only 14 percent received medical care.

We were interested in comparing people who overdose and who did not overdose in the past six months. Now, you see in this figure -- and we used
random effects model because when talking about couples and to control for dependency, we used the random effects model.

We found that people who overdose, they're more likely to mix other drugs with heroin. They're more likely to drink alcohol while they're high on heroin. They're more likely to know people who experienced an overdose in the past six months, more likely to be depressed than those who did not overdose, and also more likely to have drug-related offenses.

So we ask them how many of them, of the couples, received the kit of naloxone during the intervention. As you see here, 85 percent of the couples received the kit during the intervention, and 42 percent of the couples, at least one of them or both, went to get the naloxone from the primary care.

During this study, 89 percent reversal happened from baseline to six months. We haven't finished the study yet, but this is at the six months. Seventy-four reversal, which is
83 percent, occurred where the study participant administered the naloxone to their study partners or others in their network. And 15 reversals, 17 percent, occurred where someone administered naloxone to the study partners.

Mortality rate -- and we have not finished yet the study -- is 6 percent. And 25 percent of the deaths occurred because of overdose. I would like to highlight that two of the nine participants who died from overdose exchanged the voucher in the study for the naloxone kit. One overdose death occurred when naloxone was administered; however, heavy alcohol use was reported in this case. There was one death that was related to HIV, to AIDS. So we see that mortality rate from overdose is higher than from HIV.

We were interested in looking from baseline to six months, what happened with injection heroin use. And what you see, we're very excited to see the reduction of rate of injection of heroin from baseline to six months.

We also were interested if there is a
reduction, overdose reduction, from baseline to six months. We're also delighted to say that there is a significant reduction from baseline to six months, 18 to -- so we are delighted to see this kind of finding.

We also were interested in drug risk behavior. We looked at sharing syringes or cookers, and we are seeing that there is a reduction of all population, meaning that really the intervention so far, it's really working well.

We were curious to see whether or not having access to a naloxone kit and naloxone itself would increase heroin use or having naloxone would increase overdose. But that's a question that we ask ourselves with the implementation of this study. The good news, there is no association between having access to naloxone and injecting more drugs or having access to naloxone and increasing overdose. This is great news for us, and we're very happy about it.

So in conclusion, I'd like to say that training IDUs and their partner to administer
naloxone, it's feasible. It can be done. It is safe. It can prevent fatal overdose among not only people who inject drugs but also their networks.

Use of naloxone averted fatalities during overdose events, and participants and their social network told us -- we have a lot of qualitative data -- told us that they know how to use it, they talk about it, and it's safe to take it. The good thing about this study is not only we're collecting the outcomes, but we have a lot of qualitative data to give us information about the implementation phase.

So providing naloxone prevention, what is really interesting and we're excited about it, it increases recruitment, engagement of IDUs in the study and in treatment. That's the first really evidence to show in the region that naloxone not only saves lives but also can help participants to stay in treatment.

So the good news, we see significant decreases in the rates of overdose, injection heroin use, and sharing syringes and cookers among
IDUs participants from baseline to six months. We also see that obtaining naloxone kit was not associated with reporting injection drug use or overdose at six months. However, we know that although the voucher system helped to link some IDUs to the primary care, still it is a barrier for them to go to primary care because of discrimination, because of oppression, because of registration of drug users.

They don't want to go there. They told us they prefer if we give them the naloxone through the intervention, or they have access to it easily. Because going to a primary care in the region, it means that the drug users need to be registered, and sometimes they're forced to go to detox for months. So therefore, it was not an easy -- it's a barrier. Despite this barrier, 42 percent of the couples went and got the naloxone.

So for us, we think that given all these barriers, we believe that in future studies, we will hopefully be able to distribute the naloxone during the study, but also we were hoping that we
can provide easy access over-the-counter, where they can get it and survive. So we're excited very much that we are introducing naloxone into the region, and we're showing that naloxone can work. And it saves lives and empowers drug users to seek drug treatment and HIV treatment, which is really an important issue.

It also reduces the medical cost. And for me and for our team, what we really liked very much about the study, it improves attitude of medical staff and policymakers toward IDUs and sends an important message that IDUs deserve to live. And that's what we're seeing, that it's happening in the region.

So I want to thank very much the team in Kazakhstan who's working very, very hard to make this happen. I want also to thank my colleague who's in the room, Dr. Louisa Gilbert, who has been working very hard on this project, and Dr. Chris Beyer.

This is a memory that I have from the start of the study when we sat with the minister of
health and Republican AIDS Centre in the region to
talk about naloxone. And we were challenged and
continued to be challenged, but luckily they became
partners with us in this study.

I also want to thank NIDA for supporting our
study and believing in the work we're doing there.
And I want to thank other people that have been
working in the region for many, many years: the
Open Society Foundations for their investment in
the region, the Harm Reduction Network, the Eurasia
Harm Reduction Network, Population Service
International, UNODC, and Global Fund. They all
are working very hard to introduce naloxone into
the region.

Thank you very much.

(Applause.)

Questions and Answers

DR. COMPTON: Thank you, Dr. El-Bassel.

Now we have the opportunity to entertain
questions from the other members of the panel of
our three speakers and then from the members of the
audience. If you'll please come up to the
microphone and introduce yourselves when called.

Any questions from our panel for the

speakers?

(No response.)

DR. COMPTON: Well, I actually have a

question for Dr. El-Bassel, one sort of very basic

question.

What was the formulation of the naloxone that

was distributed? Was it injection or intranasal?

DR. EL-BASSEL: It was injection. Nasal is

not there yet.

DR. COMPTON: Thank you.

All right. Let's start up with --

DR. SOMOZA: Hi, I'm Gene Somoza from the

University of Cincinnati and the Cincinnati VA

Medical Center. This is for Dr. Walley.

I'm wondering if you can describe some of

the challenges. For example, was the Massachusetts

State Medical Board okay with this, of giving

prescriptions to people that weren't sick, those

kind of things? Were they okay with that? Or

maybe they just don't even know about it.
I mean, we're having trouble in Ohio trying to do something like you've done already.

DR. WALLEY: Right. So it's a great question. So the question was, whether the state medical board has endorsed this program. And the answer is they haven't stated an opinion on it. And it's actually not until this year that the issue may come up in front of the state medical board.

And so I'll just say in North Carolina, and I believe in Pennsylvania, there is an endorsement from the state medical boards for these programs.

But our program doesn't depend on prescriptions, and so I tried to emphasize that some. It's supported by the state department of public health and a standing order that's issued by the medical director, who happens to be me, through the state public health.

So we have about 13,000 individual bystanders who have been trained. It's about over 35,000 units of naloxone that's been distributed, and that's all under that standing order.
But I have to say, we are trying to make prescription naloxone more available because I think there's a clear rationale for it, but there are barriers to that. And it's getting it at the pharmacy. That's not easy to do. It's getting insurance to pay for it. And then the big one really is getting doctors or prescribers to prescribe.

I would point to Project Lazarus in North Carolina as kind of the model program that's been able to figure that out.

DR. SOMOZA: Thank you very much.

DR. COMPTON: Next question?

DR. LEONARD-SEGAL: Hi. I'm Dr. Andrea Leonard-Segal. I direct the Division of Nonprescription Clinical Evaluation at FDA, and I have a question for you.

I'd like to know a little bit about the particulars of the training that these users and nonusers are receiving so that they can administer the medication appropriately, and how intensive that is, and what kinds of materials you're
providing to them so that they have something for reference -- I'm assuming they've got stuff like that -- in consideration of what over-the-counter possibilities may be ultimately.

DR. WALLEY: Great. So what is the training like? And I think you're talking about the training of the bystanders, the people who actually carry the naloxone around in the community.

So as far as what's involved in the kit, I know I brought two kits, and I believe there's others in the audience who probably have kits on them from different places. And so maybe we'll have those up here so people can look at them at the break.

But essentially, they include two doses. and then the administration device, whether it's a nasal atomizer or a needle. And then they include instructions for reference. Almost all the kits that I'm aware of include those instructions. And they reinforce the training.

And the training really depends at least -- you saw the different sites where we train
people. The trainings look different at different sites, honestly. A community meeting, it's typically a half hour training that's didactic with opportunities, and then a demonstration in front of a group with opportunities to ask questions; whereas a training at a syringe access program is more likely to be one-on-one. And it really begins with an assessment of the person, the potential bystander's knowledge, so you know how much training you have to deliver. And then that training is adapted at that point.

The major elements that we stress at these trainings, before we get to the naloxone administration and how to do that, because that's always an element, it's does the person understand the risks of an overdose and how to prevent an overdose; do they understand how to recognize an overdose; and do they understand how to respond?

The response includes naloxone, but that's really only one of four major elements. The other three are calling 911, rescue breathing, and staying with the person until they are alert or
help arrives.

In a nutshell, that's the training. I hope that answers your question.

DR. LEONARD-SEGAL: Yes, it does. And based upon what you see in these training programs, how easily do people grab onto this information, and what are the problems that you have identified in the training that seems to require extra effort?

DR. WALLEY: So I would say that people, at least in Massachusetts, who get trained are very motivated. And I actually think receiving the naloxone itself from a parent who's either had the experience of a loved one overdosing or has heard of somebody, or an active drug user who no doubt has seen overdoses in the past, they're very motivated to get this, to listen at that setting. So I think that really means that people attend very closely to the training.

So the barriers, I mean we've had some cases, very few. We'll have a homeless person with mental illness who really can't perform the training. That happens very, very rarely. And
other than that, the people who come to us to be
trained, we haven't seen that many problems. It's
more implementing in different environments.

So, for example, the emergency department
for us is a place we're targeting, and it's been
harder to figure out how to do trainings
effectively in the emergency room because of
logistics of like at what point do you interact
with somebody, who does it, where does the naloxone
get kept, what are the regulations along the
pharmacy and so forth.

The incarcerated population is another group
that's difficult just because working with -- the
jails aren't set up for overdose education and
definitely not set up for distributing naloxone
when you leave.

Some of the substance abuse treatment
programs are resistant because they really have an
abstinence philosophy, and they feel like they are
curing people, and therefore they're never going to
need naloxone despite the fact that we know that
addiction is a chronic medical illness that
relapses and remits.

DR. LEONARD-SEGAL: Thank you.

DR. COMPTON: Question from the front?

MS. RALSTON: My name is Megan Ralston with the Drug Policy Alliance. I have a question about standing orders for Dr. Walley.

You mentioned it very briefly in your presentation, and yet it's such an important component of community-based naloxone distribution programs. Can you just speak briefly to -- just for the benefit of everyone in the room, just make sure that everyone is clear on what standing orders are and why that's a critical element?

And then maybe you can talk more about if we have difficulty with moving naloxone OTC, could there potentially be a strategy of trying to get other medical directors and others such as yourselves to come together to issue like a statewide or countywide standing order?

DR. WALLEY: I want to acknowledge as I answer that -- so the question's about standing orders, say more about it, and can it be more
broadly applied.

So I just want to say that in Massachusetts the only -- this is both a top-down and a bottom-up effort. So there was fertile ground among community-based organizations who were motivated to do this work, number one. And then there was incredible leadership from initially the Boston Public Health Commission and then the Department of Public Health to support this. They saw it, as an opioid overdose death, as a huge priority, and so they've supported this.

The method they came up with was, in both cases, the city and the state, was having a medical director issue a standing order that allowed nonmedical people to train people in overdose education and distribute naloxone under the medical license of the medical director without a nurse or a doctor or a physician's assistant involved in that transaction directly.

So I like the model. It's worked really well, although I think -- we still call ourselves a pilot, which makes me nervous because we're still a
pilot, which means that -- and so even in Massachusetts, I think we need to integrate this into the public health code or through the drug control regulations, or have it legislated so it's a permanent program.

Other places have had difficulty in coming up with this model, and I think largely it's because they don't have that strong leadership that we've had from the top at public health. And I know the Department of Public Health is willing to talk to other public health agencies and discuss how we've set it up.

But I don't have a great answer to your question. I support it, but I think other states, other localities, need to figure it out for themselves and need that leadership, basically.

DR. STANCLIFF: Sharon Stancliff from the Harm Reduction Coalition.

Dr. El-Bassel, I am wondering if in some of your qualitative data you've had experiences parallel to mine. Where would you say that the drug users you've seen in Kazakhstan prioritize
overdose versus HIV and hepatitis C?

DR. EL-BASSEL: A death from overdose becomes -- is the first really reason for worrying and for not being engaged in treatment, and not accessing treatment and fear of the police. It's the first topic, more than HIV, for many of the drug users. And they know that they cannot access any care if they overdose because they will be in jail. And they will be arrested for a while, and they will be put in detox for months. And that's the really first worry.

I will give you an example of a case where -- I wanted to share this with the audience -- of someone who overdosed, and they called the ambulances and debated to call the ambulance. They didn't have the naloxone -- they didn't think they had the naloxone, and the person went to the hospital. And in the hospital, they announced that he's dead because he's a drug user and they don't want to invest in him. So they were taking out his clothes, and they noticed in the pocket there is a naloxone kit that he took from
the study itself, and injected him, and he survived.

So it's really an amazing story where drug users see it as a top priority, but they cannot mobilize any kind of help. But this case made the health department and the hospital and emergency room where he was to start thinking about using naloxone. And the drug users don't think about HIV as they think about overdose as a first priority, and they won't survive because many of them die, and they don't use the services.

DR. STANCLIFF: Thank you.

DR. COMPTON: Dr. Throckmorton.

DR. THROCKMORTON: Dr. El-Bassel, I'm Doug Throckmorton. I'm from the FDA. You showed that people that received the intervention were not more likely to continue to use heroin; that is, it didn't disinhibit them.

Did you have evidence -- do you have any data on entry into treatment? So were people that received the intervention, say, more likely to receive treatment, or anything like that?
DR. EL-BASSEL: We do have data. Unfortunately, we haven't analyzed the data yet, but we have qualitative data saying that they want to be in the treatment. They want to go because they want to access this kit, and they wanted us to give them the kit more and more. In fact, we're limited how much of the study we can give it, and the primary care doesn't have a lot. So we heard qualitatively that they start going to primary care more than before. And hopefully, by the end of the study, we'll have more data to quantify the percentage of people who access care because of naloxone.

DR. COMPTON: Next question?

MS. SIEGLER: Hi. I'm Anne Siegler from the New York City Health Department. My question is for Dr. Binswanger.

First, I want to thank you for your paper. It was that paper that allowed us to get inside the Department of Corrections in New York City and start doing overdose prevention education there. We've yet to get naloxone inside, but at least
we're educating.

So my question is the issue of confounding and how do you pull apart the -- a person with dependence to a substance that is illegal by nature is going to be more likely to land themselves in jail and is also going to be more likely to overdose. So how do you actually pull apart and see the effect of the incarceration on the risk of overdose?

DR. BINSWANGER: That's a very good question. So the question is, how do you tease apart the effect of just the underlying dependence on overdose and then also from the effect of the actual period of relative abstinence.

And it's hard for me to -- I don't know. And we've thought about doing these analyses because one of the issues, as you know, how do you know that you're not just having accumulated risk that then is suddenly realized in that first few weeks, and some of those people might have died anyway if they were out in the community using.

And I think that's a legitimate concern. It
could be that the high-risk people just fall out of
the population. I think that's a definitely
risk -- a possibility. But I think from a public
health standpoint, it's very clear that there are
certain times to target. So what I'm most
interested is can we identify the highest risk
moments that will help us direct our resources to
the points of vulnerability.

So I'm not as interested in kind of the
other issue, I guess, the first issue because I'm
really interested with just the crude rates. You
know that there's a lot of deaths occurring in a
very short period of time, and I think that that
means that from a public health perspective in
terms of avoiding the most amount of mortality,
those are the times to target.

DR. COMPTON: I have a question for the
three panelists. Certainly, the primary outcome
that we're considering and the main reason this has
been brought to our attention is the mortality. So
we see death as our primary outcome for most of
these studies and most of the research that will be
conducted.

But there's a suggestion of services use and the differences in cost for these patients. And we've heard different variations from all three of you. But I was curious about your thoughts about the need for that type of health services research in this domain as a perhaps secondary outcome but nonetheless important for driving policy and practice.

DR. BINSWANGER: Well, I'll just speak to that first. I think that's a critical need because I think we really have to engage insurance companies in terms of their willingness to pay for overdose counseling and also -- so counseling and practice, so you can bill for counseling for certain conditions. And this would be a nice way of advocating for increased counseling around substance abuse treatment generally, substance abuse in general, and overdose prevention. And then I think another reason is so that we could potentially bill for the medications as well as the delivery systems that are required.
So I think there's a big role for finding ways to understand the health service use patterns and the costs associated with overdose in terms of just being able to engage health systems, healthcare payers, Medicaid, public health systems, as well as Kaiser and other large HMO-type of settings where they have an interest in preventive care.

DR. COMPTON: Thank you.

DR. WALLEY: I think to reiterate what Ingrid was saying, OEND is a brief intervention, and it should be tested as such as far as not just death but also behavior change. So I think it can be incorporated with existing efforts to do SBIRT, screening brief intervention referral to treatment. And so I think that has a health services angle.

And then the issue of nonfatal overdose is -- well, I'll just tell you. In OEND, we train people to utilize. In fact, we train them to call 911. That's what we train them to do. So the intervention on the one hand explicitly increases health services utilization.
On the other hand, there's also a strong prevention message as part of OEND, and we're hoping that we're eliminating some of the need for -- we're eliminating the overdose in the first place. So we're preventing the overdose as well with the knowledge that we're passing on. So in that case, we would be reducing high cost utilization.

So anyway, I think those -- and particularly in our study, we didn't find a difference in utilization based on OEND implementation, and that fits with sort of we're pushing the needle in both directions at the same time. It would be nice to tease that out and see if actually the mechanisms that I'm speculating about actually exist.

DR. COMPTON: Thank you.

DR. EL-BASSEL: One of our goals in Central Asia is to educate the medical staff and health services staff about naloxone. And what we have been doing is training around 200, so far, of doctors from different settings, and from trust points, the staff about naloxone. They have no
clue, and that's really our first priority in the region.

DR. COMPTON: Thank very much.

Well, please join me in thanking our presenters this morning.

(Applause.)

DR. COMPTON: And now I'll turn it over to Dr. Lurie to let us know about if there are any instructions for lunch and then what we're doing after lunch.

DR. LURIE: Yes. Thank you for an excellent morning of presentations.

So the setup for lunch is that there are kiosks that will be set up outside the meeting room and refreshments will be sold there. There will be salads, sandwiches, other refreshments that will be available.

You're to be back here by 1:00 sharp, please. We've been doing a good job of keeping to the time. I know it's the afternoon where the rubber meets the road and where we really get a bit packed, so please be back by 1:00 so that we can
adhere to schedule. Thanks.

(Whereupon, at 11:58 a.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)
DR. LURIE: As everybody's taking their seats, I just want to set the stage a little bit for the open public hearing session, which is the one after the one that's coming. The way we're going to do this is we're going to ask people who are in the open public hearing session to sit in the first couple of rows after the next break. And then we're going to call you up in groups of about six, and you'll come to the table over here to do your six. And then everybody, I think, has the list, and they know which -- they're in the second six, or third six, what have you.

So we'll call you up in groups of six, and then you'll give in turn your presentations. Okay?

With that, I'm going to hand it over to the deputy director of the Center for Drug Evaluation and Research at FDA, Dr. Throckmorton.

Panel 3 – Moderator Douglas Throckmorton

DR. THROCKMORTON: Thanks, Peter. And let me do just a couple of pieces of housekeeping as well before I get started.

First, several people have asked about the
availability of slides. Let me just say we're working through making sure that the speakers agree to have the slides posted publicly, and we're working through obscure federal regulations related to access and important things like that.

So to the extent we possibly can make these available, they will be available through the website. And obviously, that's something we're interested in making as available as possible as you can. The other thing is there will be a transcript. I don't have the time for when that will be available, but we are making a transcript of this meeting, and that will be available as well.

So with that, let's transition just a bit. This morning we heard about the complex challenge, the progressive tragedy of overdose deaths due to prescription drugs as well as other opioids and the various states and local efforts that are going on to try to address those things. Many of those efforts obviously are very encouraging, and there's a lot of interest in them.
Now, it's time to transition to discussion of drug development. This might be titled "Why the Heck am I at the FDA?"

(Laughter.)

DR. THROCKMORTON: I think there's pretty good reasons for that. First, just in general, the FDA has been highly engaged, as you've heard some this morning, around the issue of opioid drug abuse. We understand that we bear a part of this. We need to be part of the solution to addressing prescription drug abuse. We're part of the larger work that's going on within HHS, within the Office of National Drug Control Policy. We get it. We need to be part of that.

Second, given the enormity of this, the enormity of the tragedy, the thousands of deaths, and the suggestions that have been made that the state and local efforts, the pilots, if you will, are bearing fruit and need to be considered to be broadened -- whether it's broadening in the way of new formulations that are easier to use, intranasal or the like, or broadened in terms of over-the-
counter status or something like that -- those kinds of activities are regulatory in nature, and they come to the FDA.

FDA's role when they come to us is not just to sit back and say that's nice, please send us a piece of paper. FDA understands that in places like this where the public health mandate is as is important as it is here, we have an obligation to provide a roadmap, a roadmap that allows the thoughtful, appropriate scientific assessment of those encouraging data to decide whether new formulations, new means of access to naloxone, are appropriate for a broader community, i.e., the national stage.

There are good reasons for that, obviously, and they've been referred to by the speakers before me. National coverage is easier when there is an approved FDA product in-house. The impact of a national approval obviously would be larger than and perhaps easier to accomplish than states' efforts and local efforts.

To the extent that the FDA can assist with
that by providing a roadmap, I believe it's our
obligation as public health officials to do that.
And that is fundamentally what brings you to White
Oak this morning and why the FDA I think is
important, and why it's important that this session
that we're going to be starting take place.

So what are you going to hear today? You're
going to hear discussions of some of the things
that we believe are most important as far as
developing new means of accessing naloxone through
federal regulations, through the Food, Drug and
Cosmetics Act.

We're going to start with a discussion of
new formulation development, and Sharon Hertz is
going to talk about that. We're going to talk
about over-the-counter medications and what is it
that you have to do in a broad sense to think about
developing those kinds of medications.

We're going to hear from the business side
of things, some discussion of what it would take to
build a business case for a new formulation that
was approved and available for use. And then we're
going to end with some important discussions about some of the ethics around trials in this area.

I'm fortunate that this panel is being cosponsored with NIDA. NIDA and the FDA share a responsibility to work towards supporting new drugs in this area, in the area of treatment of abuse, in the area of prevention of overdose death.

Phil Skolnick is my co-moderator. He and I talk just about weekly in terms of things that can be done to develop new medical therapeutics in this area. We've been really fortunate to have that relationship. I think we've made some material progress there. And I'm looking forward to this discussion. I'm looking forward to the conversation that we'll have around the regulatory side of naloxone access.

So with that, let me transition to the first speaker. Sharon Hertz is going to be talking about novel formulation development. In this case, we're going to focus on intranasal naloxone, I believe.

She is a neurologist. She's been in the division that's developed pain medicines for
several years. She has been in the analgesics department specifically for around 13 years at the FDA. Prior to that, she did her work at the university of -- the Upstate Medical Center in Syracuse as well as her neurology training at SUNY.

And, Sharon, thank you for talking with us.

I look forward to the discussion.

**Presentation - Sharon Hertz**

**DR. HERTZ:** Thanks, Doug.

It's great to be here to share some of our experience with -- our thinking about how to develop products for naloxone for outpatient use. And I'm going to describe some of the requirements that we've considered for what would be necessary to support a new drug application.

In very broad terms, you can bring a new drug application in for review by the FDA under two regulatory pathways. In a 505(b)(1), this type of application is one in which the applicant provides all of the information based on work that they've conducted or that's been conducted for them. And in contrast, a 505(b)(2) is an application for a
drug, which the necessary investigations relied
upon by the applicant for approval were not
conducted by that applicant or for which the
applicant has not obtained a right of reference.

So a (b)(2) application may rely on the
agency's prior finding of safety and effectiveness
for a drug approved under 505(b). And, in general,
to rely on these prior findings, we ask for some
type of bridge, a scientific bridge for why it's
rational to rely on those findings. And this is
most frequently achieved through comparative
bioavailability data.

So we've heard a bit about naloxone. I'll
go very briefly over what it's currently approved
for and some of its labeling. It's, as we know,
indicated for complete or partial reversal of
narcotic depression. The labeling describes the
need for continued surveillance and repeated doses
of naloxone under this period of observation since
the duration may be shorter than the duration of
the narcotics that led to the overdose. And it's
important to note that, of course, it's not
effective against respiratory depression due to non-opioid drugs. And, in fact, even buprenorphine-induced respiratory depression may be incomplete because of the pharmacology of that drug.

We heard about some of the effects of an abrupt reversal of narcotic depression, so I'm not going to go into this again.

It's currently marketed in two concentrations, 0.4 and 1 milligrams per milliliter. And it's currently approved for use by the intravenous route, intramuscular, or subcutaneous. And the initial dosing is 0.4 to 2 milligrams -- although I don't know how many folks initially will go to a full 2 milligrams -- to be repeated as needed at brief intervals. IV is preferable. If not available, IM or SubQ are acceptable alternate routes.

So when we think about a new product being developed for treating opioid overdose, we have a few key questions that need to be answered. The first is how does the new -- a new naloxone
product -- how does the bioavailability of the new
naloxone compared to the approved product? If the
relative exposure, the systemic exposure,
bioavailability is low, then we have to wonder
whether or not there will be adequate efficacy.
And if it's high, we in general will question
whether there are any implications for the safety
profile. And I think we heard earlier that in this
instance, it's not too much of a concern.

Then, can the product be used by the
intended population? So here, in particular, we
have administration by someone other than the
patient.

There's a whole slew of important chemistry,
manufacturing, and control information, CMC
information, and I'm not going to go into that.
Our standard requirements apply, and that's not
necessary for today's discussion. And then if
we're talking about an intranasal route, we also
need to consider the device. Is it an approved
device, one that's been approved by the Center for
Devices and Radiologic Health? And if it is, has
it been modified in any way?

We also need information about the product being administered through this intranasal device, characteristics about the spray, the spray pattern, droplet size distribution, and the pump delivery. In particular, we ask for specific droplet size distribution data. The importance of understanding the smallest fraction of that is to understand what may expose the lungs directly as opposed to the nasal mucosa. And any novel devices would need review by FDA as part of the application development. And, again, for an intramuscular route of administration, we need full description of the device, and if it's novel, again, it'll require review.

Nonclinical data, the amount required will depend on the route of the planned application for a 505(b)(2) application where there are plans to rely on the agency's previous findings for naloxone. In general, we may only need some local tolerance. Generally, that would be in two species. But if clinical monitoring of the local
tissues during any clinical studies is considered acceptable based on the novel route, there may not be any requirement for nonclinical studies. So the answer on this one is it depends.

Part of it is, because this anticipated use of naloxone is single dose, perhaps two doses, and because we already have a fair amount of clinical experience with naloxone, that gives us supportive human data. And those factors may result in not requiring much of a nonclinical program. If there are novel excipients in the formulation, that may require some nonclinical studies prior to initiating clinical studies.

I'm going to give you some excerpts of advice we've actually given companies, and this would be true for any new route of administration or any new methods or devices for an existing route, for instance, IM.

The first step is to look at the relative bioavailability. And we like to see that in at least two doses compared to the approved naloxone by an approved route of administration, preferably
IM or IV. And the idea, of course, is to target the plasma naloxone levels to be detectable and comparable and present for a meaningful duration relative to the approved product. And then dose selection can be based on a variety of assumptions of different levels of absolute bioavailability of the intranasal naloxone.

So once we get that first bit of information, it will really help guide what we decide may or may not be necessary for the rest of the development program.

Depending on how the first study was structured, its statistical power, its exposure, a second bioavailability study might be needed, may be needed. And again, we would compare this with the approved product.

If the product's not bioequivalent, particularly if the exposure is less than the approved product, that's where things get challenging because in that setting, efficacy studies would be required. If we don't get a comparable exposure to an approved product, then we
can't be confident that there would be efficacy.

As you can imagine, this is a very difficult clinical situation to conduct clinical trials.

First, we have to consider the patient population. These are events generally occurring out in the community. The people involved in the study may be first responders, possibly emergency department. There have been some discussions about using a perioperative population. And there have been some other clinical settings that have been discussed that might offer the opportunity to administer the product to patients in an overdose situation.

Well, if you're unconscious, you can't very well provide informed consent. So in this setting, for a lot of these populations would require provisions that are available under the regulations for waived or exemptions from informed consent, and Skip Nelson is going to talk a bit about that in his discussion. So I'm not.

There are some populations where you could consider getting informed consent ahead of the study, for instance, in a perioperative population,
but there are pros and cons for all of these.

And then perhaps the most difficult issue is, if the systemic exposure to the new formulation is low, is it even ethical to conduct a study of administering that product in a randomized or blinded fashion to a population that's overdosed when we already have obviously effective therapy?

So really, the idea is to start off with a product that can provide exposure at least comparable to what's been approved. Otherwise, it's not impossible, but it's quite a challenge to conduct these kinds of studies.

How much safety data does an applicant, a company, need? And again, that depends. It depends on how the PK profile of the new product compares to the approved product. So, in general, we would like to get some experience with this product in actual use for a couple of reasons. It helps give us some of the safety data, and then it also gives us additional data about the usability of the product. Generally speaking, some safety data will be necessary. We're probably talking a
few hundred patients as a minimum in a product
that's got good relative bioavailability compared
to the approved naloxone.

Novel excipients might potentially raise
cconcerns for safety. In that case, there might be
a need for additional safety data. And then also
depending on the device and the systems, additional
studies, additional information might be needed.

So the key is really to come in early, have
conversations with us, start getting some early PK
data, pharmacokinetic data. And then we can really
lay out with the applicant what's going to be
required to move the product forward in clinical
and nonclinical or chemistry development.

So thank you for your time, and I look
forward to questions in a little bit.

(Applause.)

DR. THROCKMORTON: Thanks, Sharon, very
much.

Continuing the theme of regulatory pathways,
I turn to over-the-counter development. So this is
not specific to intranasal formulation. It could
be whatever formulation of a product you had that's approved that you want to make available in an over-the-counter setting.

Dr. Andrea Leonard-Segal is going give this talk. She directs the division that makes the initial assessments of over-the-counter applications. So she makes the first recommendations about whether or not a product is ready to go over-the-counter. She's going to be talking about her experiences there, which go back for over 14 years now.

Andrea comes from George Washington University School of Medicine and actually is currently working in chronic pain clinic, which I'm sure gives her a unique perspective on the use of opioids.

Thanks very much, Andrea.

Presentation - Andrea Leonard-Segal

DR. LEONARD-SEGAL: Good afternoon.

I hope we're going to have a little fun with this because over-the-counter drug development is actually a very interesting area. We get to
hypothesize a lot about things. We forge new
territory. And certainly, considering naloxone as
an over-the-counter drug is forging new territory.

So what I'm going to do today is I'm going
to try to teach a little bit about over-the-counter
drug development, and then I'm going to try to
provide some considerations about what an over-the-
counter development program for naloxone might look
like, just hypothesis.

So what I'm going to do is talk about first
regulatory requirements for nonprescription drug
marketing. Now, I know you just had lunch, and
please don't glaze over when I say regulation,
because regulations guide everything for drug
development in general. And for over-the-counter
drugs, regulations are very important and have a
lot of quirks. So I'm going to talk about that.

I'll talk a little bit about OTC drug
labeling, which is unique, and we'll consider how
naloxone could become an over-the-counter drug.
And then we'll talk about a few other issues that I
think we would need to be thinking about.
So first, regulations. The Durham Humphrey Amendment to the Food, Drug and Cosmetic Act formally differentiates prescription from nonprescription drugs. Now, this act was passed in 1951, and around that time, the world was a nonprescription world. So the way this amendment comes forth, it almost looks as though we're carving out this little niche for prescription drugs.

And the criteria that were set forth to create that niche were that drugs can be safely used only under supervision because of their toxicity, or their potential for harmful effect, their method of use, or their collateral measures necessary for use, or if somehow, the drug was limited by an approved application to use under professional supervision. That's a prescription drug. Otherwise, the drug should be available without a prescription.

Now, the Code of Federal Regulations, another regulation manual, describes the procedure by which drugs that had been limited to
prescription use shall be exempted from
prescription dispensing requirements. Now, what
does that mean? That means it tells us what we
need to know about a drug to switch it from
prescription to over-the-counter.

So how can drugs be marketed in the United
States? Currently, there are two marketing options
for drugs, prescription and over-the-counter.

Behind the counter is not a marketing venue in the
United States. It exists in Europe and in other
countries and involves a pharmacist being able to
make a determination to give a medicine to a
patient who is seeking some help without the input
of a physician. We don't have that here.

So the law has been interpreted so that dual
marketing of the same active ingredient in products
that are both prescription and over-the-counter can
only occur when a clinically meaningful -- and
that's very important -- when a clinically
meaningful difference exists between the two that
makes the prescription product safe only under
supervision of a physician or other licensed
practitioner. In other words, a drug cannot be marketed both Rx and OTC for the same indication, population, and conditions of use.

So how might the law apply to naloxone?

Well, I have two questions that I'm going to pose, and I don't know the answer to them. Would a clinically meaningful difference exist between an OTC naloxone and prescription naloxone so the current prescription products would remain prescription after the OTC switch? Would those conditions allow dual marketing?

The other question is, would a difference in dosage form between the prescription and the proposed over-the-counter product be interpreted as a clinically meaningful difference?

So this is our regulatory framework. This is regulation 101, and I'm not a lawyer. So it may not have been a very good course. But we're going to try now. We'll go on to over-the-counter drug labeling.

We have the drug facts label in the OTC world. Any of you who go into the drugstore and
you buy a box of acetaminophen or some kind of an over-the-counter laxative, if you look at the back of the box, you're going to see the drug facts label. And this label has its own regulations. It has to follow certain standardized formats. And this formatting is intended to provide clarity and consistency to consumers so that they know what to expect from over-the-counter labels and where to find the most important information. And these labels have been tested in consumer studies, and they appear to do pretty well.

Also, OTC products have limited real estate. You can't have a label on an OTC product that you can keep folding out and folding out and folding out. We just have this drug facts label on the box. And all of the information that is important for effective and safe use of an over-the-counter product must be in that drug facts label. And this would be the case for naloxone.

Here's the skeleton of the drug facts label, and all of these different elements are described in the regulations. So think about this and say,
can we make people understand naloxone with this label?

Now, sometimes over-the-counter products have consumer information leaflets inside them. And this additional labeling element is allowable as per regulations, and it may provide additional information about the drug or the condition the drug treats that can be useful to the consumer, and it can provide diagrams.

So if there were an intranasal formulation, it could show pictures as to how to use it, or it could show pictures as to how to do an injection. Naloxone products could have these, but again, all of the important information about the product would have to appear on the drug facts label.

So how could naloxone become an over-the-counter drug? We have two mechanisms. One is the new drug application mechanism. This takes months. It's proprietary. It's product specific, and the applicant pays a user fee. It's the same process that you just heard Dr. Hertz allude to for prescription products. And we also in the over-

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the-counter world have the rulemaking process, and this takes years. It's a public process. It's ingredient specific, and there is no user fee. It's regulated under this process called the over-the-counter drug monograph.

So first, we'll talk about the new drug application process for marketing, and this is where I think naloxone would most likely fall in, so I'm going to spend most of the time talking about that.

Every time we consider a switch of a drug for the NDA process, we take a fresh look at it, and this means we look at all of the components of the prescription NDA and then some. So we will consider all of the things on this slide: the chemistry, the pharm tox, microbiology, clinical pharmacology. There will be efficacy data.

Dr. Hertz just talked about some of the aspects of bioequivalence and maybe other efficacy issues that might be involved for naloxone. We would be working with a group that Dr. Hertz works with to establish the efficacy of a new formulation.
for over-the-counter switch. If we were going to
switch a current formulation, then new efficacy
data probably would not be needed.

Safety data are very important, and I'm
going to dwell on this more in another slide. But
I do want to point out that we're interested not
just in safety data from clinical trials here, but
we're interested in information from all over the
place. And we do happen to have information that
in Sweden naloxone is over-the-counter, not behind
the counter, not prescription, over-the-counter.
So we would be interested in learning about what
happens in Sweden and what their label looks like.

We also would do consumer studies, and I'll
take more about that later. And, of course, the
labeling, we discussed. An over-the-counter
application for naloxone, depending upon the
formulation, may need to contain new data to
address all of these components.

So let's think a little more about naloxone
because we're hypothesizing. We already did talk a
little bit about efficacy, so I won't go there.
But for safety, the switch of the approved prescription product would be supported by current safety database, which would be clinical studies and post-marketing. However, if there were a new formulation, we would need new clinical safety data, say, if there were a topical formulation or intranasal formulation. And if the product were more bioavailable than the reference to which it was compared, it probably would be wise to market it first by prescription to acquire a post-marketing safety database to support OTC use.

Now, more on post-marketing safety. We have a variety of different sources that we look at. We always consider for over-the-counter drugs adverse events, the FDA's adverse event reporting system, the World Health Organization International Drug Monitoring Program. We look at the public literature to see what we can find there. And we also look at drug abuse data like from the Drug Abuse Warning Network and overdose data from the emergency room databases.

For naloxone, we would need to understand
the potential for conversation into an opioid agonist that could be abused. We would want to know about that.

So a few words on consumer studies. These are conducted to support the safe and effective use in the over-the-counter setting, and there are four different ones. And I will talk about each of them individually in the slides coming up, but first, let me just say when we find them to be helpful.

We find them helpful if a drug is first in its class to the over-the-counter market, if there's a new over-the-counter target population, if there's a new OTC indication, if there's a substantial labeling change to an existing over-the-counter product. And if there are new directions for use not previously seen in the over-the-counter marketplace, they certainly would be needed to support a naloxone switch.

So the first of these four studies, the label comprehension study, is the first step in predicting consumer behavior. Can the consumer understand the label? We want to know this. If
not, we know that it's not likely that they're going to use the product properly. However, the converse is not necessarily true. We know from past experience that even when people understand the label, it doesn't necessarily predict that they will use the product properly.

So label comprehension studies test if the label communicates messages key to proper drug use. The consumer reads the label and responds to questions about it. It's not a clinical trial.

A human factors study can assess whether perspective consumers can follow the steps outlined in the directions for use to properly prepare or measure a product for dosing. It's not always needed for an NDA. It can help to improve complex dosing directions during the drug development process.

For naloxone, I think we probably would need one. Listening to Dr. Walley's talk about the fact that there is a lot of training needed even to administer the nasal formulation because of some manipulations that need to be done with the product.
ahead of time, I think that might need to be tested for instructions. Certainly, we would want to assess if consumers could properly prepare or use a syringe.

Self-selection studies, this is the third study. These tests, whether based on reading the product label, consumers can properly select to use or not to use the product. They answer questions like can consumer self-diagnose the condition for which the drug is indicated. Can they recognize whether the drug would be appropriate for them to use based upon their personal medical history? No drug is administered.

So let's consider self-selection in naloxone. For naloxone, the individual administering the drug would not be the person receiving it. But this OTC paradigm exists now. Parents self-select to treat symptomatic conditions in their minor children. So we do have a lot of precedent for this kind of drug administration.

However, for naloxone, data will be needed to assess whether the individual administering the
drug could properly diagnose the opioid overdose
and determine that it is appropriate to give
naloxone based upon the information in the drug
facts label.

Now, the fourth kind of study is an actual-use study, and this is a clinical trial. Drug is
given in this kind of study, but it's atypical. These studies provide data to enable us to predict
if a drug will be used properly and safely in the OTC setting. It simulates over-the-counter use of
a product.

We think of these as "naturalistic." I don't even know if that's a word, but it's a word
that we banter about. These studies are generally open label. They provide access to study
medication to simulate what would occur if drugs were approved over-the-counter.

So we know that people can go into a pharmacy and pick up several boxes of aspirin. And
so we would not want to falsely limit access in an actual-use study if it would not be representative
of what would occur once the drug is approved.
There is limited study investigator contact to avoid introducing bias into the study. Actual use data would be needed to support an over-the-counter application for naloxone.

Now, remember I told you there's the NDA process, and then there's this rulemaking option for over-the-counter drug development. And I'll just say one or two words about that. FDA could initiate a rulemaking on its own or in response to a citizen petition requesting that FDA do this, to make naloxone an over-the-counter drug. But the data needed to do this would be the same as for the NDA. It would not be less.

This process involves data review, multiple Federal Register publications that solicit comments from the public and comment review. Ultimately, a final rule would state that naloxone, the active ingredient, is or is not generally recognized as safe and effective OTC to treat opioid overdose when administered as a particular kind of formulation.

Now, just thinking about naloxone, there are
other things that come to mind when I think about it as an OTC possible product. Some of these are needle safety for the injectable formulation. We'd have to think about that. We'd have to think about the impact of the injectable no longer being a prescription drug if one of those laws said it can't be.

We'd have to think about management of withdrawal reactions, and that has come up this morning as an issue. We would want to know if it would encourage opioid misuse or adversely impact the use of 911. We'd want to think about educational campaigns, and this was discussed earlier this morning as well.

But this is something that is also very important to know. FDA does not control over-the-counter drug advertising. It does control prescription drug advertising. The Federal Trade Commission regulates OTC drug advertising. So if naloxone goes over-the-counter -- and the rules are different than probably how we would like to think about doing things over here. So you need to think
about what a TV ad for naloxone might look like. We would not have control over that here.

So in summary, there are different regulatory pathways to consider for the prescription to over-the-counter switch of naloxone. There are many interesting regulatory and scientific issues to address to support the expanding access of naloxone via OTC marketing. And consumer data among other data would be essential to support a naloxone switch.

Thank you very much.

(Applause.)

DR. THROCKMORTON: I was told that we could only have two regulators speak in a row. After that, everyone would go to sleep, so.

(Laughter.)

DR. THROCKMORTON: Now I want to transition to someone who's actually in the process of doing this, so a person engaged in the development of products, especially including products related to naloxone.

Dan Wermeling is the professor of pharmacy
at the University of Kentucky College of Pharmacy. He received his Pharm.D. from the University of Kentucky as well and is the founder of a company AntiOp, Inc.

Dan, thank you very much for coming.

Presentation – Dan Wermeling

DR. WERMELING: Thank you very much, and I wish to also thank the organizers for inviting me to this day. And I also wish to thank the granting agency through Dr. Skolnick, who was provided funds for some of the work that we're going to talk about in developing a formulation. And I've also worked very closely with Dr. Hertz's office in preparing to submit an IND for an intranasal formulation.

Part of my task is to think about drug development broadly, and so I have to look at a whole bunch of issues at one time to see if it's feasible or not. And so it requires science, integration of regulatory issues, and business and economic issues in the marketplace. And to sort of make all of these things line up, if I can, to the best degree that I can, and it's sort of a test of
feasibility overall.

So what I want to do is just slowly go through a number of these issues that I have to think about sort of all at one time and integrate these things into a plan that follows the regulatory paths that have just been so carefully explained to us.

So the first thing that I have to do is think about the label. So basically, as has been described, we can take an old drug and put it in new clothing, and we are able to take advantage of some of the information that's already on file about this drug and make some assumptions about safety and efficacy regarding the active ingredient.

And so we then have to think about that context and that label, and then visualize what the new product look like, and can we say naloxone hydrochloride nasal spray is indicated for. And so we have to then basically introduce and transpose these notions to understand if it's possible or not.
We could also think broadly about different kinds of transmembrane routes. Now, I do a lot of work in intranasal delivery, but there are all kinds of other companies that look at all these different routes technologically either for formulation capability or that they have device technology that allows or enables administration.

But for each of these for the test, back to the label, you would then want to look at all of these different considerations -- and this is just a quick summary -- of applying this active ingredient and its formulation in a device, the product, and then look at all of these conditions and apply it back to each of these routes of administration to try and see if the problem is solvable.

So some of these you could see right away might not be all that useful, like rectal, for example. We have emergency products with rectal diazepam gel, but that's not really highly accepted. Other things like endotracheal are pretty challenging to think about of instilling
drugs to the lung. That's not something simple.
And some of these others have all their various
considerations about what might optimize them or
not.

Intranasal in one sense works usefully here
because consumers are used to it. If you look at
your grocery shelves and pharmacy shelves, you'll
see more shelf space for nasal delivery products
for allergy and these other kinds of things than
many other kinds of delivery systems that you could
think about. So the public is used to nasal
delivery. And in many cases, we have lots of other
products that are used in nasal delivery, both
prescription and over-the-counter. And so a lot of
these considerations are manageable with nasal
delivery, at least scientifically.

If we try to apply the nasal delivery in
designing a product, we have to have something that
looks functionally equivalent to injection, as
Dr. Hertz has stipulated. We would like to take
needles out of the system for the obvious reasons.

In general, powders can work, but it adds an
additional step. It's nice if the drug is in solution because that's how drugs get absorbed. The molecule can cross a membrane if it's in solution. If you have to have a powder dissolve, then it doesn't work as fast. So aqueous is probably better.

You hope that it's nontoxic so that your drug and the excipients aren't causing local reactions. In this case, a unit dose disposable nasal sprayer is probably more appropriate than something like your Afrin nasal sprayer where you could get 15, 20, 30 doses out of a bottle.

It needs to be usable. So can people manipulate it with their hands and actually get it in? Two- to three-year shelf life would be pretty standard. And in the end, some of the environments that I've heard discussed today about drug administration are relatively austere. And so it has to be durable. It has to be in a condition that will protect it from things that break down drugs, like light and heat and oxygen and people bashing things and not taking care with their drug.
And so it has to be durable.

Then we have to think about all these things and integrate it with the requirements that have been explained earlier. And in essence, what I'm doing is a gap analysis. I have to resolve what it is that we know and what it is that we don't know. And the research then is targeted hopefully to what it is that we don't know to meet statutory requirements.

The chemistry, manufacturing, control section for this is well written in the guidances, and so the directions on how to actually prepare, working with the active ingredient using excipients and solvents and putting it into a device is fairly well understood.

The toxicology for most systemic purposes is well understood. As we have as a difference is really regional toxicity. And as Dr. Hertz has said, because of the limited nature and use of this product, perhaps it has limited meaning in this circumstance.

But we still have to define clinical
exposure. We have to understand the biopharmaceutics of how this product performs. And to date, there is no literature that describes a nasal formulation of naloxone's biopharmaceutics. There is no data. And so that's the challenge for me, is that I have nothing using pharmacokinetics and other kinds of tools that I can use to try and design a product and understand what might happen. I would just be guessing. But I'll tell you how I guess in just a minute.

But first I have to think about the drug itself. And I have worked with this drug a little bit, but mostly I've delivered three other drugs nasally that have very similar chemistry. And so I can rely initially on a chemical understanding of the molecular weight because drugs less than 1,000 tend to be available across the nasal membrane. If you get the molecular weight up, the drug doesn't want to go through.

We need to understand the pKA. This tells us about some basic chemistry about how it solubilizes in water. And so this drug will be
dissolvable in water, which is great. We can understand ionization from this, meaning that drugs cross membranes when they're in their un-ionized state. If they're ionized, then they're harder to get across. The challenge here with opioids is that they're also unstable if you raise the pH. So you have to have a low pH to keep it stable in solution.

Then lastly, the Log P defines how well drugs cross membranes, and so a higher Log P generally means that a drug will cross the membrane faster. It's how quickly it dissolves into the lipid membrane of a cell. And so this gives me a sense of naloxone and how it compares to three other drugs that I have given nasally. And I have data, and I'll share those with you.

We can also look at the chemical structure to understand them, and the chemical structures fit, again, general nasal paradigms, and so that works nicely. And the general core structures are all the same. And it's just one side chain in general that creates the difference in its
pharmacologic activity but doesn't have a lot of influence on the chemistry.

The biopharmaceutics of these other drugs are known. Hydromorphone was a product that I was involved with at a prior company and has been published, and so it has a bioavailability of about 50 to 60 percent. If you give 2 milligrams, you'll get a peak of around 3.5 nanograms. And a Tmax, how long it takes to get the maximum concentration, of 20 minutes, so it explains the slope of absorption.

Now, naltrexone is a drug, also is an opioid antagonist, and has very similar chemistry. And I've given that compared to oral and obtained very good, excellent bioavailability nasally with naltrexone.

Butorphanol is a marketed drug. It's Stadol nasal spray. You can look it up on the package inserts or in the labeling available on the website, and you can see that it does also have very excellent bioavailability of 60 to 70 percent, Cmaxes of 5.5 nanograms per mL, and is absorbed a
little bit faster. And that's because it has a higher Log P. So butorphanol nasal spray, all these drugs have very similar core chemical structures and very basic, similar chemistry and formulations.

So then if we look at how these things perform in terms of biopharmaceutics -- I've pulled these charts from some of the papers. The left one is hydromorphone, and the top bar shows an IV versus two different nasal doses. And so you can see how IV achieves very high rapid concentrations after an injection. And then there is somewhat of a dose proportionate exposure from 1 versus 2 milligrams of hydromorphone. And so you could say 1 and 2 milligrams hydromorphone, and 1 and 2 milligrams naloxone, maybe these profiles are going to look somewhat similar. And so that might be a good marker.

The butorphanol does a similar kind of approach where we can see that 1 and 2 milligrams provides about 4 to 5 nanograms per mL peak concentrations. It's those proportionate. And so
this is again a fairly good marker. And
naltrexone, again, this is an expanded scale, but
it shows that you can get again very rapid
bioavailability of the other antagonist.

And lastly, the closest example I can find
of giving naloxone nasally is in a paper that was a
drug abuse liability study performed actually at
the University of Kentucky by one of our
colleagues, who crushed suboxone tablets and let
subjects snort, if you will, suboxone powder. And
so then a half a milligram in one group and
2 milligram naloxone powder was administered
nasally. Just think of in the movies like cocaine
straws, right, that kind of concept.

And so what we see here is a Cmax of about
1.6 nanograms per mL, Tmax of 20 minutes, which is
about what I would expect, and a relatively low
bioavailability of 30 percent, sort of mid-range.
And I believe that part of that relationship again
is that this is powder. Right? So we have a
dissolution step that has to occur before the cilia
in the nasal cavities sweep the drug away. The
drug is not bioavailable orally, so if it's swept and you swallow, it's lost.

So why is this? This last one is sort of a very good clue about what might happen with 2 milligrams of nasal powder with a peak at 1.6 and a bioavailability of 30 percent.

So then you can go back and look at other studies where pharmacokinetics of naloxone has been published -- the most recent one is Dowling in 2006 -- and you can see there are two charts there of 0.8 milligrams IV and 0.8 milligrams intramuscular, which might be the route of administration of greatest interest for comparison.

And so what you can then at the bottom chart is that 0.8 milligrams IM, which is a generally clinically relevant dose, provides a peak of around 1.7, 1.6 nanograms per mL in about 15 to 20 minutes. And so this might compare something close to what an intranasal administration might look like if you were thinking back to this. So there might be some relationship then between IM and intranasal delivery from these two studies.
The link that I use is really that
0.8 milligrams IM is known to be clinically
effective. Right? So ambulances and clinics and
other places, injection centers, are able to use
this. But what we don't know is the exposure from
an optimized nasal formulation. The injection used
with the MAD device is about 10 times more dilute
than what is typically formulated for a nasal spray
product.

If you had an Afrin nasal sprayer or Flonase
or whatever, that delivers 100 microliters, one-
ten-th of an ml per activation, because that's about
the volume that the nose can actually physically
handle without drug either going this way or this
way. It's not going to stay. It's going to run.
And so the effective dose of giving 2 milligrams
with a MAD device isn't effectively 2 milligrams.
We just don't know what that is. Nobody knows what
the exposure of that means, either.
So we don't know what the exposure looks
like from an optimized nasal formulation or the
exposure from the current off-label practice.
However, there is a lot of clinical practice going on off label. And this is from, I believe, Karl Sporer at UCSF for the intranasal naloxone protocol for their EMS services in San Francisco. And so you'll see that they have a standard of care written that the 2 milligram syringe with the MAD device can be used to reverse opioid overdose in the field, pre-hospital. And the paper suggests that this works about 70 to 80 percent of the time in the patients that they come across.

And then if you look at that dose compared to the doses below, the recommendation is to then give intramuscular 1 milligram. So I don't know how he arrived at that dose, if that was empirical or from clinical experience, or what was used to actually derive that recommendation. But it would appear that he is contemplating generally equivalent clinical outcomes from using these two doses in that route.

Then there's another paper in Denver where this also started with the MAD device, and Denver EMS services compared 2 milligrams intranasal using
the MAD system with 1 to 2 milligrams of IV naloxone. And their main outcome interests were
Glasgow Coma Score, which is a measure of cognitive
function and how well people can interact with you.
And so a higher score of 15 means you're normal,
and a lower score means that you're impaired.

And so they were looking at pretreatment
versus post-treatment, comparing intranasal to
intravenous delivery for Glasgow Coma Score and for
respiratory rate recovery. And so you can see that
both IV and intranasal had patients who were
significantly impaired and that both products were
able to return patients back to a more normal
state.

The important part of this element is that
you were able to administer the drug as soon as you
came upon the patient. You don't have to set up an
IV, particularly in a population that's going to
have difficulty getting an IV established, so
you're losing time, in essence.

And so if you look at the right side of this
chart, you'll see that the drug-to-clinical
response time does take a little bit longer for nasal delivery, 13 minutes versus nine minutes. But if you account for drug administration time, the five minutes you might need to actually to get the IV in, then the outcome times tend to be equivalent. And so you're not really losing anything hopefully to time-to-clinical response by using nasal delivery in pre-hospital setting.

Now, there are some other issues I want to bring not just about the science but some other topics. And so I represent a startup pharmaceutical company. We're relatively virtual. But after reading Maya Doe-Simkins' paper two or three years ago -- one of my colleagues handed it to me, and they said, "You should probably take this up because you can design a product." And I said, "Yeah, I probably can."

But there are some business issues with this. One is that naloxone is 41 years old this year, and so the patent has expired on the active ingredient. Also, the very first patent for nasal delivery of naloxone was in 1981. That's expired.
So nasal delivery has expired.

    You might be able to combine with a specific technology like using a special sauce, something that's special in your sauce that's proprietary, or that you have a device that's proprietary, to protect your presence in the marketplace. But as was mentioned, if you embed new technology into this to protect the marketplace, you're going to need a lot more research, which means a lot more money to get it done.

    Now, larger companies, they are driven by market exclusivity. And without a patent, the regulations provide three years of market exclusivity for a 505(b)(2). That's about how long it takes a company to reach market penetration, max, where they start to get to where they can really do something with this.

    If you had to include children in your plan, then you got an additional six months. And if you convert and do additional research to get OTC status, you will get another three years. So you can see where the whole series of sequences of
research requirements, you might get up to six and a half years.

I have applied for orphan drug designation, and that was rejected. So there's not another way to protect it that way.

So the question that's come up a lot today is, what is the best mechanism to ensure greatest public access? Well, this embodies another body of law, and that is how do you get reimbursement, or how do you pay for this? What's healthcare finance look like?

And, in general, Medicare, Medicaid and private insurance reimburse for prescription drugs, and so healthcare finance and distribution of drugs follows traditional models. And that's because this new drug going through this division would have an NDC code on the box, and that's what everybody looks for in these transactions. Medicare does not reimburse for OTC drugs, so people would have to pay out of pocket for that.

One other element to think about, because I've heard a lot of training mentioned here as an
issue, and that is, for every prescription, it's required for a pharmacist to offer counseling on every product. This is not required in an OTC setting.

So then with these conditions, how do you get the money to actually do this work? The current naloxone market nationwide is $22 million for the injectable market. For a drug, that's not a market compared to other things that people invest in.

And, in fact, the development costs, depending on what is negotiated with the Food and Drug Administration and how well your product actually performs -- the development costs could easily exceed the market size that exists today. There's no intellectual property unless you have a device or excipient. You would have unlimited duration of market exclusivity.

This expanded access about no prescribing as an additional market to sell more units is unknown. It's untested as a market. And it's unknown whether prescribers of pain products, which is the
largest population of all, in the millions versus hundreds of thousands -- will prescribers embrace the kinds of practices that you espouse today, these harm reduction principles? That's an unknown. I don't know to a great extent how the pain management world has been approached with these topics.

Also, as I found out in the state of Kentucky, where I live, where we're I think the fifth or sixth worst state for opioid overdose deaths per capita -- I tried to get some laws passed, and I was immediately informed and reminded that state laws dictate through medicine, pharmacy and nursing practice acts who can prescribe, who can dispense, and who can administer a drug. And so now you have 50 individual test cases on trying to manage these circumstances.

And then lastly, healthcare finance is uncertain. I'm hearing a lot of calls for over-the-counter status, but if I look at the amount of money that has to go in versus trying to get money out to reimburse for the costs and the risks
associated with investing in such a product that may cost 20 or $30 million to do, will that money come back? Can you entice capital into this setting? It's a real interesting question, one I'm just starting to engage in.

So in conclusion, we've had a very nice explanation of FDA rules for drug delivery and how to put an old drug into a delivery system. The development of this drug is contextual, and we've seen the options presented on slides from Food and Drug Administration as to how to think about these things. There's different populations, pre-hospital, peer to peer, injection centers and other countries.

There are other kinds of patient populations throughout, but which one will actually allow you to generate the data that would satisfy a new drug application? Which one has the most rigor in the ability to collect data to the standards that are required by FDA?

Right now, to my sense, it's pre-hospital, but that's hugely expensive. I went and costed
a -- wrote a protocol, sent it to a CRO for a 500-patient safety study, and the price came back as $10 million for a single trial, $10 million. That's a serious number. So the development is contextual across these different uses.

Will there be acceptance of an increased price? I've heard a lot of things about affordability. But I can't imagine if a 5-dollar sterile product today for an ampule of naloxone is considered expensive, that's the cheapest sterile product that's probably in our hospital pharmacy at the University of Kentucky. I can't think of a cheaper sterile product you can buy.

AUDIENCE MEMBER: Morphine.

DR. WERMELING: Morphine might be interesting, but I bet even those are not cheap.

Development and marketing then, feasibility is a real question and planning for this. The considerations and the regulatory structure that was explained are really pretty standard. I brought five different products for development to Dr. Hertz's division over 12 years, and they're
very consistent in explaining what is required to
demonstrate safety and efficacy in chemistry for a
new drug product, even if it's a reformulation of
something that's very well known. The standards
are the same, and the public demands in general
that those standards be met.

So the tests for feasibility -- as I
mentioned at the start of this talk, the tests for
feasibility are really the same. Regardless of the
drug product, we still have to demonstrate the same
things. And it was somewhat interesting -- I
didn't see Dr. Hertz's slides beforehand, but
there's a lot of parallels between what we've
presented, as what I understood as a developer,
versus what she explained as a regulator.

Thank you for your time.

(Applause.)

DR. THROCKMORTON: Thanks, Dan, very much.

The last speaker before we have a break and
then we move to the public speaking period is Skip
Nelson, who comes from the Office of Pediatrics at
the at the Office of the Commissioner level at the
FDA, but is also, more importantly, one of our
ethicists, and one of the people that we turn to
when we have trials that raise challenges regarding
assessment of patients, enrollment of patients,
informed consent, and the like. And he's going to
be talking to you about some of those issues.

He is currently the senior pediatric
ethicist at the agency. Before joining us -- was
it just 2009, Skip? Gosh.

DR. NELSON: Well, part-time in '06.

DR. THROCKMORTON: Okay. Seemed like you've
been here for longer than that. He was a professor
of anesthesiology and critical care medicine and
pediatrics at the University of Pennsylvania at the
Children's Hospital in Philadelphia. His M.D. is
from Yale University with a Ph.D. in religion
studies from Harvard.

Skip, thank you very much.

**Presentation - Robert Nelson**

DR. NELSON: Thank you, and it's a pleasure
to be here.

So with the prior presentations, I think
I'll be able to go through some of my slides more quickly to stay within my allotted time. And I want to just sort of highlight some issues, depending on the kinds of clinical development challenges that are in the pathway for getting naloxone on board.

I'm not going to dwell here. You've seen this indication before and the formulations and route of administration that are available. The key point is that using naloxone intranasally is an unapproved use. Now, caveat, I'm not talking about off-label clinical use. I'm talking about it being an unapproved use. It doesn't say that a clinician -- a physician, if the state laws allow it, couldn't use it off label. In fact, that's what's being done in many circumstances.

So I think there's three facts that I'd like to highlight as I then go on to some of the ethical considerations. First is there are two populations that are generally being discussed here. One's the prescription, those who are at risk from prescription drug and those who are risk from
overdose from illicit opiates.

Now, although IM administration has been used, as I reviewed the literature, intranasal administration obviously would have some advantages. I point out also that an auto-injector possibility would exist for IM administration.

The other thing I would make as a point is that it appears to me at least the public health benefit of distributing either IN or IM naloxone to injection drug users appear to be largely from the recipient intervening in a witnessed overdose, not in them giving it to someone else and saying if you see me overdose, please use my kit on me. It appears to be mostly them using it on someone else. Now, I could be wrong on that, but that's at least how I read the literature.

So the question is, well, who are the study subjects if you're going to do a clinical trial? The point is the person who's receiving the naloxone is the study subject. Now, depending on your research question, the person you're training to give it may or may not be a study subject, but
the person who's getting it is the recipient of the investigational product.

So the bottom line is if you're obtaining informed consent from the person who you've given the naloxone to, but they give it to someone else, you don't have consent from the person who they gave it to. And that would not meet the FDA requirement for getting informed consent from the study subject, who is the person who actually got the naloxone.

So what does that mean? So as I walk through this -- I mean, you've got a very nice presentation of some of the issues. So if you need to do a bioequivalence study, that can be done in a population who does not have an acute overdose. So basically, that would be with standard research procedures, standard informed consent, fairly straightforward trial.

Well, if you need an efficacy study and you're doing that in those who are at risk from prescription drug overdose, that as well could probably be done with fairly standard procedures.
because they have a family. That family could be administering it to them, but you've got consent from them to do that, and at least probably been able to train their family under that.

Question, whether that would be sufficient in terms of sample size and the like is a whole separate question, but that could be standard procedures.

Now, you could do an efficacy study of individuals at risk from accidental overdose. However, if you administer naloxone only to the person with the overdose kit, that could be done with standard informed consent. The difficulty here is that the main use, as I mentioned, appears to be for witnessed overdoses. Excluding those witnessed overdoses may be difficult.

Are you going to tell someone, I've given you a drug that could save your life, but don't save the life of your buddy if you see them get an overdose because that would be against the regulations. I mean, I would hope they wouldn't follow your advice on that.
And the bottom line is, if you include those witnessed overdoses and you don't have consent from everyone that that person may come into contact with, which would be an operational nightmare, basically, you're in the setting of needing to do what's called an exception from informed consent. I'm going to walk you through those regulations.

Now, finally, you heard the discussion of an actual-use study. Well, again, you may not need an efficacy study, but if you convert to OTC and need to do an actual-use study and then include witnessed overdoses given the context of use, then you would likely also need to do that with an exception from informed consent.

So what is an exception from informed consent? 21-CFR 50.24 is the regulatory citation. There's a guidance on the FDA website about doing that, and I will walk you through the different components of that.

So first of all, it's conducted in -- it's a study subjects who cannot provide informed consent. And obviously, if someone is acutely overdosed,
they cannot provide informed consent. You also
have to have a therapeutic window where the product
has to be administered before you can get informed
consent. Obviously, giving naloxone to someone who
is in acute overdose I think meets that therapeutic
window requirement.

The human subjects must be in a life-
threatening situation. Again, it would appear that
giving naloxone to someone who has an acute
overdose would, in fact, meet that. And it must be
an emergent situation, not just some sort of long-
term chronic coma. It would appear that it must
meet that, too.

You also need to have a requirement that the
data are necessary to address the safety and
effectiveness. So again, I'm not talking about a
bioequivalent study but about where efficacy and
actual use may be required.

The other thing is available treatments must
be unproven or unsatisfactory, and I think you
could make an argument that in the field,
intrasanal naloxone is better, that IM naloxone may
be unsatisfactory unless there's an auto-injector. So you get into the situation of saying even though naloxone is approved and has been used by paramedics, if we want to move it into a setting where it's being used by the community, in fact, at risk themselves, that that would be an unsatisfactory alternative to just say here, here's the IM naloxone, although I believe that's been used in one program.

And again, obtaining informed consent is not feasible, and it's not feasible because you don't know who they're going to be in the first place unless you want to get consent from everyone, which is not feasible. You have to administer before consent and before you can find their legally authorized representative. I suspect in this context that would be very hard to do. And there's no way you can identify them.

And again, the intervention must hold out a prospect of drug benefit. Well, I think that's fairly evident that this intervention would. We have plenty of clinical efficacy data in the hands
of paramedics that it would. So presumably, putting it into someone else's hands would also have that prospect and that the risks would be reasonable, and it appears to do that.

So what I would suggest is that naloxone fits those characteristics, but then there's two other things that need to be added, which are added because you can't get informed consent. One is called community consultation, and the other is public disclosure. So in other words, you consult with the community about whether this kind of a trial would be acceptable to the community, and then you also disclose to that community that you're going to be conducting that trial. And then after the trial, you disclose to that community the results of that trial.

So as you can tell from my presentation, I would argue that an efficacy study or an actual-use study of the use of IN naloxone would, in fact, meet the criteria for an exception from informed consent, provided that community consultation and public disclosure are conducted. One caveat, this
approach is not permitted for prisoners. So that's a population where this approach would not apply.

So what is community consultation? From our guidance, it basically says there is no single acceptable way to accomplish it. And I'm going to offer you some of the ways that that has, in fact, been done because it does depend to some extent on the protocol itself.

And at least as I went looking through the literature, I saw a reasonable amount of data on the views of the appropriate community. In other words, what do intravenous drug users think about getting naloxone so they can have it? And by and large, my reading of the literature was that the community felt pretty favorable about that.

So I suspect if you went out to engage that community, which doesn't appear to be difficult, if you hire a sociologist or an anthropologist to go talk to them, that, in fact, you would discover that this is an acceptable trial to do for that community.

So I personally didn't get a sense that this
would be a hard bar to meet because it's been met in many communities that have done that kind of work anyway. Well, you'd have to do it again for the trial. You can't just rely on what you did a few years ago.

So what are some of the examples? So first of all, as I said, community is protocol specific. It's defined by the protocol, community of prescription drug users who are at risk, community of intravenous drug users, illicit, who are at risk. It's specific.

And the required feature of community consultation is that it's a two-way communication. So people have done that through public meetings, either a town hall meeting, please come and talk to me, or the investigators going to an existing community, either church or, et cetera, synagogue, or whatever, community council groups, focus groups, face-to-face interviews, ways that you actually talk and have an exchange.

Some people have used random digit dialing telephone surveys or surveys. I think that's all
right, but you've got to have that two-way communication. This is really not meant to be a poll. That's not what community consultation is meant to be. So random digit dialing to just find out how many people would go into the trial isn't community consultation. That needs two-way communication. One-way communication is public disclosure.

Now, let me give you an example of a successful one. Public access defibrillation trials. Here's a technology that was only in the hands of paramedics or clinicians in a hospital, and they did a trial to get it out into the community. And I don't know where ours is, but I'm assuming there's a sign outside the door here that says where you can go find this. And anyone one in this room can use it, even though if I raised a hand --

How many here have CPR training?

(Show of hands.)

DR. NELSON: All right. How many here have ever used a defibrillator?
(Show of hands.)

DR. NELSON: All right. Well, the rest of you, who are the majority, could actually use this machine without any training, and that's what they did. So they basically randomized buildings and did training in the one building. Everybody got trained in CPR in both buildings, and then in one building, they hung the automatic defibrillator, and then looked at how many people died in one building versus another, basically.

Not too dissimilar a study design is what you might do if you want to do a cluster randomized design between one city and another city or one borough and another borough if your city is big enough, about different programs. Not suggesting you'd have a placebo-controlled trial in naloxone. That probably would not be acceptable.

They had two groups. So there were the volunteer people who basically received the training, but then there were the people who actually suffered a cardiac arrest. Now, you don't know who that's going to be. So the one, they had
informed consent from. So that's the people that
would go out with the naloxone. That was easy.
The people who had the arrest, that's hard. Aunt
Millie is over for Thanksgiving dinner and suffers
a cardiac arrest. Well, she wasn't in that
building. She didn't get no consent, et cetera.
So they did various aspects of community
consultation.

So the bottom line is this is doable. This
is not -- in my mind, frankly, if I had to rank it
on the level of regulatory burden, I would put it a
lot lower than some of the trials one would
actually be expected to conduct.

So what bothers me about this is given that
using naloxone for witnessed events may have a
greater public health impact, and including such
events may actually make a clinical trial both more
feasible and relevant, what's the ethical
justification of excluding administration of IM
naloxone to non-consenting subject simply to avoid
the ethical requirement of consulting with the IDU
community?
What I'm suggesting is that from a public health perspective, you could argue that to design a study simply to avoid the need to do community consultation could be criticized as being unethical.

Do you need an IND? Clinical studies on the dosing, safety, and/or efficacy of naloxone are FDA regulated even if IND exempt. IRBs often don't realize that.

Commercial development of a novel formulation may benefit from conversations with FDA, and this is certainly -- Sharon and Andrea would be the people that you would be talking to, depending on what you wanted to develop, about the data necessary for an NDA submission.

So what do you need? You've heard exactly what the different issues are. What would you actually need? And that would be in differing kinds of meetings, a pre-IND meeting, et cetera.

An efficacy study or an actual-use study requires an IND unless all of the exemption criteria -- and I didn't list them under 312, but
one of them is, say, that you're not using a study population where the risk of using it would be considered any different than its current approved use. And I would argue at least that if you're going into vulnerable populations, that you should have an IND to do that.

I might point out as well that if you decide to perform a study that requires an exception from informed consent, even if you are IND exempt for any other reason, you need an IND to do the exception from informed consent because that's the way the data then comes into the agency. And these regulations require a submission of data around your community consultation process and public disclosure.

And finally, admittedly, if you have to do an efficacy an actual -- the data collection here I think will be a daunting issue. How do you structure that? How do you get data around measurable endpoints for efficacy?

I saw one innovative publication where they looked at the number of deaths that occurred after
12 hours of receiving naloxone, and then someone refused to be transported by the paramedics to the hospital. And they showed that there were no deaths within that 12-hour period, arguing that just because I then refused to go to the hospital, I wouldn't walk down the street and then die because the naloxone has worn off.

I mean, that's one way of trying to collect data, but I think we're going to have to be very creative.

And how do you get adverse event data? We all think it's fairly safe, but we need data to look at that. How do we get that data? I think these are some of the challenges that would face anyone trying to do a clinical trial.

Here are some references that will be available in your slides. I know since I have no tables or graphs that my slides would, in fact, be fully 508 compliant, as they are now, but that's something that Doug's going to have to work through to get them posted.

Thank you.
(Applause.)

Questions and Answers

DR. LURIE: Doug, could I just ask a couple of, I think, quick questions and then -- I don't want to take away from the public questioners. Sharon, I just want to make sure that I've got these take home messages correct. It's true, right, that it's entirely possible that no animal studies would be necessary. It's at least possible that that's the case, right?

DR. HERTZ: Yes, that's true.

DR. LURIE: And it's true also that -- gosh, I can't even read my own handwriting here; this is terrible -- that basically a bioequivalent study could be all that you would need?

DR. HERTZ: Yes, but chances are good we would require some type of safety actual-use data in addition, given -- depending on the nature of the device and the route.

DR. LURIE: Okay. And for the bioequivalent study itself, what would you, just in rough terms, estimate of the size of the study might be or the
size per arm might be?

    DR. HERTZ: So typically, this would need to be powered to show bioequivalence, so that's going to depend on the variability. For a parenteral, it might be a little bit less than an oral. I would say -- because I'm not a clinical pharmacologist, and I don't want to be misquoted. I know what will happen. I'll give a low number. Someone will come in, and it'll turn out to be wrong. So I would say certainly not more than 100 patients.

    DR. LURIE: Per arm?

    DR. HERTZ: No.

    DR. LURIE: For the whole study?

    DR. HERTZ: For a bioequivalence study. I would not expect that --

    DR. LURIE: Yes, from the crossover. I see.

    DR. HERTZ: Let me rephrase that. I would not expect it to exceed 100 patients, 100 subjects total.

    DR. LURIE: Gotcha. Okay.

    A question for Andrea is, the data that people have collected in the field over the years,
it's conceivable at least that some of that data could satisfy some of your requirements, right? I mean, it could be submitted as part of a package, or do you need fresh data?

DR. LEONARD-SEGAL: Certainly, data collected over the years, if bioequivalence is shown, could provide, if we're talking about new formulations --

DR. LURIE: Actually, my question is more about the actual-use type studies, not so much the bioequivalence.

DR. LEONARD-SEGAL: Okay. Well, first of all, data accumulated could help with the safety database. That's a given. Okay? And we'd be very interested in seeing all of that.

I was going to say that if there's a new formulation, like you have an intranasal formulation, we might want to see safety data on the nose and what happens in the respiratory tract, depending on whether this gets sniffed back or not.

So there are different aspects to safety. If it somehow were topical, we'd be interested in
dermal safety studies. There are a variety of
different kinds of things that we didn't talk about
because we're not really discussing formulation
specific things.

For actual use, my guess is that there are
no -- I have not looked, okay? But I'm just going
to hypothesize knowing about -- based on my history
of 14 years. I doubt that there are studies in the
literature that would be able to supply us with the
actual-use information that we would need to see
because they would not have been done in the way
that I am suggesting, without bias in terms of
limiting of access and perhaps that open-label-type
approach that we look at.

It doesn't mean that we couldn't have a
blinded approach, I guess, but we'd really need to
think through the study designs that are best. And
I don't know that a blinded study would even be
ethical here for an actual-use study. We'd have to
talk about that with Skip.

I did want to make one other comment,
though, if I could, on the animal stuff. Depending
on the formulation, I agree with Sharon totally on
naloxone, but if there were excipients that were
not qualified in a new formulation -- and that
means that they're new or they have never been used
in the quantity that they're used in this product;
in other words, they exceed previous -- there might
be some qualification of inactive ingredients that
would require some animal information.

DR. LURIE: And then my last question is
actually for Phil. And that is, some of these
actual-use studies that have been described, I
presume that they're candidates for applying to
NIDA for funding, right? I mean, obviously you
can't promise, but one could apply to NIDA for such
a study?

DR. SKOLNICK: Yes, that's correct. I think
Dan Wermeling mentioned he is being supported by a
NIDA grant.

DR. THROCKMORTON: Other panel members?

Skip?

DR. NELSON: Just one quick on the -- my
reading of the literature was that most of the
programs had a component of training. And so that
wouldn't really be the OTC model where there's a
clinician under appropriate state law or local
regulations are distributing naloxone with a
training component about the use of naloxone. It's
very different than the OTC.

And then if one went the auto-injector model
for IM, I mean that would be a prescription
approach as well because I don't think there's
any -- I don't think epinephrine is an over-the-
counter. That's a prescription auto-injector,
although there's not a whole lot of training one
would need for that.

So I don't think what's in the literature,
at least that I read it, were done in the way that
it would meet -- I would agree, would meet those
characteristics.

DR. LEONARD-SEGAL: I actually would totally
agree with that, and I don't know if there are
other elements in the literature besides the safety
that could help. But we certainly would want to
see the studies done with the proposed drug facts
DR. THROCKMORTON: Let's move to the questions.

DR. STANCLIFF: Hi. Sharon Stancliff from the Harm Reduction Coalition. We've had a lot of focus on new formulations, and the one that we have, the injectable, looks just like insulin. It's a mystery to me, why isn't insulin over-the-counter? How did it get that way?

DR. LEONARD-SEGAL: I will take a stab at that. That is very, very, very, very old history. And, in fact, the newer insulin formulations are not over-the-counter. I think that -- but the thing is that you will notice that they've never been available just on the shelf. They've always been with the pharmacist. They didn't, per se, require a prescription for access. Once somebody already had a prescription, they could sort of get the medicine based on refill.

But, in fact, I'm not even sure if you can even get insulin any more without a prescription. It is old history. And I know that the newer
insulins are not available that way.

DR. THROCKMORTON: As we thought about this meeting, we looked for sort of medical product examples that moved from a prescription only or a use only by professional to a very unregulated space. The AECDs were really sort of the best example that we found as far as a place that something had moved through all of those steps. Things like insulin and those, as Andrea said, are old and fall under other kinds of regulation that may not still be around.

DR. LEONARD-SEGAL: As a matter of fact, I can tell you that my division does not oversee insulin. It's actually overseen by the review division that's not -- it's a prescription review division. So although it used to be available, it was never actually regulated by the groups that do the over-the-counter drugs, which is very atypical.

DR. THROCKMORTON: Next?

MR. RAYMOND: Thank you. Daniel Raymond from the Harm Reduction Coalition.

I just had two quick questions. One was, in
the OTC discussion, there was a reference to other considerations, including whether this would encourage opioid misuse or discourage 911 calls. And I think that there's a body of experience out in the field that's been discussed already today documented in the MMWR article.

And in the interest of having kind of predictable pathways for developers, I'm wondering if you could elaborate on what the scope of those questions would be and whether they'd be satisfied by reviewing existing literature.

DR. LEONARD-SEGAL: That kind of thing might be able to be satisfied in terms of looking at existing literature. It would be up to the applicant to be able to provide that information for us in a way that it convinced us that we had enough knowledge about it. But, yes, literature that's out there certainly can help to support unanswered questions.

MR. RAYMOND: And similarly, in the context of a potential intranasal formulation, as we've heard, there's a lot of experience in the field
right now with both community-based programs and fire departments' first responders using unapproved off-label intranasal formulation.

I'm wondering in the interests of being creative and advancing regulatory science whether there might be ways to bridge the field experience or to start by collecting some data on that, even if that's not necessarily going to be the product that gets submitted; if, for example, you could document sufficient bioequivalency to what's being used in the field or based on the safety parameters about what's being documented in the field experience with these off-label uses.

DR. HERTZ: So I think there's a lot of information available in the literature, in the history of the use of this off label, that can go a long way to support answering some of the questions that will be asked of a new applicant. And right now, we as an agency haven't made a finding about the existing literature, what it can support; the existing experience, what it can support. And typically, the context in which we'll do that will
be the first application that comes in.

So, yes, I think that the fact -- for instance, the vast clinical experience -- I don't know about vast, but the existing clinical experience will help us decide in some circumstances that nonclinical data may not be necessary.

So that's going to take a big chunk of work out of an application to move this forward. And what we'll look at is how the application in front of us, the formulation compares to the existing product. So the closer they are in terms of composition, we can rely more and more on that off-label experience.

So, yes, we're going to look at all of that. And we really will try very hard to make sure that the data that we require of a new company to market this formulation and to get this indication will really be the minimum that's necessary to fill in the gaps.

And so when I listed the key questions, anything that's out there already, it does not have
to be generated by the applicant. So existing information out there will be reviewed in the context of any new product that comes forward.

MR. RAYMOND: But just to make sure I'm understanding you correctly, that review is subsequent to a sponsor and applicant initiating a process of approaching you? There's not necessarily -- is there a role for FDA in terms of sort of front-loading that process in the hopes of incentivizing more applicants to come to the table by clarifying what work could already be taken off the table? Do you understand --

DR. HERTZ: Well, I think that's kind of what we're doing today, a little bit, by making it -- I mean, we've had conversations with individual companies about what will be needed. Here today, we're describing this process, trying to make it known that we will work together to try and define what's necessary, what isn't necessary, so that we can really help to fine tune the process. So, yes, we're willing to do that.

In terms of us actively seeking companies to
do this, I don't know that we really have --

Okay. That's not what you're asking?

MR. RAYMOND: No, no; just in terms of what level of review of the existing data would you initiate independently of being approached of an applicant so that --

DR. HERTZ: Well, but the problem is the extent to which that data is going to support a new program is going to depend on the degree to which it's similar. So if somebody has an idea, we need to interact with them specifically to see what can and cannot be considered supportive from that information.

So, for instance, if somebody wants to come in with an intranasal formulation, or if somebody wants to come in with an auto-injector, or if somebody wants to come in with something that we haven't considered yet, the extent to which the current experience supports those development programs may be different.

So there's no way sort of a priori we can -- I mean, there's so many variables here that
it will be very hard for us to come out with a position paper saying because we have this information, this is the exact thing you need to do. And that's why my comments about what's necessary included "it depends," because it will always depend on how similar or different, how innovative, if there's novel excipients; everything depends on the individual situation.

That's also why I said the closer you can get to bioequivalence with existing products, the less information will be necessary to complement the application. So from a regulatory perspective -- and I think --

Dan, did I see that you were going to comment?

I mean, I think to the extent -- for somebody who is actually interested in developing it, I think we've signaled -- perhaps in a little too much reg speak -- that we are prepared to use as much of that information as possible.

DR. THROCKMORTON: I'll take my prerogative. I'll make a short comment, and then if there's
other conversation, we can talk about this at the break.

In other places where we've done similar things, pediatric development of midazolam labeling for seizures, that sort of thing, typically what we've done is worked with outside groups that have been able -- as Sharon said, starting with a formulation that exists to collect that information that's necessary. Because it really is, as Sharon said, just a challenge for us to sort of anticipate all of the possible things that would be needed, depending on how closely that formulation mirrored the bioavailability of the currently approved.

It's just hard for us to do that. It's much better to start with that formulation than have that conversation with a willing outside group that's able to convene and collect that kind of information for us.

So why don't we go to the next couple people, and then I'm afraid we're going to need to take a break. I apologize.

DR. SOMOZA: I'm Gene Somoza from the
University of Cincinnati and the VA Medical Center there in Cincinnati. I just want to make a comment about the fact that several speakers have spoken about what's ethical and unethical in all of this. And when I try to put this whole day together, it seems to me that the most ethical decision that could be made today is to expand what Dr. Walley talked about this morning, also, the Lazarus program that's similarly going in North Carolina, and what's going on in San Francisco to the rest of the country.

For one thing, we're talking about thousands of people that are going to die this year and more next year. And we can already use the drug that's already available and can give it intranasally or IM or IV or subcutaneous. What else do we want? I think to come up with a new product that's going to take a lot of time and a lot of money, this is totally crazy, from my perspective, when we have something that works and is very safe already. And it seems to me the best thing is to expand these programs. And while we're doing that, as
we're treating the people that are going to be otherwise dying, we can go on -- same thing with over-the-counter. Apparently, even over-the-counter takes a long time.

So I think we should try to just keep what's going on right now and try to solve some of the minor legal problems, maybe even major legal problems, so it can all happen.

And also from the perspective of the cost, $5 for a vial of 0.4 milligrams of naloxone is not that bad. This is for people that are spending hundreds of dollars to get their twice daily heroin dose. And if they can't afford it, I'm sure their family members can afford it. At least in Ohio, we had a hugely --

DR. THROCKMORTON: If you could --

DR. SOMOZA: What's that?

DR. THROCKMORTON: -- keep your comment -- I just want to give other people an opportunity to comment.

Do you have anything last -- if not, let's let someone else have a comment.
DR. SOMOZA: Okay. That's fine. Thanks.

DR. THROCKMORTON: Thank you.

DR. BELETSKY: Hi, Leo Beletsky from Northeastern Law School. Actually, I wanted to kind of echo what the previous commenter said. I just want to point out that FDA has a history of innovation in the face of public health crises, like during the AIDS epidemic and after the 911 attacks. And so I think that there is space for regulatory innovation. Obviously, we're -- I'm a lawyer, so I do care about regulations and rules, but I think that there are ways to be innovative in using this discretion.

I also wanted to specifically address the issue of the safe-use OTC program that was announced just last month by the FDA. I don't know if you have -- do you know about the proposal?

DR. LEONARD-SEGAL: Yes, I do. There was a part, what we call the Part 15 hearing, which as an attorney, you probably are well familiar with, where FDA listened to lots of different people from different stakeholder groups talk to us about the
pros and cons of OTC products with conditions of
safe use. It would be sort of a different kind of
a paradigm, which would still be over-the-counter,
not behind the counter. And we heard lots of
interesting talks on that. And actually, someone
did talk about naloxone during that presentation.

The conditions for that program do not yet
exist. They would require regulation. So
certainly, if we move into that kind of a
regulatory environment, then we have opportunities
that we don't necessarily have today. But that is
what we need. We have to be thinking about what
regulations would be written and which of them make
sense.

DR. BELETSKY: Yes, I just wanted to point
out that --

DR. THROCKMORTON: I'm going to hold you and
give the last person an opportunity. And thank
you.

DR. BELETSKY: Okay.

DR. DASGUPTA: Thanks. Dr. Hertz, a
question for you.
Can you expand a little bit on what the justification is for -- if there was a formulation that was bioequivalent to IM, what the justification is for the actual-use studies? And specifically, with the -- and not for OTC but for a prescription. And specifically in the context of the more recent labeling for suboxone sublingual films are very similar -- the safety and efficacy data in the label are largely drawn from solid oral dosing form -- or the sublingual dissolving tablet.

So I'm wondering has any of that experience, is that relevant here in terms of what was done or what could be done to abbreviate the development process? Thank you.

DR. HERTZ: It depends -- I know I say that too often -- on what the actual device and method of use will be. So depending on how simple and straightforward it is, there may not be much needed. The more complex or the more instructions necessary, then perhaps something will be needed.

So, for instance, we have asked for FMEA, failure mode evaluation, examinations for
instructions just to make sure. Because the last
ting we want is for a physician to prescribe this
naloxone product, it goes home with a
atient -- let's say it's a pain patient. There's
an accidental exposure in the home. Somebody grabs
this, and then they can't figure out how to use it.
I mean, that's not helping anyone.

So it's going to depend on what it is and
how much instruction is necessary, what the
structions look like, how intuitive it is, and
what are the chances for doing it improperly.
Again, this is a pretty high stakes thing. If it's
there and someone's counting on it working, and it
has the opportunity to fail if it's not used
properly, we really want to minimize that risk.

So depending on what it is, that will
describe how much information we think is
ecessary. Frankly, how do you write the
structions? I mean, it seems so self-evident
until you see things in their initial forms that
are quite bad. And if you actually give it to a
population that's not been working on it for the
last three years, they can't interpret the
instructions, and that's when it has to be
modified. So that's the kind of information we
look for.

Again, we don't want any of the requirements
to be burdensome or to delay any kind of
development. We're doing as much work as we can,
even outside of the normal formal channels that we
use, to provide advice to try and help move some of
this forward. So we'll do whatever we can to
facilitate, but we need to make sure that it's
something that's useful and can be used properly.

DR. THROCKMORTON: Thanks, Sharon.

We are 10 minutes over, so I'm going to take
discretion and reduce the break to 10 minutes. So
at 2:55, the auctioneer will call us to the room
once again. Thank you.

(Whereupon, a recess was taken.)

Open Public Hearing

DR. LURIE: Okay, everybody. It's time to
start the open public session, and this is the
point where we at FDA and the other sponsoring
agencies get a chance to hear from you. So we're really looking forward to this part. We look forward to a diversity of opinion.

The unfortunate part is that there are so many diversities that time is limited, and so we're going to adhere to a very rigid two-minute limit for everybody. That two-minute limit is going to be administered electronically by Brad, with the sonorous voice over here, and he's going to do so through the mechanism of this horizontal traffic light, which will go red, yellow and green in the other order. And I'm going to be the one after that who complains once it becomes red. So we really do ask you to respect everybody else's chance to speak as well.

So I think there may be a small amount of confusion because there seems to be two different lists of people, and some people are up here from having looked at the other list. But why don't we start with the six we have, and I'll call the next six when this first set of six are done.

So on my list, Leo Beletsky is first, and
he's a lawyer from Northeastern. So, Leo.

DR. BELETSKY: We're here today because for
tens of thousands of overdose victims, professional
help came too late. To address this, community-
based organizations and local and state governments
have innovated by expanding naloxone access through
prescription programs and equipping first
responders.

These efforts demonstrate great promise.
For example, since the Quincy, Massachusetts Police
Department was trained on naloxone administration
in 2010, officers have reported over 60 reversals.
This is a piece we haven't talked about today.

As I detail in my written comment, FDA
action is vital to facilitate this innovation.
First, the agency must ensure adequate supplies of
naloxone available to meet the rising demand. The
drug shortage program should reexamine importation.

Second, naloxone's prescription status is a
regulatory bottleneck. This drug should be
available over-the-counter, but its purchase could
be predicated on computer-assisted training at the
point of sale under, for example, the safe use OTC
program, which we just discussed.

Third, REMS provider training and patient
communications should raise awareness about pre-
hospital use of naloxone.

Fourth, the agency should help bring a
naloxone auto-injector device into the market.

Fifth, the FDA's regulatory stance on
naloxone-based overdose fatality prevention should
be clarified to reduce legal uncertainty.

And finally, the FDA should expand access to
intranasal naloxone either by relaxing some of the
human subjects requirement under the emergency IND
or by activating the emergency use authorization to
address this veritable public health epidemic.

The FDA has a history of leadership in
responding to unfolding public health crises like
AIDS and bioterrorism. Such agility and leadership
are critical in tackling opioid overdose.

Thank you.

DR. LURIE: Okay. Next.

MS. BELL: My name is Alice Bell. I've run
the overdose prevention project in Pittsburgh, Pennsylvania since its beginning 10 years ago. Since 2005, close to 800 people have received naloxone through our syringe exchange. We've documented 621 successful rescues, and other speakers today echo my own experience hearing hundreds of reports from people who have used naloxone to save a life or had their own life saved.

To address skyrocketing deaths from prescription opioids, we've broadened our efforts beyond urban syringe exchange, working with physicians and pharmacists to encourage prescribing naloxone whenever opioids are prescribed.

Two HIV clinics, a free clinic, and a traditional family practice are adopting this protocol. Two methadone programs offer naloxone prescriptions. One hospital emergency department plans to offer take home naloxone to patients at risk. One community pharmacy encourages physicians to prescribe naloxone when opioids are prescribed and provides training on opioid safety and naloxone...
But these remain small-scale efforts in the face of burgeoning deaths. And this progress is already being reversed. This week the nurse at one clinic told me they can't get naloxone anywhere in the U.S. There's a national shortage. At the syringe exchange, facing multifold increases in price, I imagine a face I will look at when I have to say, "We don't have enough naloxone for you. We can't afford enough for everyone who needs it."

Many of us here today register the fear in the voice on a phone call from someone asking how they can get naloxone to avoid death of a loved one, or anger in the voice of a parent learning about naloxone too late, or describing having a child come home from treatment and going into their room at night to make sure they're still breathing -- incredulous that they do not have access to this medication, asking why is it not in every home first aid kit.

I come here today to speak for them.

Surely, in this room, we have the expertise,
practical experience, regulatory and administrative power to make this life-saving medication quickly accessible to those in desperate need.

MR. BIGG: Hello, my name is Dan Bigg. I'm the director of the Chicago Recovery Alliance. CRA has operated outreach with people injecting in Chicago for 20 years and opioid overdose prevention with naloxone for 16. CRA has reached over 24,000 people with OD prevention and received nearly 3200 reports of lay overdose reversals.

I'm here to applaud the FDA for holding this meeting, affirming life, and to urge sufficient access to naloxone. Sufficient access means both reasonable pricing and adequate supply. Today, the price of naloxone is so high, its widespread use is impossible for many, such as happened with buprenorphine. Although available through private physicians, the cost of the medicine, around $500 a month, severely limits its availability to those needing it.

When our OD program started in '96, CRA was paying less than $2 for a 10 cc vial of naloxone.
Competition was the only thing keeping the price of this life-saving medicine low. Today, there is only one manufacturer of naloxone, and the price has increased eight to tenfold. What was less than $2 in the last '90s now lists for $35. OD prevention efforts will at best be greatly curtailed because of this high price.

In order to let the pure opioid antidote work its magic, we must create a marketplace for naloxone where price and supply are optimal. For example, creating an EpiPen equivalent around $90 for naloxone would price it out of the reach of most. Only through creating a large competitive OTC market can naloxone begin to have the life-saving impact we have demonstrated among thousands of people for 16 years.

Thank you.

MR. CHILDS: My name is Robert Childs, and I'm the executive director of the North Carolina Harm Reduction Coalition. And I'm going to tell you something today about the situation in North Carolina and why the prescription requirement for...
naloxone needs to be removed.

For the last six years, I've run community-based overdose prevention programs, syringe exchanges, harm reduction programs, jails and drug detox. And I'm somebody who has personally administered or coached people to use naloxone to save lives. It's a wonder drug, and I'm here to advocate for it to be made available over-the-counter.

In my home state of North Carolina, every day we lose around three people to drug overdoses. These deaths are not only unacceptable but also preventable had there been greater access to naloxone.

In 2011, North Carolina Harm Reduction Coalition trained over 3,000 people, mostly incarcerated people and people at drug detox centers, to recognize and prevent drug overdoses. Whenever I do a training, half the room will raise their hands saying they've personally witnessed a drug overdose or know someone who has lost their life to a drug overdose.
I hear lots of stories such as Stan. Stan lost his friend Will who was using “oxy” to manage chronic pain. Will restarted his use after a brief stay in jail and drug detox due to his inability to manage his chronic pain. Will didn't know that you could lose your tolerance to drugs when you have not used for a while. When he got out of detox, he took his regular dose of “oxy” and overdosed. Stan was present and not able to reverse the overdose because he was afraid to call 911 due to fear of arrest and because he did not have access to prescription naloxone. Stan watched his friend die.

If naloxone were more easily available and affordable through over-the-counter use, people like Stan would have the tools to reverse drug overdoses.

In North Carolina, our program does not have access to a costly prescriber who can issue prescriptions whenever we do trainings. This roadblock has made us unable to provide naloxone to the majority of the people we train.
Naloxone is a life-saving drug and the most effective tool in stopping drug overdose deaths. Without easy over-the-counter use to access naloxone, we're going to see many, many more people die.

MS. GREGORY: My name is Susan Gregory, and I'm from Sterling Heights, Michigan and a part of a grassroots community action group called Families Against Narcotics.

This here is a picture of my three sons. My oldest son Danny is in the middle with his arms around his brothers. Danny died five years ago from an accidental heroin overdose, and he was only 20 years old. Words cannot describe the pain or the hole that has been left in our family without him.

His drug use began at the age of 16 with marijuana and quickly progressed to Vicodin and oxycodone. By the age of 19, he was using heroin only because it was cheaper. He battled his addiction for three and a half years, and as his family, we did everything we could to try and stop
it, including expensive out-of-state rehabs and professional interventions.

But Danny eventually stole to support his habit and was arrested. He was denied treatment and placed on 120-day tether at our home. "Mom, I'm so done with drugs. All I want to do is turn my life around and become the respectable man that I was meant to be."

I was afraid for him, and I knew that this was a very high-risk time period for him. But I didn't know what to do. With eight months of sobriety under his belt and only two weeks left on this tether, Danny confided in me that he was beginning to relapse mentally. He was terrified. "I don't want to die, Mom. I need treatment."

Danny was white knuckling it, as they say in the program.

The next morning as he started to leave, he had a few hours off on his tether for good behavior, and I tried to stop him. I said, "Danny, wait. Don't go."

"No, Mom. It's okay. I love you."
Those were his last words to me. Danny left, and he went and he passed his drug test. Then he went into Detroit to buy heroin, and he used with two other using friends in a local grocery store restroom. And when things went wrong, his friends ran, and they did not call 911. My son died alone on a bathroom floor. And on the other side of that door was a store full of people, a pharmacy, and a major hospital less than a mile away.

I didn't know about naloxone then. What if the addicts with my son had been trained to save his life or not afraid of being prosecuted? My son would still be here and given that second chance at treatment.

Why wasn't I told about naloxone? If my son was a diabetic or allergic to bees, I'd be prepared with the right medication. We have defibrillators on hand everywhere to save lives. To me, any risk of using naloxone, of which I can't see, is very minimal compared to death.

MS. LYNCH: My name is Pam Lynch, and for 13
years, I have worked advocating for naloxone
distribution and programming starting with Dan Bigg
in Chicago, since in New York, New Jersey and
Michigan.

On March 9th in Traverse City,
Michigan -- that's four hours northwest of
Detroit -- 21-year-old Billy M. reported to his
community corrections officer that he had violated
his probation and that his urine test would show
positive for benzodiazepines and opiates, his own
prescriptions. He was promptly escorted to the
county jail, where they put him in a cell to sleep
it off. The next time they checked on Danny (sic),
he was dead. We are now working with local county
jails to have naloxone on site.

Nick G. is an 18-year-old that I met at the
drug treatment facility where I work, from Midland,
Michigan, who has buried five friends in the last
two years from overdose, the most recently of which
was March 20th. Nick himself has overdosed three
times and continues to medicate his emotions with
substances. Nick doesn't have much hope. No
amount of jail time will change Nick's investment in life or death. Naloxone can buy Nick and the Greek grandmother who loves him another chance until someday he may care enough about living.

Our country is full of Nicks. Let's do what we can to give people second chances. I am also a person in recovery from long-term drug use, heroin and cocaine addiction, and am extremely grateful for those who did not give up on me. Yes, IDUs deserve to live.

My experience in naloxone advocacy is that a number of community systems would be in support of naloxone, at least in the state of Michigan, such as the state police, and community and mental health -- the community and mental health system already has a built-in system of prescribers -- if an affordable intranasal delivery system was available. People that would jump at saving a life, buck at the idea of distributing intramuscular naloxone to drug users because of the hypodermic needle.

Of one thing I'm confident, if we leave here
today, if it was your child, mother, brother, 
sister, you want naloxone in the house, whether by 
needle or intranasal device. Ethical? I don't 
think so.

DR. LURIE: Okay. That concludes the first 
panel. Thank you very much.

And let them be a lesson to you. They're very, very good at keeping their time.

(Laughter.)

DR. LURIE: The next panel will be Nab 
Dasgupta, Whitney Englander, Marianna Kate Duncan, 
Steven Jones, Phil Coffin, and Christopher 
Heneghan.

Please start.

DR. DASGUPTA: Good afternoon. My name is 
Nab Dasgupta, and I'm a pharmacoepidemiologist at 
UNC and cofounder of Project Lazarus in North 
Carolina. We've heard reference to the current 
naloxone shortage. The main manufacturer of 
naloxone in the U.S., Hospira, has been unreliable 
and unable to even tell the public when naloxone 
will be regularly available in the United States
On at least two occasions in the last 15 years or so, the agency has allowed importation of naloxone from foreign countries. The irresponsible monopoly in the naloxone market is contributing to preventable overdose deaths. Some of the overdose prevention programs in this room are about to run out of or already have run out of naloxone. For what other disease condition would we allow the supply of the antidote to lapse in the middle of the epidemic that we heard about this morning?

FDA should be encouraged to take more aggressive action to address the shortage. To that end, we have compiled a list of over 50 naloxone manufacturers worldwide, including major U.S. companies that sell naloxone in Western Europe for less than 50 cents a vial, but not in the United States, where it goes for $9, $10 for the generic intramuscular, and it's approaching $20 for the intranasal. By comparison, the street price for a milligram of oxycodone is 80 cents.
While costs are not usually the agency's focus, there is precedent for federal agencies to coordinate the supply and stock of critical medications, notably antidotes for nerve agents and influenza vaccine.

Second, overdose prevention education among drug users has not been part of the long-acting opioid REMS discussion. The evidence presented today on naloxone effectiveness is far more supportive of effectiveness than the narrow set of unproven tools that are currently part of the opioid REMS. It's time to bring naloxone prescribing and overdose prevention education into that discussion.

Further, the public health agencies that have had success in reversing overdoses have not been recognized as stakeholders to contribute to long-acting opioid REMS. Today's meeting represents a coalescing of the political will and scientific gravitas that has been lacking. Now it's time to have better representation from civil society as well.
MR. RAYMOND: Whitney Engander had to step out. I'm Daniel Raymond. She asked me to present her statement for her. She's the government relations manager of the Harm Reduction Coalition and will submit her full statement to the record. But she wanted to be very clear that she would not be here at all if not for the fact that somebody had been able to revive her with naloxone eight years ago.

And over the past several weeks leading up to this meeting, Whitney and I have reached out to a number of public health organizations, organizations involved with healthcare, with pain management, to talk about the importance of this meeting and generated a letter from us and these groups thanking FDA and the other federal agencies for convening it.

And we are grateful. However, we also need more. I think that you hear in our voices the sense of urgency around this epidemic. Just on Monday, I lost a friend of mine to overdose. Many of us have lost friends, family, loved ones, and
we're looking to the federal government to share our sense of urgency because we've all thought, what more can we do, what else can we do.

I think we've heard a number of examples today of where there are opportunities but also where there are constraints and where there's potentially a market failure that's going to create an impasse where the things that we would like to do may not be possible because the incentives in the pathways aren't there.

And I am asking, on Whitney and myself's behalf, for all of us to look at how we can accelerate this process. As Nab said, we have similar models in terms of public health and regulatory science combining to move things faster than the traditional models have allowed, and this is clearly a case where we can no longer afford to wait.

Thank you.

MS. DUNCAN: My name is Marianna Kate Duncan. In September 2009, we lost our only child, Nicholas, to an accidental heroin overdose. He was
25 years old. Despite Nick's struggles with alcohol and drug use, he established and maintained a productive role in society. For the last five years of his life, Nick was a teaching assistant with preschool autistic children. He was seriously conscientious about his work, rarely missed a day, and he was well loved by the students and well respected by the staff.

A week before his death, he had applied to East Tennessee State University for the admission into their music education program. We received his letter of acceptance three days following his death.

From what we understand, Nick had been using heroin for only a short time. He was not injecting the drug. We believe that he had an erroneous idea that heroin would help him reduce his dependency on prescription pain killers. Heroin was more easily accessible and less expensive.

At the time of his death, he was surrounded by friends that were not using heroin and had no idea how to deal with an overdose. By the time
they recognized he was having respiratory distress and could not be resuscitated, they called 911. Unfortunately, the rescue came too late. Nick suffered brain death and was removed from life support four days later. Nick did not have to die from an overdose. Had these friends been provided with information about overdose prevention, recognition and treatment, or had they had access to naloxone, Nick would still be with us today.

It is my hope that in the future, other parents and anyone that has association with a heroin user can gain easy access to this crucial information and whatever might be available to them in recognition and treatment of overdose. In our case, it is too late. Our future is forever changed. This does not have to be the sad reality for everyone.

DR. JONES: I am Steve Jones, a retired staff member of the Centers for Disease Control and Prevention. I want to speak today about the nearly unique status of Italy, where naloxone is not a
prescription medication. Some copies of this flier summarizing the status of naloxone in Italy and including pictures of the packages of the medication have been distributed. See me, if you didn't get a copy, after the talk.

In the United States, the prescription medication status of naloxone is a substantial barrier to wider distribution of naloxone. For example, most community programs must have a licensed clinician on site to prescribe naloxone to each person. Because most programs have very limited on-site availability of prescribers, many people interested in naloxone cannot receive it.

In Italy, in 1988, more than 20 years ago, the Italian ministry of health removed the requirement of a medical prescription for naloxone. Currently, a 1 milliliter vial of naloxone for injection can be purchased without a prescription from any pharmacy in Italy. All pharmacies in Italy are required to stock naloxone.

We have made some effort so far to find more information about the distribution and any problems...
associated with this status. So far, we have anecdotal reports of no problems related to the non-prescription status of naloxone. We are planning to ask the Italian equivalent of the FDA for data on naloxone distribution and any adverse events.

The example of Italy should help in converting naloxone to over-the-counter status in the United States.

Thank you.

DR. COFFIN: Phillip Coffin, I'm a clinician investigator at the San Francisco Health Department. Dr. Sean Sullivan of the University of Washington and I developed a cost-effective analysis of naloxone distribution to heroin users, incorporating repeat overdoses -- as like heart attacks, overdose begets overdose -- and calibrated to established epidemiologic findings.

In this extremely conservative model, only three lives would be saved for every 2,000 people who receive naloxone, resulting in an incremental cost of $400 per quality adjusted life year gained.
similar to checking blood pressure to screen for hypertension. Maximizing the price of naloxone under current circumstances would increase that to $900.

Assuming lay administered naloxone does almost nothing to reverse overdose would increase the cost to $1300. Assuming overdose is rarely witnessed and recipients rarely carry naloxone with them would increase the cost to $1600.

Doing something never done in economic models and charging surviving heroin users by applying the national expenditures on drug abuse and criminal justice to active heroin users would increase that cost to $2,000 per quality adjusted life year.

And doing all of the above in a cynical, worst case scenario would increase that to $20,000 per quality, still far below the 50,000-dollar per quality traditional cutoff for cost effectiveness.

Thank you.

MR. HENEGHAN: I'm Chris Heneghan. I work as the director of the Windham Harm Reduction
Coalition. My agency operates a syringe exchange program in a rural county in northeast Connecticut.

Between 2009 and 2011, 4 out of 80 clients utilizing our syringe exchange program died as a result of accidental opioid overdose. The deaths of 5 percent of my agency's clients could have been prevented if these individuals had access to naloxone.

In the event of an opioid overdose naloxone provides -- the window of opportunity for a life-saving intervention closes rapidly, often before EMS is able to respond. In Connecticut, the benchmark standard for EMS response time is eight minutes, however, this varies significantly across the state, particularly in rural areas.

The American Heart Association reports that only 21 percent of Americans feel confident they could perform CPR during an emergency. Even if an individual on site during an opioid overdose is confident with their ability to perform CPR, rescuer fatigue can occur in as quickly as two minutes or five breath cycles.
Research shows in all cases of opioid overdose, it makes intuitive sense to reduce the time it takes to administer naloxone by getting it into the hands of those best positioned to respond rapidly. Naloxone provides a 30- to 90-minute window of opportunity to call 911 and get someone to the emergency room. This action can sometimes make the difference for getting someone into treatment and getting their lives back on track.

Naloxone has no abuse potential and a favorable safety profile. I'm asking the FDA to take responsible action to fight this epidemic by facilitating rapid approval for the relabeling of naloxone as a non-prescription product. Doing so will provide increased access for consumers who need it most.

My agency cannot afford to employ a prescriber to provide naloxone to our clients. If naloxone is relabeled as a non-prescription product, we can afford to purchase it and train our outreach workers to distribute it through our syringe exchange program.
This cost-effective reduction in mortality of the population most at risk cannot be achieved without your support. Please ensure the FDA is a leader in preventing further deaths, in fighting this epidemic by facilitating rapid approval for the relabeling of naloxone as a non-prescription product.

Thank you.

DR. LURIE: Great. Thank you, everybody. Dr. Dasgupta, I'll take that list, if you don't mind. Thank you very much.

The next set of speakers are Joanne Peterson, Hillary McQuie, Marilee Murphy, Megan Ralston, John Dombrowski and Eliza Wheeler.

If Terri Kroh is here, she should tell me, and so should Mary Torsch or Sherri French. I'm assuming you're not here.

I don't think the order matters. Yes, it doesn't matter. You can start.

MS. RALSTON: My name is Megan Ralston. I live in Los Angeles. I work for the Drug Policy Alliance. I have written extensively and have been...
fortunate to have been quoted and interviewed extensively about the urgent need for expanded access to naloxone and other overdose fatality prevention programs.

When people Google things like "overdose prevention" or "naloxone saves lives," they tend to come across things I've written. As a result, I have spent the last several years answering phone calls from strangers that always begins in more or less the same heartbreaking way. "You don't know me, but I found your name on the Internet and wanted you to know about my son who died of an overdose."

I have had more gut-wrenching conversations with moms and dads who lost their children to opiate overdose than I can remember. You truly can't imagine how massive and national the need for naloxone is. I know firsthand because I answer all of those calls and e-mails. It's horrible to experience that much pain and grief.

The majority of the parents and surviving spouses and family members I speak with aren't just
dealing with the trauma of losing their loved one
but dealing with the added grief of discovering the
existence of naloxone only after the death of their
loved one.

I was at a conference last week in Tampa
presenting on overdose issues to grief support
group leaders from around the country whose own
children had died from a drug overdose. I was
explaining the role naloxone is playing to help
reduce the number of overdose deaths.

I was explaining that it's affordable, safe,
effective and has been used to reverse opioid
overdose for 40 years. A man in the back row
raised his hand. "Wait," he said. "So if naloxone
is so safe, and works so well, and is so
affordable, and it can't be abused, and you can't
get addicted to it, why didn't I know about this
when my son was still alive? Why can't we get
this?"

What should I have told him, and how will we
answer that question?

MS. ODENHAL: My name is Marilee Odenhal
from Freeport, Illinois. I am here on behalf of my son and my family.

As we listen to the statistics and the research, we must also consider the devastating toll of overdose death for tens of thousands of families like my own. I speak to you as one parent to another.

My only son's name was Ian Murphy-Mitchard. He became addicted to heroin as a young man. He also suffered the burden of mental illness. But Ian was much more than the sum of his illnesses. He was incredibly intelligent, kind and talented. Ian was a good son and my greatest joy, and he never lost his hope for recovery.

Ian died of overdose three days after his 28th birthday. He died four days before he was to be baptized at his church. He died too young.

The FDA considers matters in scientific terms. Well, scientific fact is that naloxone could have saved Ian's life. I live with the certain knowledge that had my son suffered from cancer, doctors would have exhausted their skills
and tried every possible drug to save his life. But no doctor ever mentioned naloxone to me. I never even heard the word until four months after Ian's death, and that from harm reductionist. Why naloxone hasn't been touted on every media outlet and shouted from every rooftop, I will never understand. It makes me livid. I have the rest of my life to live without Ian, and I cannot describe that kind of loss to you. Most of us have children, and none of us thinks they will die of overdose. But it happens every single day to families just like yours and mine.

If foreign countries can make naloxone available and the sky does not fall, then so can we.

MS. PETERSON: Good afternoon. My name is Joanne Peterson. I'm from the organization Learn to Cope in Massachusetts. Today, we have seven chapters across the state and nearly 3,000 parents registered to our website, all parents, siblings, grandparents with sons and daughters that are addicted to prescription opiates and/or heroin.
I feel very fortunate today. My son is alive and well and in recovery, and I also feel very fortunate to be from the state of Massachusetts where we do have this pilot program.

We see people, parents and grandparents, save their kids' lives. Back in November, we had 14 parents trained through the Massachusetts Department of Public Health's Bureau of Substance Abuse pilot for Narcan. And we started distributing it at every chapter every week at every meeting. We started distributing it in December, and in two weeks, we had a mom save a daughter and a father save a son.

Back in 2007, long before we had that, we lost nine kids in seven weeks. And that's when Narcan started to become available, and ever since then, we've been very lucky to have access to it. And my heart goes out to the families that do not have access to it that have kids or loved ones that are addicted to these terrible drugs. Nobody should suffer the pain of losing a child or even witness an overdose--its trauma, its pain-- and
it's something that they will live with for the rest of their lives.

I only hope that Narcan will be available around the country. I hope that it will be easily administered in an easier to obtain container that's easily sprayed. I can't imagine any reason why we wouldn't have it, especially with this epidemic and the way these opioids are just flooded all over the streets and in homes. It's a must.

MS. MCQUIE: Hi, my name is Hillary McQuie. I'm the California director of the Harm Reduction Coalition. The Harm Reduction Coalition runs two community-based overdose prevention programs, one in California, the DOPE Project that you heard about earlier, and one in New York.

But today I want to talk about the issues that we come across doing technical assistance and networking with overdose prevention programs throughout the country and the kind of shortages and access problems that people are having: increasing prices, which you've heard about already; supply shortages which are extreme;
the lack of overdose prevention projects in most regions of the country; and finally, the lack of funding for existing programs.

The programs that you heard about today, such as the one in Massachusetts, the extension of those is rare. Usually, the programs are quite small. Often, there's no dedicated staff. Often, there's no paid staff. It's just another activity that a syringe exchange program adds on, and they have no dedicated funding.

There's very few of those 188 programs that have any funding whatsoever, and there is no real funding stream for this kind of work. It doesn't seem to fit anywhere. Nobody wants it really to fit somewhere.

So I was very happy to see SAMHSA here today because I completely agree that there needs to be integration between treatment and overdose prevention and harm reduction. When people are leaving treatment, they should be given referrals for harm reduction. And when people are coming to harm reduction, they should be given referrals for
treatment. And not just referrals like here's a list of places; referrals like here's some slots that we have, some program that funds these kind of linkages to make them more formal, because just talking about it without funding it really doesn't do the trick.

I think what the FDA can do is support this in terms of your negotiations with other federal agencies and, again, approve the foreign manufacturers and perhaps educate physicians that they can prescribe now without any problems.

DR. DOMBROWSKI: Good afternoon. My name is John Dombrowski. I'm a physician. I'm an anesthesiologist specializing in pain medicine at the Washington Pain Center. I'm the chair of the American Society of Anesthesiologists' communications committee. I'm also a member of the committee on pain medicine.

Now, opioid-related deaths have reached epidemic proportions, and the means of avoiding deaths related to respiratory depression need to be improved on, on multiple fronts. Prior to
prescribing naloxone, it's been imperative that physicians educate patients, as well as patients' friends or family members about naloxone.

Education should include how to recognize opioid overdose, how to administer naloxone, the importance of calling 911 immediately after administering naloxone, how to administer rescue breathing, and information on the shelf life of naloxone.

We recognize that the side effects of naloxone, such as negative pressure, pulmonary edema, or extreme high blood pressure can be severe. However, naloxone is a patient safety tool, and these side effects are treatable and preferable to an opioid-related death.

For this reason, the American Society of Anesthesiologists sees the importance in patient access to naloxone. The ASA, however, has a serious concern about making naloxone available over-the-counter. A physician who evaluates a patient, determines opiates are medically indicated, and counsels and educates the patients
about opiates should also be involved in counseling and education, educating the patients about naloxone and prescribing the medication.

Naloxone is not the only step in combating the misuse and abuse of these prescription drugs. However, it is an important safety tool for those taking opiates.

We thank the FDA for considering whether naloxone should be made more accessible to patients outside conventional medical settings.

MS. WHEELER: Hi. My name is Eliza Wheeler. I run the DOPE Project in San Francisco. We've been distributing naloxone to drug users since 2003 and have had over 600 reports of lives saved. I've provided access to naloxone for over 10 years in both San Francisco and Massachusetts. I have literally heard hundreds of stories of people using naloxone to save someone's life. I myself have used it four times, and I'm here to tell you that it's not rocket science and that those four people are still alive today.

Using naloxone during an overdose is easy,
and it's also an intensely powerful experience. Many people say that it makes them feel different, like a good person to have been able to save a friend's life. Sometimes the act of saving someone is actually what's life changing for people.

I've heard parents say that they let out a sigh of relief as soon as they got that naloxone kit into their hands and that it gave them some peace to know that if their child overdosed and they happened to be there, they would know what to do.

For the same amount of time that I've been distributing naloxone, I've been hearing all of the criticisms and concerns about what we do. What's happening here today is clearly a shift in that which I am grateful for, and thank you. But, frankly, I'm also really sick of hearing about how there's not evidence that this can work and that people can't recognize an overdose, they can't use naloxone, they can't put it together, they don't know how to use a needle, it might not be safe, it might increase or encourage their drug use, it
sends the wrong message, they won't call 911. It gets a little tiresome to keep having to hear this when we see the evidence in front of us every day.

So I encourage you to move forward in any way you can to make this easier, and I'm here for Brian, Ariel, Billy, Tim, and Paul, who didn't make it.

DR. LURIE: Thank you, everybody.

I think we can get everybody who remains on the last panel. Roxanne Soucier, Sharon Stancliff, Jo Sotheran, Azzi Momen, Steve Lankenau, Thomas McNally, and Gary Langis.

MS. SOUCIER: Hello, my name is Roxanne Soucier, and I'm a consultant with the Open Society Foundations. We support naloxone programs in Russia, Vietnam, Thailand, Georgia, China, and Central Asia. Though far away from this room, the FDA's decisions about naloxone have impacts in these settings, too.

In all of the places we work, drug users report that seeking emergency services is often unrealistic. People live in remote and mountainous
areas. Ambulances charge fees. They refuse to go to drug hot spots, or if they do, police come with them. In some countries, registration by police as a drug user means years in forced labor camps.

Because of these factors, to insist that naloxone must only be available through emergency services and hospitals is to insist that people die. Instead, we support programs that train laypeople in naloxone administration and make the medicine available. In most of these countries, naloxone is less than $2 a dose.

Drug users witness overdoses frequently, so are well positioned to respond. In one city in China, 90 percent of drug users reported witnessing an overdose. Through the programs we support, more than 680 reversals have been documented to date. In China, drug user groups have formed overdose rescue squads where trained responders with naloxone arrived quickly on motorbikes.

I would like to close with a quote from one of these participants. "I had another overdose earlier this year, and again my friends called the
overdose rescue team for help. They didn't blame
me but asked me with great care what I felt. It
was easy to talk to them. They introduced naloxone
to me and shared their knowledge on drug abuse
prevention and treatment. Now I take part in their
harm reduction activities. Now that I know what
they do, I trust them.

"I called the outreach workers right away
when my companions had an overdose. I saw how they
used naloxone to save my friends and its magic
effect. In the past, we helped each other using
stupid methods like kicking and slapping.
Sometimes a person wouldn't recover and would be
lost forever. Now I know these actions are
dangerous.

"As addicts, we don't trust others easily.
We are afraid to be arrested and sent to the drug
detention center if others report us to the
authorities. But the outreach workers keep our
secrets and help us from the goodness of their
hearts."

DR. STANCLIFF: I'm Sharon Stancliff, the
medical director of the Harm Reduction Coalition, and I oversee the SCOOP Project, the sister to the DOPE Project, in New York.

This SCOOP Project, we have dispensed, prescriber to person, something over 8,000 naloxone kits in the past six or seven years. Our biggest barrier in New York is about having a licensed person on site at a needle exchange offering this. Right now, two prescribers cover eight syringe exchanges with multiple sites. So we're there a fraction of the time that people are seeing that the clients are there.

Syringe exchange, I can give them all the needles they need to prevent HIV, but I can't legally hand them this life-saving vial unless you're right here. It just doesn't make a lot of sense.

Thinking of the vial, I'm talking about over-the-counter -- and I don't want us to forget about the intramuscular form. This is not so scary. We've had a lot of success using this.

Two things. New York City, we offer a
choice of the intranasal or the intramuscular. We have a lot of illicit drug users that are like, yeah, that's fine, that's what I want. But I also see people that are afraid of needles initially say this just looks really simple, and somebody can figure it out just by looking at it. I think I want the intramuscular one.

We've also helped something over 60 agencies -- whether in New York, we worked a little in Vietnam with them -- in setting up programs. And outside of New York City and New York State, only the intramuscular is available.

We're doing it with Daytop Village, a therapeutic community. We're giving this out in abstinence-based programs. So I think in this process, we need not to forget that the intramuscular has already been through a lot of steps, and we need to do that maybe while we're working on the other stuff.

Thank you.

MS. SOTHERAN: Hello. I'm Jo Sotheran. I'm a long-term board member of the National Alliance
for Methadone Advocates, sometimes known as NAMA Recovery. We're a recovery community organization dominated by the methadone patients who exist within the silence and stigma of the addiction treatment clinic system.

The country's 300,000 patients have a unique perspective on naloxone because both naloxone and methadone are life-saving medications. A lot of patients say that methadone treatment just plain saved their lives. So we know that the very availability of a pharmacological intervention matters.

Methadone patients also know a lot about overdoses because they can occur before, during, and after treatment. Usually, the period before treatment is one of out of control drug use with a lot of risks. Although being in methadone treatment decreases overdose risk very sharply, some deaths do occur even so, usually in the early induction period when the appropriate dosing level is being established and there is still common polysubstance use.
Finally, patients who leave treatment -- and there are many of them -- often relapse rather quickly into drug use and go back to the risks. Many patients have seen overdoses, some have lost partners and friends, and some have survived overdoses themselves. As a result, they understand the danger of overdoses, and they often want to help others like themselves.

Fatal overdoses among people both in and out of treatment could be reduced if naloxone were available in settings that are connected to the community of people who can actually most effectively use it. Methadone programs can be an excellent platform for distributing naloxone just as for many other health interventions. And the patients and those close to them could use it in their own communities.

But for reasons that Sharon alluded to, mostly including the limited clinic workforce and funding, despite the fact that many programs want to have this, a major barrier is the prescribing requirement. If that could be reduced, many more
could have access to yet a second life-saving medication. And we would ask any help you can give in helping us with this.

Thank you very much.

MR. MCNALLY: My name is Thomas McNally, and I'm a board member and volunteer of the Windham Harm Reduction Coalition in Windham, Connecticut. I come before you today to speak for my friends who cannot be here.

My friend Timmy, who is dual-diagnosed with mental illness and drug dependence, had been in and out of treatment in mental wards often. Tim came out of his last away time and overdosed on heroin injection, injecting the amount he was using prior to being in treatment in a treatment facility. Tim was found dead in a restroom. I have known Tim for years, and I will miss him.

Jason is a young man who is an opiate dependent. Traveling to the capital city with his girlfriend, Jason got a much stronger bag of heroin than he was getting locally. And after injecting his usual dose, he overdosed and became...
unresponsive. Thankfully, his girlfriend had naloxone with her and was able to administer the naloxone until assistance arrived. Jason related this episode to me during a visit to our agency.

My last story is about a young man, Chris, who died of an overdose of methadone. He was found dead in his room after working during the day. We don't know how this happened, and we hope somebody was with him at the time. Unfortunately, Chris did not know about the problems with methadone and was not aware of naloxone. Chris was my grandson.

Epinephrine pens are available to persons with insect allergies. They save lives. Naloxone also saves lives, and the death of just one person because of the lack of an antidote has an impact on many others, including the person's family, friends and community.

I ask that you allow naloxone to be made available to those whose very lives depend upon it and having naloxone easily accessible without creating additional obstacles to our opiate-dependent citizens.
Thank you.

MS. MOMEN: Hi. I'm Azzi Momen from the Open Society Foundation, where we support community-based naloxone distribution worldwide. Internationally, naloxone distribution is increasing thanks to low-cost naloxone and donors like the Global Fund. I'm pleased to note that the U.S. government through PEPFAR has also agreed to support these programs. And in countries like Kyrgyzstan and Tajikistan, USAID has provided ongoing technical support to NGOs and medical professionals on implementing naloxone programs.

Because naloxone is something that drug users want access to, these programs attract drug users into existing health services. They strengthen the bond between clients and healthcare providers and increase the uptake of other critical healthcare interventions like needle exchange and HIV testing and treatment. In Russia, for example, the NGO Tomsk Anti-AIDS attracted 900 new clients when they started the naloxone program. That's representing an increase of 60 percent.
The bottom line, naloxone saves lives, especially when it's given to those who are most likely to witness an overdose and respond first. And that means other drug users, their families and friends.

These programs give people like my colleague Twan (ph) from Vietnam a sense of pride and purpose to life. Since Twan cannot be here, I'd like to read his testimonial to you now.

"I was also a drug user, and I witnessed many painful overdose deaths. My best friend died of an overdose right in my arms. That was an unforgettable moment, and it helped me want to live and start over. I've stopped using drugs. And I'm currently the leader of a peer support group for drug users in Ho Chi Minh City, implementing a naloxone response program.

"Being able to save lives is the most meaningful thing we have ever done in our lives. And the residents where we work have seen us in a different light, knowing the good things that we're doing."
"I want to pass on something that a drug user said when he was revived. He said to me, 'Maybe I won't be able to quit using drugs after this, but now I know that there's someone who cares about me. And that will be my motivation to live.'"

Thank you.

DR. LANKENAU: Good afternoon. My name is Steve Lankenau. I'm an associate professor in the School of Public Health at Drexel University and also principal investigator who conducts research on substance misuse.

My comments, which are in support of expanding access to naloxone, are based on current evaluations of naloxone prescription programs offered by community-based organizations in Los Angeles and Philadelphia. The L.A. study is supported by a grant from NIDA.

Programs in both cities target injection drug users. Our studies which recruited 150 IDUs across both sites for in-depth qualitative interviews compared to two groups of IDUs, those
who had received naloxone prescriptions and those
who had never received naloxone prescriptions.

In both L.A. and Philadelphia, IDUs reported
successfully administering naloxone to reverse
recently witnessed overdoses. Reversals often
occurred in public places by both housed and
homeless IDUs.

Despite these successes, IDUs frequently did
not have naloxone with them when they witnessed an
overdose. Two typical reasons reported were
naloxone was confiscated by police, and IDUs did
not feel comfortable carrying naloxone in the event
of being stopped by police. Similarly, some
untrained IDUs reported discomfort with the idea of
carrying naloxone on them as their reason for not
gaining a prescription.

While naloxone is not a controlled
substance, changing its status to over-the-counter
could reduce concerns among IDUs, particularly
those who are homeless or who have ongoing criminal
justice involvement, about carrying it with them
and lessening the chances of naloxone being viewed
suspiciously or confiscated by police. These changes could increase the likelihood of IDUs having naloxone on them when overdoses occur.

Furthermore, during our research, it was much easier locating IDUs who had never received doses of naloxone compared to those who had. Expanding access and availability of naloxone may reverse this dynamic, which in turn may help reduce deaths due to opioid overdose in communities across the country.

Lastly, expanding federal funding for research on naloxone prescription programs is necessary so that policy changes are based upon well-designed scientific studies.

Thank you.

MR. LANGIS: Gary Langis. I've been working on several overdose prevention projects in Massachusetts over the years, and I'm here to talk about Josh.

I was on an outreach route one night -- one afternoon, and I came across a house. And people called me into the house because there was a
gentleman overdosing. I walked into the house, and
I met Josh. And Josh was ash gray, blue, not
responsive, and I pulled him to the floor, and I
started to do rescue breathing. I didn't know
Josh, didn't know if he was going to use the next
day. I had no clue who he was.

I went through the rescue breathing,
administered Narcan, brought him back, and he
didn't call 911. He didn't want to call 911.
Well, I stayed in touch with the people in the
house all during the day for the next six hours,
and I didn't see Josh for a couple of months.

He came walking into my office one day, and
he looked really healthy and wonderful. And he
said -- I said, "How you doing?" I said, "Jeez,
you look great."

He said, "Yeah. You know, the next day I
went into treatment after my overdose, and I'm
doing volunteer work over at Cambridge Cares About
AIDS."

This is two months later, and I kept track
with him. And Josh ended up working at the
exchange, training people in Narcan, testifying at
the statehouse at our celebration of our 500th
reversal.

We don't know what the outcome is going to
be. I don't know if he's going to use. I don't
know if he's going to get into treatment. But you
know what? It's a life. Every life is precious,
and I have to remember that.

Listening to Susan and Marilee and Marianna,
I know what it's like to lose a child. And the
first thing I thought when I lost my child -- he
took his life -- was I never want another parent to
go through this. And I know. I've talked to many
parents, and that's what they say. And I didn't
want Josh's parents to go through this.

Thank you.

DR. LURIE: Thank you everybody for some
very moving testimony about, really -- it puts a
human face on the problem we're dealing with today.

(Applause.)

DR. LURIE: I also want to particularly
thank this device here in the middle, which I'm
going to ask to borrow to limit my children's videogame time from now on because it seems rather effective.

We'll get back at 4:00 exactly, if that's okay. And then we'll get into the very final session, so 4:00, please.

It's been pointed out to me, sorry. I thought we had a break scheduled here, so let me retract. Sorry about that.

Let's bring Greg Zimet up instead. Sorry. I misread the schedule.

Greg, can you come up?

(Pause.)

Panel 4—Moderator Peter Lurie

DR. LURIE: Sorry for the confusion there, my mistake.

So in trying to put together this meeting -- and sorry for the confusion about there not actually being a break. In trying to put this meeting together, one of the things we thought about was the concern that the availability of naloxone in some greater fashion might have a
disinhibitory effect upon people's behavior in terms of increasing drug use. And this is something we've heard before in a number of different settings. We've heard it in needle exchange. We've heard it with contraceptive pills. We've heard it with Plan B. We've heard it in a number of different areas.

And so we thought that it would be helpful to bring along somebody who has actually looked on the data on this question, not with respect to naloxone, of course. But I searched the country, and I came up with Greg Zimet, who is a clinical psychologist in the department of pediatrics in Indiana University School of Medicine.

He's interested in the application of social science and biomedical approaches for prevention and detection of sexually transmitted diseases. And most of his research, or much of it, relates to attitudes and behaviors related to STDs, and in particular to HPV vaccination, the vaccine Gardasil.

So he's going to go through that experience
and some other related experience as well. Thanks.

Greg.

Presentation – Gregory Zimet

DR. ZIMET: Thank you, Peter.

I'm very pleased to be here and hope that you find this information relevant. I think you will.

So briefly, what I'm going to cover here is first to talk a little bit about the theory behind disinhibition, or the worries about disinhibition or risk compensation. And then I'm going to review in some detail, but quickly, the application of these issues to HPV vaccination. And then look at the evidence for disinhibition or risk compensation with respect to HPV vaccination; briefly talk about other behaviors as well, and then end with some recommendations, some summary and recommendations.

So when you look at the theory behind risk compensation and disinhibition, the theory sort of suggests that individuals have an inherent set point that determines their willingness to take risks. So that it follows then that interventions
that reduce risk will result in persons increasing their risk-taking behaviors to maintain their set point.

The theory -- and if you look at some of the literature and how it's applied -- sort of implies that there's this universal trait that applies to all persons across all situations. And I'm going to call that into question actually.

But first, with respect to HPV vaccination, there have been two major issues that have been discussed, largely covered in the media. And the first is sexual disinhibition. And this is the concern that HPV vaccination will be seen as protection against sexually transmitted infections in general, not just HPV, and that HPV vaccination would somehow be interpreted as permission to engage in unsafe sexual behaviors. And the result of this, then the concern is that it would lead to earlier initiation of sex, decreased use of condoms, and perhaps an increase in the number of sexual partners.

That's been where the major focus has been,
but there's been a little bit of discussion as well that young women who get HPV vaccine years later will feel protected against cervical cancer, and therefore will not -- their participation in cervical cancer screening, Pap testing, will decrease.

So I think the first question I want to quickly address, in terms of evidence, are parents really concerned about this because you would think with all of the exposure in the media that this would be something on every parent's mind.

So across multiple research studies, what we have found is that worries about sexual disinhibition are sometimes associated with opposition to HPV vaccination. And these are just correlations, and we certainly find significant statistical correlations. But a very different question, and I think a relevant question, is: are many parents actually really concerned about disinhibition?

The fact is few parents express this concern. When you look at research on reasons for
non-vaccination that are surveys of parents and interviews with parents, the main kinds of reasons brought up is that the physician or healthcare provider didn't recommend vaccination, the parents had worries about vaccine safety – unsubstantiated I might add -- and concerns that the vaccine is too new.

Here's just an example of one study. This is out of British Columbia in Canada. This was a survey of nearly 2,000 parents. In this study, as you can see from the graph, about 65 percent of the parents had their daughters receive the first dose of vaccine, and about 35 percent or almost 700 of the parents declined to have their daughters vaccinated. This is unusually low for Canada, actually. Most of the other provinces, it's much higher.

But the parents who declined vaccination were asked to indicate the reasons for the decision. And here you see a breakdown of their reasons. And they were allowed to endorse as many reasons as they wanted to, which is why the
percentages add up to over 100.

So you can see that over 40 percent of the parents indicated that they wanted to wait until their daughter was older. So this isn't really opposition to vaccination at all.

A little over 40 percent had safety concerns. A little over 20 percent said they didn't have enough information. Somewhat over 10 percent thought their daughters were not at risk. Maybe 7 percent or so said the vaccine was too new. And then less than 5 percent brought up sexual disinhibition as a reason for non-vaccination, which is about the same percentage that brought up the belief that HPV vaccine was a conspiracy of the pharmaceutical industry.

So is there actual evidence for disinhibition after HPV vaccination? I'm going to review a few articles. I have to start by saying that this is a question that is almost impossible to answer definitively, but we begin to get a sense of it from these research studies.

This is a study that Nicole Liddon from the...
CDC published earlier this year. It's a survey of over 1200 women, 15 to 24 years of age. Nicole found no association of vaccination with initiation of sex or with receipt of sexual reproductive healthcare. Sexually active women who had been vaccinated reported actually more consistent condom use than those who were not vaccinated. Findings were limited in this case by the cross-sectional design, again, which is the problem with all of these studies. You can't randomize people to receive vaccine or not receive vaccine.

In another study that I was a co-author on, Tanya Mullins published earlier this year. This was research with about 339 young women, 13 to 21 years of age, who were surveyed after the receipt of the first vaccine dose.

Now, it was interesting when the media reported on this because you got two different perspectives. So about half of the stories said that 24 percent of the young women perceived themselves to be at less risk for STIs other than HPV, and this was touted as a real concern. But to
my mind, the most important statistic here is that nearly 100 percent endorsed the need to continue to practice safe sex behaviors. And those who didn't endorse that were actually less knowledgeable about HPV vaccine and reported less mother-daughter communication. So to my mind, the findings are actually encouraging and actually suggest that what we need is more communication.

Again, it's a cross-sectional study. It's retrospective, so those are limitations. But it begins to give us a picture that disinhibition, risk compensation doesn't seem to be much of an issue.

Two additional studies I was involved with, one was published earlier this year, the other hopefully will be accepted for publication soon. We recruited 75 female adolescents from our urban health clinics, 14 to 17 years of age. They self-reported their HPV vaccination status. And in the Stupiansky study, we compared that to medical records as the gold standard for vaccination status.
In the Cummings study, from a previous study, we matched these 75 to 150 young women who were recruited prior to HPV vaccine licensure and compared them on a number of different measures. So in terms of self-report versus medical record, if you look on your left, you'll see these are the young women who had been vaccinated according to medical record. And what you see is that about 45 percent didn't remember. So 30 out of the 66 who were vaccinated said that they had not received HPV vaccine. On the right side is the eight young women who had been vaccinated, and all of them accurately reported that they had not received vaccine.

So I think the important point here is nearly half of these girls who had been vaccinated couldn't remember. So for them, to assume that any disinhibition is possible for an event that they couldn't remember seems silly.

This is the pre-vaccine to post-vaccine comparison. This shows on the left the number of sexual partners in the prior two months. And what
you see is that the post-vaccine group actually reported fewer sexual partners. It was not statistically different but certainly not more. On the right side, you see the number of unprotected sexual events in the previous two months, and this means -- in our twisted lingo, what this means is the post-vaccine group actually used condoms more frequently than the pre-vaccine group. And this was statistically significant, again, in the opposite direction of the sexual disinhibition idea or risk compensation idea. We also found no differences in diagnosis of gonorrhea or chlamydia between the two groups.

So with respect to Pap testing and the concern that somehow vaccination will lead to decreased Pap testing sometime in the future, we have no evidence. And we won't have -- I don't know if we'll ever have evidence, but we certainly won't for quite a while. We probably will never have adequate evidence because the guidelines for Pap testing will keep evolving over the next 10 to 15 years as they've recently changed, actually.
What about other research on sexual behavior? The empirical evidence is somewhat mixed, but I think the important point here is from a review study that involved mathematical modeling that Steven Pinkerton from Wisconsin did.

What he found is that it's possible that some risk compensation may occur with condom promotion programs. But it generally does not neutralize the beneficial effects of increased condom use stimulated by the programs. And I think this is a very important point to think about.

So which means ultimately the condom promotion programs increase protection, and therefore did not increase risk for infection from STI or HIV. It actually decreased those risks.

There's also research on protective equipment in childhood injuries, and this involved slightly less than 400 children, 8 to 18. They had an injury while participating in an activity that could have involved the use of protective equipment. And by protective equipment, I mean a bicycle helmet or a wrist guard, something like
that. And they looked at users and nonusers of protective equipment, and they found no evidence that the use of protective equipment led to greater risk taking behavior or greater severity of injury.

Other domains, this is risk compensation area has been looked at with respect to a lot of areas, not just health but actually many, many different areas. And some of the questions are, does requirement for seatbelt use lead to reckless driving? Does the use of ski helmets reduce head injuries? Does the use of bicycle helmets lead car drivers to drive more closely to bicyclists? Which may sound strange, but there is a study that seemed to suggest that when drivers see a bicyclist with a helmet, they'll drive closer to them. And then do antilock brakes lead drivers to brake later?

So the research evidence overall is somewhat mixed, but I think the problem is that research is really, really difficult to carry out in ways that you get very clear cut results.

So in summary, although concerns about sexual disinhibition predict the opposition to
vaccination, few parents express such concerns. Parents rarely mentioned decreased Pap testing as a worry. There's no evidence for sexual disinhibition after HPV vaccination, and there are no studies yet on the effect on Pap testing.

Risk compensation, in summary, is clearly not universal, and it's not inevitable. And it's likely dependent on the prevention strategy that one is looking at, whether it's vaccination, wearing helmets, flossing, et cetera.

The target of the strategy, whether you're talking about prevention of HPV, HIV, sports injuries, individual characteristics, there are going to be some individuals who are very impulsive, and it may be that they're more prone to risk compensation. And so you have to consider the larger social context. Condom use, for instance, occurs in the context of romantic relationships, and it's often not individually determined.

And I think again -- I really want to emphasize -- the increase in risk behavior -- and I put risk behavior in quotes -- may not lead to
increases in adverse outcome; that a lot of these
areas of health promotion or injury prevention,
even if there is a certain degree of risk
compensation, it doesn't negate the positive
effects.

So I would say the question should never be
and should not be to vaccinate or not to vaccinate.
I think it's ethically questionable to withhold
vaccine or often other preventive measures because
of unproven fears about disinhibition and risk
compensation. Research is important. We want to
know when risk compensation may be more likely to
occur and with whom but not to withhold treatment
or prevention from those individuals.

Focus should be on how to deliver vaccine
most effectively and how to best communicate about
the benefits and possible risks associated with HPV
vaccination.

Thank you.

(Applause.)

DR. LURIE: I think that was a model of
clarity, so I'm going to assume that there aren't
any questions unless someone has a clarifying one.

(No response.)

Panel Discussion

DR. LURIE: And not seeing one, I think I'd like to move on to the next group, which is our panel discussion. And here in this, we will consider a number of issues -- or we certainly hope we do -- that go beyond some things that FDA has concern or jurisdiction about. It's things that the government more generally might be more concerned about, including cost, ethical issues, what have you, things beyond FDA, though.

We hope and expect that we'll have a free-ranging and even -- what's the word -- adversarial conversation, if that's what it takes, because it's important to bring out the complexity and the difficulties of the issues involved here. So we've selected a panel that we think will do a good job for us in this respect, and here they are.

I've asked them to take three minutes to reflect upon what they've heard so far during the day, react to anything that seems particularly to
merit that. And then once they've done that, then we'll go to an open discussion between them, including --

Greg, you're still at the table? Good. And finally, there will be a short opportunity for questions from the audience as well.

So why don't we start with Ed Boyer. And by the way, it's three minutes for the opening statement, as it were, not really an opening statement, but a reflection and summary of what you've so far heard.

DR. BOYER: I was going to say a three-minute introduction of myself might be a bit long.

I'm Ed Boyer. I'm a medical toxicologist, and I practice at University of Massachusetts, where I'm chief of the Division of Medical Toxicology and at Children's Hospital Boston. For those of you who don't know what a medical toxicologist is, our area of practice is poisonings and overdoses. So I don't prescribe opiates to
anybody, but I give naloxone to the folks. I'm an emergency physician primarily.

And I guess my thoughts on this thing today, one of the things that struck me was how rapidly the distinction between opiate and opioid got blurred very, very rapidly. And I think that pharmacologically, that's kind of an irresponsible thing to do for the most part.

The reason is opioid analgesics, either because of their pharmacokinetic properties or because of their formulations, often have long-acting properties, which dramatically exceed that of single-dose naloxone.

So does naloxone reverse heroin overdose? Does it reverse opiate overdose? Yes, it does. Does it truncate opiate overdose? I think the data is pretty clear. Yes, it does, because only a minority of individuals who overdose on heroin require a second dose to maintain respiratory effort.

Does naloxone reverse opioid analgesic toxicity? Yes. Does it truncate it? And I think
the answer there is a pretty clear no for most cases.

So when I put that in the context of should this be available to everybody, heroin addicts, yes, I think it should be. I mean, if I were a scientific purist -- and I'm sensitive to the "Oh, for gosh sakes; quit talking about the need for more data." But if I were a scientific purist, I would say the data is pretty good, but rigorous data, in all honesty, is lacking.

To say that about opioid analgesics, to say that it can save lives, I think that might actually be a questionable if not dangerous clinical assertion. And I think that that does require better data than what we have right now. And there are places that clearly can do that sort of thing, but that hasn't happened yet to, I think, the extent it needs to occur.

This has implications in other things as well. If you move into an over-the-counter medication, we know that over-the-counter medications are relatively safe things, and that
means that they can be misused a little bit more
with a little bit less penalty than prescription
drugs.

So I'm just worried -- work as I do in a
pediatric facility, what would it mean if a kid is
exposed to an opioid analgesic? We know that kids
have delayed onset of toxicity. We know they have
longer onset of toxicity. And if somebody walks up
and treats them and doesn't do the right thing,
like call 911 and bring them into an emergency
department or a healthcare facility right away, I'm
afraid that you're going to see increased mortality
in highly susceptible populations.

Those are my initial thoughts, and I'll just
start there.

DR. BRASON: My name is Fred Brason, and I'm
one of the founders and head up Project Lazarus, a
comprehensive community approach to address the
opioid overdoses that have been occurring
specifically in North Carolina and now elsewhere.
And I also am project director for the North
Carolina Community Care Network case management
system for Medicaid for their chronic pain initiative, addressing chronic pain and the prescribing of opioids and, unfortunately, the overdoses within the Medicaid system.

With that, a couple of comments that I do have, and what I'm hearing today, and what I know from what we've been doing in North Carolina, is the epidemic amount of opioid overdoses that have been occurring, both from those individuals who clearly have had addiction problems and issues but also clearly with those who were simply patients who unfortunately misused their medication, either by taking more because they had more pain or not, realizing that the benzodiazepine or something else with that was going to have the adverse effect of an overdose -- so our project has been to reach the prescribing population as well as the general public in our communities for that education, so that they could also have the rescue component of naloxone for those times when someone might slip into that overdose mode. And hopefully, the education would allow them to be able to administer
and save those lives.

So what I'm hearing today and what I had been hearing is that naloxone, yes, it does reverse overdose. Yes, it does provide an education moment between the person who's doing the training or the person who has administered. And the person wakes up, and there's that opportunity to address the issues and what happened and what occurred, and then hopefully get that individual into treatment and into help.

So it does all of those things, which to us is the perfect remedy for the epidemic status that we're currently in, especially with the opioid prescriptions that are occurring in our communities, both for those individuals who definitely need that medication, we want to ensure that they do not have an access to care problem by removing those opioids, but at the same time, making sure that a patient is safe and that those individuals do not have easy access to prescriptions that aren't theirs.

But in so doing, we've got to cover the
whole gamut as far as the education component from
the addiction and problems in that community as
well as simply the patient, no matter age, in that.
So it's the issue of having it available, having it
in the right device, and having the education
component to all aspects of our entire population,
our entire society because we have gone into a
cultural society issue with this overall, and it
needs to be addressed.

So in North Carolina, everybody is on board.
The entire state hospital system, state medical
system, and our opiate treatment programs have now
decided that they are going to co-prescribe
naloxone to those patients who are new enrollees
into treatment.

I can tell you that in February in Wilkes
County, we had our documented utilization of
naloxone where a sibling saved the life of another
sibling. And that sibling within four days was in
treatment and getting help because they decided at
26 years of age, they did not want to die that way.
That was reached because of a community-based
project, and that's where we need to be.

We talked about the Indian Health Services earlier today; it was mentioned. And we are now initiating Project Lazarus and the naloxone component to the Indian -- the Koala Boundary Eastern Band of Cherokee Indians.

We heard today that the average overdose was around 40 years old. The Koala Boundary is 18 to 24 and well exceeding state averages for overdoses. I do not want to meet with them next month to do the training to the medical staff -- the suboxone buprenorphine program and pharmacy and those in the emergency department -- and tell them that here is your training, here's how to do it and to tell them that naloxone is not available to save the lives of those on the Indian reservation.

Thank you.

MR. BURRIS: Hello, everybody. I'm Scott Burris. I'm a lawyer, and I've been working on the law related to naloxone and harm reduction for a long, long time. And certainly, the law is all over here as we've heard. I think it's important
to mention that there's a lot that can be done at
the state level to cope with the fact that naloxone
is a prescription drug and to make it more
available, given the rules we have at the state
level. And we're seeing that happening. So that's
a bright spot, and it shows the work that local and
state level advocates and public health people have
done.

Of course, I also think that we've heard
today about a host of very hard regulatory burdens
that stand in the way of wider access to naloxone,
and that it's much harder for advocates to deal
with.

I was almost getting depressed by that as I
listened this morning. It's such a big burden, and
it was going to be such a big advocacy challenge.
Then I realized -- actually I've been working with
people who have taken responsibility for naloxone
access themselves, and they have gone out on the
streets and made overdose prevention happen.

But really, it's not their responsibility
anymore. I think the panel previous to this one
really handed responsibility off to you people in the government. And I think to some extent rightfully so.

When I think about whether you're going to rise to that challenge and how you should rise to that challenge, I reflect on some of my own experiences first as a kid growing up in Wisconsin in the '60s. I still essentially lived in the New Deal. Hard to believe when you think about Wisconsin today, but back then it was a time -- it was a place where we expected that government was going to help solve problems, and that government could be effective, and that government would rise to challenges when faced with challenges.

And then, of course working in the AIDS epidemic, I saw government rising to challenges, this agency rising to challenges. Of course, also sometimes being pushed by consumers to rise to challenges. But still we had some success stories. And I think the question before us now is whether we're going to have a success story here, and that lies in your hands.
We know we have a drug. We know how it works. We know it's generally effective for the use to which it's being put. We know that the nasal formulation has been successfully used by a variety of different providers over many years. We have very few stories of disasters. We really don't have any stories of disasters. We have some concerns and some anecdotes, and we certainly have reason to continue to do research.

But what we don't have now I think is reason to wait five, six, seven, eight years for a solution to this problem. Maybe it isn't OTC status right away, but we could throw money at this problem. Hillary talked about the fact that naloxone programs now are working on a shoestring. We could provide a lot of shoestrings, as Phil Coffin says, in a way that would be very cost effective.

We could have stronger encouragement and coordination from the federal government to states to encourage them to make the legal changes they need to make to allow naloxone programs to go
forward, albeit with licensed prescribers, at least with licensed prescribers in a less intense role.

What we can't do is walk away from here and wait a decade for real change. And this is a great first step. I think this was a really great learning experience we had today, and it was great to see the involvement from the really key federal agencies. But I want you guys to walk out of this room with the responsibility on your shoulders.

DR. MADRAS: Hello. My name is Bertha Madras. I am a professor of psychobiology in the department of psychiatry at Harvard Medical School. And I formerly was the deputy director for Demand Reduction for prevention, intervention and treatment in the White House Office of National Drug Control Policy.

I have seen substance users. I have seen the addicted in stories, in manuscripts, in scientific meetings. I have seen it all, and I'm delighted that this meeting has occurred today because I think this is a very crucial and important convening of stakeholders in it.
This topic with regard how to address overdose covers every single spectrum of human endeavor. It covers the science. It covers biomedicine. It covers public policy, social policy, ethics, morality, legal issues, just as every other substance abuse problem does. It is one of the few areas in science that spans all the domains of human activity.

My overview with regard to this issue is my foremost principle is to save lives. That is number one. And this meeting is an FDA regulatory meeting that responds to the large increase in opioid overdose. The regulatory issues are clear. The biological rationale is clear. Naloxone is a pure new opioid receptor antagonist. Over activity, these receptors leads to respiratory failure, possible death, and naloxone can surmount the agonist activity of opioids to rescue people.

But we should -- and I encourage operating within the constraints of sound FDA regulations because we've seen when states try to take control of these regulatory mechanisms. And I trust the
FDA as the ultimate resource with regard to sound scientific approval of drugs.

Unlike EpiPens for bee stings, we have to assume that the majority of overdoses are among people that have substance use disorders, and that leads to my secondary principle. And my secondary principle is that you have to save more than a life after an overdose crisis. You have to try to prevent a recurrence or save a person from a lifetime of addiction, from depression, or from noncompliance with pain medications because lives are truly in danger here. It is not like an EpiPen where you can simply rescue a person because by happenstance they have a bee sting.

In recent studies in Norway, one-third of all patients with substance abuse poisonings reported previous suicide attempts, and one-third of suicide attempts reported daily substance use.

So with regard to how to address this, let's look at some of the constraints and some of the guidance that we have from the United States Preventative Services Task Force. They look at
preventative services with regard to morbidity and mortality, not only mortality, not only saving lives with also quality of life and sickness.

Very little has been discussed about addiction here and the quality of life. And what we haven't heard is patient education. We've heard of three programs from Dr. Binswanger, Dr. Walley, Dr. El-Bassel, but we have not -- we have only skirted the issue of after the rescue, what is being done. And I think that should be formulated as part of guidance with regard to Narcan rescue.

We've heard of no interventions, no SBIRT, no counseling, no data on referral to treatment. We know that Narcan can assist. We know that it is critical, but the elephant in the room is that the people who overdose are in grave danger. And that is not being addressed at all, and I would like to see that part of the dialogue.

I will now defer to the clock and allow my colleague to continue.

DR. BARTOSZEK: Hello, everybody. My name is Dr. Mike Bartoszek. I'm board certified in
anesthesiology and pain management, and I'm the chief of the interventional wing in the pain clinic at Fort Bragg, North Carolina. And I have to say first that the views that I express are those of our clinic at Fort Bragg, not necessarily the views of the Army or the DoD as a whole as I talk today.

Just so you get a background of where I come from and what we're doing down at Fort Bragg, we've had a problem with chronic pain for a long time at Fort Bragg. And after 10 years of war, we've added comorbid conditions like post-traumatic stress, traumatic brain injury, anxiety and depression, and all of the polypharmacy that's come from that.

And that has resulted in sort of an unexpected, unacceptable high rate of overdose and death in our highest-risk patients. And so we at Fort Bragg recognized that problem, and we've emphasized many of the sort of standardized risk reduction principles such as the sole provider programs, prescription monitoring, year-end drug monitoring, and then emphasized non-opioid pain treatments like interventional care, psychological...
care, alternative therapies like acupuncture.

But to that, we've also added the naloxone piece. And we began collaborating with Fred from Project Lazarus, and we came up with a broadened program of patient, family, and community education, in addition to naloxone, prescribing, for our highest-risk patients.

We began this sort of robust education program with an emphasis on the risks of overdose and also the indications and the instructions for a naloxone rescue. And since we've been doing that in our highest-risk patients, what we've noticed is we've had absolutely zero naloxone reversals at all.

We've also had zero overdoses and zero deaths at Fort Bragg in the past one year since we've been doing all this. And I think that from what I've heard today -- I've heard a lot about naloxone reversals -- the point I think we've seen, and what I'd like to emphasize, is the prevention piece.

For us, it's almost like when I prescribe
the naloxone for the patients and their family and
support system, there's the education, but then
there's that actual moment where you give them the
naloxone. And there's that realization of how
important this is and how serious this is in their
eyes. And it's not just the soldiers' families.
It's the soldiers' unit that is not about to let
one of their own fall victim to their medication.

And so I think what we've found and what I
emphasize from what I've heard here today is really
the teaching and the prevention that we can be
doing. It's not necessarily the rescue. The
rescue is secondary prevention. I think it's the
primary prevention of education and actually
prescribing naloxone that we've seen the effect of
at Fort Bragg.

We have 50,000 soldiers there on active
duty. We've studied this, or at least piloted this
in about 500 or so. And we're about to roll it out
to the entire Fort Bragg community through our
primary care clinics. And we've come up with I
think a cost effective way to risk stratify
patients so that we treat with naloxone or educate
only the high-risk chronic pain patients who raise
red flags for problematic use and kind of leave
alone the thousands of people who get opioid
prescriptions who take them as prescribed for a
medical indication.

So we're looking for research money to sort
of study that and try and get some good outcomes
from our program at Fort Bragg.

DR. LURIE:  Great. Thank you very much.

So I think perhaps I heard less disagreement
than I heard a variety of perspectives. So that's
very helpful, I think.

I think what I'd like to do next is to give
each of you a chance to ask questions of each
other, whoever wants to go first. If you have a
question of other panelists, if you have a question
of another panelist, you can ask it for all or
ideally, to one person.

MR. BURRIS:  This is for you, Dr. Madras.
Maybe it's a disagreement. Maybe it's just a
clarification. But I didn't hear that naloxone
reversal programs are not addressing substance abuse disorders. What I heard is that people are drawn in. One of the advantages of a naloxone program is that it draws more people in to get an opportunity for treatment and to get a referral for treatment.

So it sounds to me, what I heard you -- the only way I can understand what you said is that we should be -- that naloxone programs should be designed to provide substance abuse treatment or substance abuse intervention at the time of reversal. Even EMTs don't do that.

Can you clarify?

DR. MADRAS: Yes, I'd be delighted to clarify.

There were two things that I looked at the data on the slides that were presented, and I was curious about how many people had actually entered treatment post analoxone rescue, how many people had had secondary, tertiary, quaternary overdose events after the fact.

We did not see one of the slides, which I
did receive earlier, and that was from Dr. Walley, showing that drug use had essentially not gone down. It had gone up from benzodiazepines. So there seemed to have been a very constrained view of how to present the data, and that is the fact that this rescues lives.

I understand that there is an opportunity to engage in treatment. I'm far more interested in outcomes rather than opportunities.

DR. LURIE: Would anybody like respond to that?

I think that what Dr. Madras is suggesting here is a research agenda that relates to -- I know that in other areas analogous to this, there were data about numbers of referrals to treatment, perhaps the outcomes of treatment. And I think it's a fair point that we heard a little bit less about that than we heard maybe in the needle exchange literature. So I think that's a challenge to people to try to put that together.

And I think the other methodological challenge you seem to be putting forth is that you
want an, in effect, I guess you can call it prospective data on how a person who is reversed does subsequently. Not a tallying of overdoses, but whether that person who is reversed later overdoses. I think that's -- is that fair?

DR. MADRAS: When I was serving at ONDCP, the Narcan issue came up because I had organized a fentanyl meeting to try to gather as many stakeholders as possible to try to avert and prevent the disaster of fentanyl overdoses in Detroit and Chicago and Philadelphia and other cities.

And we heard presentations on naloxone, and during that time, I was very curious to see whether or not the rescue would give rise to improvements in outcomes. To me, outcomes means trying to get on medications, trying to get people to reduce the drug use, reduce risky behaviors, whether or not they would re-overdose in a period of time and whether or not these rescues would reduce the number of secondary and tertiary overdoses.

So when we heard that there were a thousand
rescues at the time, I asked staff to find out the nature of the data. And they called the source of the data, and they were told that they had called needle exchange programs throughout the country. And they had said, well, we had 100 here, 100 there, 100 there.

And I said, "What was the nature of the rescue? Was it an opioid, an opiate? Was it a synthetic opioid, a derivative of morphine? And what were the longitudinal follow-ups?"

And there was no data, and it disturbed me because, as I said, I do think that people who are rescued from an overdose should be treated the same way as a suicide attempt or anyone who is in danger of their lives. And there needs to be follow-up. There needs to be an intervention. There needs to be a sense of the sacredness of their lives beyond saving their lives.

    DR. LURIE: Dr. Boyer.

    DR. BOYER: I see Alex standing at the back. I know I've seen your talk a couple of times, and I just don't remember the slide.
Does it say that there was no change in utilization rates or no increase in utilization or acute hospitalization, whatever it was? And if that -- if I'm remembering the slide correctly, does that mean that people were not coming into the emergency department after? Is that the implication?

DR. WALLEY: Would you say the last part of your question? I just missed that part.

DR. BOYER: Jeez, I don't know if I remember it.

(Laughter.)

DR. BOYER: Let's answer the first part first.

DR. WALLEY: Okay. So I think you asked about emergency department and hospital utilization. And almost any way we model it, our independent variable is implementation, so the number of people for whom we have a documented OEND enrollment. There's basically no association with either -- there's no increase or decrease in ED or hospital utilization.
DR. BOYER: Does that imply that people are not calling 911 after a reversal?

DR. WALLEY: So I talked a little bit about it this morning. I think there's two -- I do think there's two things going on. Number one is that we are explicitly training people to call 911, and so some people who otherwise would not have called 911, I believe actually are. And then at the same time, we're also training people to prevent overdoses in the first place. And so those people would not go to the emergency room at all.

So we're doing two things with OEND, that one would increase utilization by encouraging people to call 911, and the other thing, other, would decrease utilization by preventing the overdose in the first place.

So that's how I speculate that interpretation. But what's interesting is we see a substantial reduction in death rates in places where we implemented. So that is -- I think that's --

DR. BOYER: So we can't interpret the data,
but who cares, people are surviving?

    DR. WALLEY:  Pardon me?

    DR. BOYER:  We can't necessarily interpret the data, but who cares, people are surviving better now?

    DR. WALLEY:  No, no.

    DR. BOYER:  People are alive --

    DR. WALLEY:  I did give you an interpretation of the data.

    DR. BOYER:  I mean, the ED utilization rate data --

    DR. WALLEY:  No, I gave you an interpretation of it. I mean -- do you have another interpretation of it?

    DR. BOYER:  Well, I just -- it sounds like there's a bidirectional opportunity here. Either people are not overdosing, therefore, they're not coming in, or they're overdosing and not going.

    DR. WALLEY:  That is for the non-fatal measure of overdose --

    DR. BOYER:  It seems like there's so many contributors that haven't winnowed out --
DR. WALLEY: -- which is ED utilization -- excuse me. I'm sorry. I'll let you finish.

DR. BOYER: No, no, I --

DR. WALLEY: So that's for the non-fatal overdose measure, which is ED and hospital utilization. That's the best proxy for non-fatal overdose that we could come up with.

But fatal opioid-related overdose, that's a hard outcome, and I don't -- there's no -- I mean, there's no ambiguity about how to interpret that. It's there.

I think Dr. Madras was referring to another issue, though, which was whether -- and I didn't show this slide, but I hope it's available to people who have access to the slide set after, and I hope it's included.

So we are a program that is funded as a program, not as a research study. I think I mentioned that. It's a public health program. We do not have systematic follow-up. The people who come back to us, report their overdose, it's
self-reported. And those come back, and it's really convenience sample. I would love to get funding for a prospective trial -- or not a trial, a prospective cohort study to systematically follow up people who we enroll, but we don't have access to that.

There's an accident that happens. Because we're a large system, we require each program site to enroll people newly if they come to a new site. So, for example, if you're enrolled in New Bedford and then you go to Lynn and say I was enrolled in New Bedford, give me my refill, we don't allow that. We actually require Lynn to enroll that person.

So what that means is in 380 cases, we've gotten two points in time where we have enrollment information. And with that enrollment information, we have their 30-day drug use history. And so what we've done on that slide is looked at whether that 30-day drug use history, the number of days they've used, goes up on the second enrollment compared to the first enrollment, goes down, or stays the same.
And essentially, there's no change in the drug use information except with benzodiazepines, which I think is an area that we need to continue to look at it.

But the important aspect of that is I think it addresses what Dr. Zimet was talking about. It's one of these imperfect studies that looks at whether there's an enabilization of higher risk by the intervention. And we see no evidence of that for opioids, which is in biological terms, that is the use that would be enabled by naloxone, not benzodiazepines. In fact, we counsel people not to use benzodiazepines.

So I do think that's a concerning finding, but it does support the concerns I think that Dr. Madras is bringing up. Her concern now has shifted from enabling worse drug use to the fact that we're not aggressively promoting treatment. And I mean, we're doing the best we can with what we've got.

I mean, I don't -- you've heard the testimony from parents. They are doing everything
they can. They just want a little naloxone to help
them as well. It's not like they're not going to
refer their kids to treatment just because they
have naloxone.

The natural history of addiction is
recovery. That's the miracle, right? The natural
history of addiction is for people to get better.
Now, treatment is helpful in that, but it's not
necessary. Actually, most people who get better
from addiction do it without treatment.

(Applause.)

DR. LURIE: Let's give Fred a chance to
comment.

DR. SZALAVITZ: I just want to --

DR. LURIE: I'm sorry. I see you. Let me
just give Fred a chance because he --

DR. BRASON: I just want to respond to this
whole dialogue because as Project Lazarus, we're
not a naloxone program. We're not just a
standalone trying to reach individuals on the
street and dispensing that way. Our whole goal was
to introduce naloxone into mainstream medical care
as best practice for those individuals who are at risk for an overdose because of their opioid medication.

And a whole list of the factors -- because of comorbid conditions and going to the inmate being released from prison, we've heard all about that -- we reach all of the segments with that. But in doing what we're doing, we are heightening treatment for everybody who wants to have treatment. And those of you who are out there working with individuals, if somebody doesn't want treatment, they are not going to get it. But we certainly have that -- treatment facilities rise to the occasion to meet that.

But in the context of the medical community and with naloxone and overdose education, we are introducing that into SBIRT as a brief intervention so that those individuals will have that opportunity. We are introducing it into general medical practice that when the physician sees an at-risk category, boom, they get a naloxone script and they get education both for themselves and
their family. That will open the doors more to treatment, we hope. We have seen that. There's evidence of that.

But it's also going to reverse the deaths. It is going to lower that amount as Alex Walley has already seen. So there will be that hard outcome, but at the same time, it becomes common within our society and in our communities that naloxone is an antidote to an overdose and can be used for heroin. It can be used for opioid medications and should be readily available to those who need it at the time of the overdose. And then all the factors within the community rising up to meet the need after the overdose, so that that individual does have the opportunity and does have the avenue for the help.

That's kind of the crux of our program because it's comprehensive, addressing all of those issues, making naloxone just common, and that's what we're after.

DR. LURIE: Let's take a question or a comment from the --

MS. SZALAVITZ: Yes, I would just like to
say --

DR. LURIE: -- and now this can go to the microphone I think at this point.

Questions and Answers

MS. SZALAVITZ: Oh, sorry. I would just like to ask why naloxone is being held to a higher standard. If this was a drug for cancer, we wouldn’t ask it to cure AIDS as well.

I am myself a former IV drug user who was saved by information about needle exchange. And we were having the same exact debate that we had 20 years ago when I first got into recovery about is this going to enable people. And I'm just really curious, like how can we say to a mother who's lost a child, we don't want this available because it might not work or because it doesn't cure the addiction?

I just would like the panel to address this.

DR. MADRAS: First of all, I would like emphasize that not once in my comments did I say that naloxone should not be made available. And you've misinterpreted what I said, so I regret
that, or I did not explain it clearly. I clearly said the most important principle of all is to save the life of anyone who is an overdose crisis.

I also said that the life that is saved also requires secondary intervention because unlike cancer, this is a biobehavioral disease, which could lead to further death. It could lead to death. It could lead to a lifetime of addiction. And therefore, the rescue should be phase 1 of at least a two-phase project.

That's what I'm trying to say. I never once implied that naloxone should not be made available.

MS. SZALAVITZ: I thought your position used to be --

DR. MADRAS: Pardon?

DR. LURIE: Can you identify yourself, please?

MS. SZALAVITZ: Didn't you used to oppose it?

DR. MADRAS: That was a profound, profound misinterpretation of some of my statements. I always said it should always be available. It
should be made available to people who are in need of overdose rescue, but it should be made available under circumstances that are also going to help the person recover.

DR. LURIE: Let's take another comment.

Can you identify yourself before your comment or question?

MS. BERGER: I'm Carol Berger. I'm with the Chicago Recovery Alliance.

I really appreciate the discussion around treatment. I think treatment is really important, but I feel a little saddened by the presence of still pervasive stigma in some of the comments in this room. And I feel like if this was a discussion about other diseases that also have behavioral components, like the discussion about making defibrillators available in the hallway, I wonder how much of that discussion was nuanced with, well, we need to make sure as soon as we intervene and do something with that; that's phase 1. And then this person needs to go and have other intervention to address the behavioral
components that might have caused their heart
attack.

I feel like with addiction we're always
doing this. It's different. It's different.
We're making it different. This isn't different.
This is a life-saving medication that we have that
people should have access to.

We should also have treatment, but that's
not what this discussion is about. This discussion
is just simply about saving lives and making the
medication more available to save more lives,
something we've been doing in Chicago for a long
time. We're very, very proud of and that we can do
a much better job with. And we're really just
asking for help in making this diffused to more and
more people so that there are less deaths.

Thank you.

(Applause.)

DR. LURIE: Dr. Bartoszek, you had a
comment.

Dr. Bartoszek had a comment, I think.

DR. BARTOSZEK: I'll just respond real quick
to what she said. I don't think what she's saying is that we shouldn't reverse the -- or the ID analogy. If someone is defibrillated, they then go to the cardiologist to have an evaluation and maybe something implanted, or whatever it is that caused the problem is treated.

And so I think the same thing with naloxone for this problem, that if you have a reversal, then you're then going to go on to have more services. I think she's just calling for more services. But nobody is saying -- at least I don't think anybody is saying that we shouldn't have naloxone available.

If anybody else can --

DR. LURIE: Okay. Scott?

MR. BURRIS: I feel a little bad for having asked that question to start with. I think we all agree that it's great for the USDA to keep our beef from having salmonella even though they don't make us all into vegetarians.

(Laughter.)

MR. BURRIS: I think another thing that we
can actually all agree on now is how well proven, from a public health and scientific point of view, and from an epidemiological point of view, harm reduction has been. We don't really have to talk about harm reduction or treatment.

Harm reduction has always incorporated a real desire to get people into treatment, helped to get people treatment when they're ready for it, when they want it, when it's the right thing for them. There's no conflict here. And harm reduction has worked.

We have good evidence from the observational studies of needle exchange that they are entry ports into treatment for some people. We have no other population of people at risk for HIV where the rate has gone down like it has with drug users. Everybody else has pretty much stayed where they are in our long fight against HIV. And now the same thing is really true here with naloxone. We've got a lot of miles behind us showing that this is a feasible and effective intervention.

So I think we should be proceeding upon this
together, as I think we all agree we're going to be
doing. And really the only question is now the
urgency with which we kind of work all these thorny
details.

DR. LURIE: Okay. Let's take a question
from the audience.

MS. PETERSON: I just wanted to -- my name
is Joanne Peterson from Learn to Cope, and I just
wanted to clarify a few things and make a few
things very clear.

In the trainings that we do with our
families at all our chapters, they're very
organized, and they're very professionally done.
In fact, some of the people that are trained are
parents of young sons and daughters, who some of
them actually were prescribed Oxycontin or the new
Perc 30, which is really oxycodone and became
addicted and then turned to heroin. And then these
poor parents are left with how do I -- what do I
do, how do I find treatment.

And then they come to our meeting. We give
them resources. We always encourage treatment. We
always encourage 911, which is not many parents that would not call 911. So that's always the first thing that we encourage them to do. The training that we learn through our department of public health, we give them that training. Then we give them resources on top of it.

And I can give you a scenario. In December, one of those moms who went home that night after receiving her Narcan, she heard a thump at about 2:00 in the morning. And her daughter fell out of bed, overdosed. She gave her Narcan. She was med-flighted to Mass General. Her life was saved, and she's been clean ever since. She went to treatment. And the same thing with the man's son.

I just want to clarify also that my husband is a diabetic, and when he came down with his type 1 diabetes, our entire family was brought into the medical office. And we were taught what are the signs and symptoms of hypoglycemia versus hyperglycemia, how do I give him insulin, how do I know when to give him insulin, how do I know whether to give him orange juice or candy.
This is really not much different for anybody to be able to learn how to save another person's life. I don't see what could be wrong with that as long as they're properly trained to train that other person and, of course, offer them the resources to go to treatment.

And I wish I could put every person in this room today that is now in recovery that has been "Narcan-ed," and it saved their lives. And like my son today, he's clean and sober. I didn't have to use Narcan. Back in the days when he was suffering from his addiction, I didn't have that option. And I didn't even -- no one really knew to teach me what the signs of an overdose was. And I actually saw him turning gray and blue. I heard him making that snoring sound, and I am just so lucky that he didn't die. And I didn't have that information. I didn't have Narcan.

Now we have it. People are literally saving other people's lives. These people are going on to treatment, not all of them. But there's also diabetics out there that are going to eat brownies
and drink beer and soda and hamburgers and not use their insulin. Should we, well, if their life is saved, that's it? Is that what we should say?

So let's just look at the nitty-gritty of it all. It's to save a life. And if we're going to have this many opiates out in the public, out in the market, we're going to need a lot of Narcan. And it should be very available, and you should be able to walk into any pharmacy and just get it.

Thank you.

(Applause.)

DR. LURIE: Thank you.

DR. BARTOSZEK: I just want to respond real fast about the education piece. I think that we found that this very key, and I think there needs to be a little bit of distinction made between the naloxone in the chronic pain clinic prescribed by a pain doctor, co-prescribed with their Oxycontin or Percocet, and the use in the community at IV drug clinics.

I think that there is a definite role for naloxone in our pain community, which what we see
at Fort Bragg and other pain clinics, what Dr. Dombrowski said from the ASA earlier. I think there's a role for that that is not really discussed, and I think that that needs to be brought up a little bit more because the problem is IV drug use, but it's also prescription medication misuse. I just want to make that distinction.

DR. LURIE: Yes. That's very helpful. Thank you.

Pam.

MS. LYNCH: Hi. My name is Pam Lynch, and I am an advocate in Michigan working in a drug treatment facility right now, and just a couple of points.

I went to residential treatment when I was 24 years old. Because of sexual abuse that went on in that facility, I was not successful after that experience and had other outpatient experiences after that in drug treatment.

There's good drug treatment, and there is bad drug treatment. So getting people to drug treatment isn't necessarily the answer to all of
it. I can say that drug treatment was a part of my toolkit that I use to be who I am today. I can say that harm reduction interventions have also been a part of my toolkit that allows me to be here today and to do the work that I do.

But I also want to point out that this is an occasion that I hope that the FDA and the federal government are recognizing it for what it is. It's very confusing to people.

Three years ago we did a film festival where we just -- we had a local behavioral health program who had a film that they made about a woman who was doctor shopping, and their movie and some of the other movies for overdose prevention were on the screen that night, Project Lazarus. And we had 272 people from the community walk through the doors of that theater that day, not because they knew who I was, not because they knew who this woman in Munson's film was, not because they knew who Project Lazarus from North Carolina was, but because they want answers. And they're confused.

It's confusing to people why Pam Lynch,
who's got no recognition in the community, is the one going to the jail to say, hey, you need to have one of these here. It's confusing to them why they can't go to the trusted, established public health and substance abuse coordinating agencies who are the recognized experts in this and get answers on how to help their children.

It's confusing, and people don't understand how come they've never heard of this. How come it's the small programs who have brought this to the table and not -- like Scott refers back to the times where it was established government entities who played this role.

And so I'm asking you to please recognize this opportunity for what it is. Things need to get -- something needs to happen here.

Thank you.

DR. LURIE: Please make sure to identify yourself for the transcriber.

MS. WHEELER: So with all due respect, Dr. Madras --

DR. LURIE: Wait. Name?
MS. WHEELER: Oh, hi. I'm Eliza Wheeler. And I just feel like possibly you feel like your statements have been misunderstood or misrepresented, but to us, you've come out publicly multiple times over many years in opposition in various forms to naloxone distribution. And maybe not explicitly so, but bringing up issues like encouraging drug use or being a barrier to drug treatment in some respect. And those concerns have been echoed here again.

And I understand that you are possibly the one dissenting voice here, and that might be uncomfortable. But at the same time, I feel like it's -- number one, it's insulting to the work we do to imply that we don't offer drug treatment when someone wants it. It's also insulting to folks who are using drugs in their process to say that the overdose or the potential death has to be the catalyst for them to get treatment. That often is not the case for people. They have multiple scary overdoses through their drug-using life, and those are not the things that necessarily push them
towards treatment.

And also, just in terms of sort of a little nit-picky thing about the data that you asked for several years ago, our programs are not funded. We have these small programs that run on shoestring budgets. Just in the last few years, there have been some state departments of health that have put money towards this.

We don't have standardized data collection tools. We have one staff member slinging Narcan out on the street to the people who need it. And it's regrettable that we didn't have all the data points available about how many folks that were reversed were then into treatment, but we don't have it.

DR. MADRAS: May I respond?

MS. WHEELER: Yes. We would love to answer those questions.

DR. MADRAS: Thank you.

First of all, I'd like to respond with a few things. Number one are the issues about whether or not this would encourage drug use, whether or not
it would lead to higher doses was a statement that was not my opinion. But it was a manuscript that was published from the San Francisco survey, the only one in existence at the time, that said a number of people claimed that if they had Narcan, they would probably use higher doses of heroin. Now, what the press did in that one interview was leave out the fact that I was quoting a manuscript and said it was my opinion.

So you have to realize that the press at times will misinterpret in order to make headlines, and in this case, they did.

SEAL reported the study, and that concerned me because when one engages in public policy -- which is this. This is a forum for public policy, a forum for change with regard to availability of Narcan for this purpose. It's going to be based on science, but policy is based on more than science.

When you discuss public policy, you discuss unintended consequences. And the only thing I had at that time was the SEAL article with regard to
unintended consequences. And I said, "In order for us to change public policy," and by that I meant instead of calling an EMT, having people with take-home Narcan. I said, "I am concerned that this report was published that stated these unintended consequences of increased use, increased doses, walking away from rescues." And that was not my view or my opinion or my feelings. That was a scientific survey done of -- but that was the only one that was available at the time. So that was number one.

Number two, with regard to bringing people into an emergency department as opposed to doing an at-home Narcan, what I found was another paper at the time -- I wasn't looking for negatives. I was simply looking for the literature. And there was a report on how many people who were brought in could be released after two hours of observation and how many others had to stay for four hours or 24 hours and longer because they needed extraordinary measures beyond the Narcan rescue.

And that paper, which was done with a large
population of Narcan rescue in the emergency department showed that, in fact, there were approximate -- and I don't know the -- I don't recall the numbers now, but there was a percentage of people who required overnight stays.

And my overall principle was to save lives, but that did not get through in the press because the press wanted to take a different interpretation of it. And I said, "If people are safer in an emergency department because 72 out of 400 are going to need observation, then those 72 lives will be better served."

That was the only data that was available at the time. Since then, there has been a lot more data published. It is still not perfect, but there are many people who engage in this research. These are not community-based studies. These are based in hospitals. They're conducted by physicians.

And I understand your vantage, but what you have to realize is that I was quoting the only literature that was available at the time. And in order to make policy -- my concern was to try my
very best to have an opinion that was in the best
interests of a person who could die. And I did not
want them to die.

        DR. LURIE: Okay. I think that's very
helpful, clarifying. Thanks.

        I think, Dr. Boyer, you had a response.

        DR. BOYER: Yes, and I'll be honest. I
don't know who said what or when or about what or
anything. But what I will tell you is that it is
possible to do research on a shoestring budget, and
it is possible to get the sort of data that I think
would persuade a lot of naysayers. And there a
bunch of folks who don't necessarily think that
this is a viable thing to do. It's possible to get
that data easily and cheaply with a staff of one.
I've done ethnographic studies with a staff of one,
which was me, and it was unfunded and it got
published.

        As far as like data, like standardized data
collection forms, that's just a sheet of paper with
questions asked the same way in identifying things.
So a little bit of forethought and a little bit of
attention to study design can lead to good, compelling results.

And candidly, there's a lot of responsibility being pointed at the policymaking authorities here, but for the rest of us here, I think there's a lot of responsibility on all of us to get good data to support a decision that we'd like somebody to undertake.

MR. BURRIS: And I think we all agree. If anybody says there's more data that's needed, nobody in this room is going to disagree. But if people are not doing it now, probably they could use some help. Although they might do it with a shoestring budget, they might do a better job and a more compelling job with a bigger budget. And they might do it much better with the expertise and leadership of agencies that specialize in doing this kind of research.

So no one's going to disagree with that. Let's get the data. I think the only thing people are saying here is innovate and evaluate. Let's do things to evaluate and not just wait until we have
some mythical, perfect picture of the data.

    DR. LURIE: Okay. Doug?

    DR. THROCKMORTON: Scott, and I want to follow up on what the comment you just made, and the comment -- I believe -- if I understood your original comments, you were suggesting that one area of additional research that was needed was the non-addict population and the efficacy of naloxone distribution in that setting.

    If I understand what you were suggesting, it was the data were very good as far as the addict population, that expanding access and availability for naloxone in that setting had a positive impact, but that you were less convinced by the available data with regard to opioid analgesics --

    DR. BOYER: Opioid analgesics.

    DR. THROCKMORTON: -- opioid prescription drugs.

    DR. BOYER: Yes. Some of the opioid analgesics, if it's an immediate release formulation, then naloxone should be good enough.

    But let's face it, there are a lot of non-immediate
release formulations that have -- I think there are long-acting opioid analgesic formulations out there, which people commonly abuse and often die from. And if you just get back to -- like in absence of data, if you just back to what we know, what's the pharmacology, what are the pharmacodynamics of the drugs, what's the pharmacology, what's the pharmacodynamics of the antidote, it's not compelling that a single dose would be enough, which gets back to the question of who calls 911 and who doesn't.

DR. THROCKMORTON: So you're saying it's not compelling based on pharmacology.

DR. BOYER: Correct.

DR. THROCKMORTON: Not based on Project Lazarus data that we've heard about earlier in the day?

DR. BOYER: Well --

DR. THROCKMORTON: I mean, are you characterizing those other data as --

DR. BOYER: I just --

DR. THROCKMORTON: -- two or --
DR. BOYER: -- you know -- you know, I've
had so many people who come in who say I took X and
actually took Y, and the only reason I know this is
because my fellows have just started sending off
comprehensive toxicology screens at UMass. And we
can analyze for just about anything that we truly
want to. And the validity of self-report is -- for
someone who's overdosed, engaged in a stigmatizing
behavior, and has sufficient incentive to distort
or outright lie, the validity of self-report is
just not that great.

DR. LURIE: Okay.

DR. DASGUPTA: Nab Dasgupta from the
University of North Carolina.

The question that you're raising, Dr. Boyer,
about -- you're talking about comparing the
molecular pharmacology to the molecular
pharmacology of that agonist and that antagonist,
right? But there's also the behavior pharmacology
that needs to be considered in there as well.

We know that in rats there's a strong place
dependent conditioning effect for opioids and for
pain relief, right? I mean, Siegel's work has been
doing this for decades.

We also know from the empirical evidence
that folks are more likely to overdose -- to go
into respiratory depression from an overdose in
environments that they're not familiar with, like
hotel rooms, SROs, right?

DR. BOYER: Yes. And I'm pretty comfortable
with the condition tolerance literature --

DR. DASGUPTA: Just a second, please.

So maybe drug -- so when we talk about the
data in EDs and how long people have to be left in
the ED, maybe it's because we don't usually spend
time in EDs. People who overdose don't spend time
in EDs, are not familiar with that environment, and
it -- it actually accentuates that overdose.

So possibly -- and I think this is a valid
hypothesis -- that maybe drug overdoses are better
treated in the community, not all of them but a
good portion of them probably will require less
medical intervention --

DR. BOYER: And that's a testable hypothesis
that, candidly, I think is reasonable to be tested. But to say that it's a hypothesis, ergo, it's true, I think is scientifically irresponsible. I mean, I just -- I love living in my own ignorance, which is a pretty vast place to be sometimes. But what is the extent to which conditioned tolerance in a clinical trial, in a fairly well controlled set of circumstances, how well does that translate to the real world? I mean, I think we're saying the same thing. It's a hypothesis. It's a testable hypothesis.

DR. DASGUPTA: And with the drug --

DR. LURIE: If you don't mind, let's take the next question because we're getting late in the day.

MS. BELL: Dr. Boyer, I was a little confused by what you're saying about Narcan, naloxone, not being demonstrated to be effective for opioids. I ask this because we do a lot of education about prescription opioid use, particularly in the jail where we have the opportunity to do longer trainings and talking
about different types of opioids and the importance
of knowing what you're talking and how long it
acts, and that some things are long-acting and some
things are short-acting, and getting people to
think about that information, and that
not -- whether it's somebody who's taking somebody
else's pain medication for pain, which people often
do -- we know that people often say my back is
acting up, and I'm going to take my husband's
Percocet from his surgery last month; it's
something people know they shouldn't do but often
happens -- or whether they're taking something to
get high, that people often don't know what they're
taking and that it's important to think about that
and that's a risk of overdose, that's something
that we do a lot of education on.

So is the issue that if it's something
long-acting, and someone is given naloxone for it,
that they might go back into an overdose? It's
effective immediately? But that if they're -- if
they don't take into consideration --

DR. BOYER: If I have somebody who winds
up -- and I understand about condition tolerance
and everything. But if they've overdosed on
methadone and wind up in my emergency
department -- and it doesn't have to be just
methadone; it can be long-acting oxycodone
formulations; it can be somebody who eats a
fentanyl patch; it can be the person who applies
multiple fentanyl patches -- we'll give them a dose
of naloxone or the paramedics will. They'll be
awake for a while, and then their respiratory rate
begins to drop off, so we give them more naloxone.
And they're awake for a while, and then they get
respiratory depression. And then they get more
naloxone. And that's the point at which we say
let's just make it easy on everybody. Let's just
start a naloxone drip.

I don't see how a single dose of intranasal
naloxone, in the field, without getting that person
to care, is going to save that person's life if
they have died multiple times in front of me that
I've just managed -- and I've reversed it because
we've given more naloxone.
MS. BELL: In our program, that's not what we promote. I mean, we talk about methadone being very long-acting and that if you give someone naloxone, you still need to get them to the emergency room. You need to stay with them. You might need to give them another dose. You need to get them to the emergency room.

So we're not -- I don't think any of the programs are just promoting give them a single dose of naloxone --

DR. BOYER: No, and I'm not suggesting that you're not. What I'd like to know is how many of those folks wind up in the emergency department after they've overdosed on, say, methadone.

DR. LURIE: Okay. There are three more people in line after you, and those will be the last three in the interest of finishing more or less on time. Try and keep it a focused question, if you don't mind.

MS. KIRSCHNER: My name is Jen Kirschner. My question will be for Professor Burris.

First, I do have a comment that we talk a
lot about opiate addiction is a brain disease within the individual. But I'd like to quote Dr. David Edelstein from NIDA at a talk he gave at Johns Hopkins the other week, "That addiction is also a social pathology and that treatment can only get us so far without changing the socioeconomic landscape."

Anyway, my question for Mr. Burris is, I feel like today we've heard about physicians and other qualified people like nurse practitioners who can prescribe naloxone to former or current drug users, or on the other hand, making it over-the-counter.

What would it look like if we want to do something like have these prescribers give it to third parties?

MR. BURRIS: Well, that's the rub. There's no question that any licensed prescriber can prescribe naloxone to a person for whom it is personally indicated. When you start giving drugs to someone to give to someone else, you're going very quickly into a fuzzy or even across-the-line
kind of zone because essentially what you're doing is deputizing them to be a medical provider.

Now, we don't care about that, as has been mentioned a couple of times. We talk about parents. We just actually sort of pretend that line isn't there. We don't apply it to parents. Parents can give to their kids, or I can give it to my aged mother or something like that. And, in fact, a lot of programs are operating in that kind of fuzzy zone now, and it may be that that'll work fine.

What this big fight here is really about is how we go from having -- well, I don't want to say pathetically -- a bravely small band of people who are taking this issue on to have a comprehensive solution, or at least a comprehensive intervention, that will reach most of the people who need it most of the time they need it. And I think for that, we won't be able to deal with the fuzzy lines. We're going to have to have clear rules.

One kind of clear rule is it's an over-the-counter drug. So you don't have to worry about
prescribing. Another kind of clear rule is where a state authorizes a broader range of people to prescribe to a broader range of other people, which states can do under their law.

You know, we're now 25 years into needle exchange, and we still have very poor coverage on the state level. We don't want to be in this same situation 25 years from now with a condition that is currently killing more people than car accidents. So we're going to need some big change fast.

DR. LURIE: Okay. Dr. Coffin?

DR. COFFIN: Phillip Coffin. I think we -- well, an epinephrine pen often times gives you a window of opportunity in anaphylaxis to get somebody to medical care. So the nice thing about naloxone is that it gives that window, whether it's medical care or a hypothetical intervention after an overdose, which I have never seen or heard about at this point, that might increase treatment uptake; although there are data that 20 percent of people -- at least in Baltimore from
Dr. Robin Pollini, that 20 percent of people who
overdosed enrolled in treatment within 30 days,
which is a pretty impressive number.

As an investigator, I've heard a lot of talk
about sort of our failure to provide adequate data,
and I would like to propose and ask -- I understand
there's been a great increase in funding for
overdose research in the last 10 to 15 years.

That increase is from, honestly, close to
zero to a handful, a small handful of studies. And
with 15 to 20,000 opioid overdose deaths a year, I
think this demands a greater national response.
And I wonder, especially with the reorganizations
at NIH and, of course, all of the horrible budget
shortfalls everywhere, how we can prioritize
overdose investigations and help the investigators
find some of the data that's being requested.

DR. COMPTON: I'd like to respond just a
little bit to that. First off, that wasn't really
a question. That was more of an encouragement to
people like me and the others from NIH to consider
this a high priority area.
You can certainly take our presence at this meeting and our sponsorship of this meeting as an indication that we think this is a very serious issue, and we look forward to applications from you and many other colleagues to help expand the research database.

I would also -- this is a little bit of comment and a little bit of question for the panel in terms of I certainly heard a major theme of the need for medical education and looking at how do we move from a grassroots-built set of initiatives around the country to something that's more integrated within the broadly defined medical system, whether that's the substance abuse treatment system, the methadone programs, general medicine, emergency departments that interact with, at a minimum, drug addicts.

But also, I'm hearing pain patients and those at risk for overdose because of high dosages of opiates, or opioids. And I think that I'm putting on the table the need for research on this, but also for practice developments in this area as
well.

DR. LURIE: Go ahead.

DR. BRASON: Addressing that in the medical community in North Carolina, we have done some research -- and obviously with what we've done just on our Wilkes County as Project Lazarus -- we are reaching the entire medical community now in North Carolina. We have created a toolkit for prescribers on prescribing opioids, patient education for addiction, how to manage the chronic pain patient.

We've created a toolkit for emergency departments so that they can understand the proper prescribing for that individual, how to monitor, how to use the PMP, all of those aspects. And the North Carolina Hospital Association, North Carolina College of Emergency Physicians, division of public health, medical society, medical board are all on board.

So we are doing a comprehensive medical education to all prescribers, whether it's MD, PA, nurse practitioner, and reaching every hospital,
every emergency department, and essentially, every practice in North Carolina over the next 18 months to just do what you were talking about so they have that education so there can be that intervention and prevention on the prescribing and on the dangers of overdose.

While at the same time, if in fact an overdose does occur, here's the naloxone so that you are aware that you've just been discharged from the hospital. You've had a brain injury from that car accident, and here's your pain medication. Don't take more medication just because you have more pain. Call me and let's find out what else is going on because we've essentially lost individuals in our community just because of that.

So that's sort of how we're addressing the medical community, not really going at it from a research perspective at this point. Just saying this is the epidemic that we're at today. We have to intervene now and not later.

DR. BARTOSZEK: And we're doing the exact thing at Fort Bragg, and we have -- to train all of
our hundreds of primary care providers. And we actually have a grant written and a protocol written to study it, to look at the outcomes of the education piece plus the naloxone, and all the other primary preventative measures that we do to decrease opioid risk.

    DR. LURIE: Okay. Then the final question from the audience.

    MS. SOTHERAN: Yes, Jo Sotheran from National Alliance of Methadone Advocates. This is a question primarily for Dr. Burris and Dr. Brason.

    Anybody who comes out of the world from methadone treatment knows two things. One is about regulation, because we have it up to the eyebrows. The other is about methadone is the most researched medication in the world, and we still have problems.

    The other thing was somebody pointed to the role of big government. And I'd like to ask about how you would maybe envision that because eventually methadone treatment did change, and we've seen the effects. It actually used to be
regulated by the FDA, in fact. Now it's regulated by another agency. And this happened in spite of very complex differences in state regulation.

So I'd like to kind of ask for some ideas about how the feds, particularly the FDA because they now control it, might develop a constructive relationship with the states going forward in this.

Thanks.

DR. BRASON: I can speak to it from methadone in specific opiate treatment programs that are under SAMHSA CSAT. And we heard from Nick Reuter this morning when he gave us the table of contents on the toolkit that SAMHSA will be -- we were hoping this afternoon. I guess that didn't happen, so sometime soon, the prescriber's toolkit for the opiate treatment programs.

In that table of contents was from SAMHSA the naloxone component with overdose education as part of that. So that's one answer that the government is providing regarding methadone. And, as I mentioned, the OTPs in North Carolina now have decided each one is going to now co-prescribe
naloxone to every new enrollee because,
unfortunately, last year, we did lose 20
individuals who were new enrollees into methadone
programs, and that needs to stop.

So we have the state division of health and
human services supporting that and encouraging that
as well as SAMHSA and the federal government
working directly to do that, as he said, the first
agency to perhaps do that.

MR. BURRIS: That was such a wonderful
softball. I know I'm going to lie awake tonight
thinking of all the things I missed to say. But
let's start with the surgeon general's summit on
drug overdose and what we should do about it.
Let's find somebody in the federal government who's
going to be the overdose czar who's going to take
responsibility for coordinating all the different
pieces of CDC and NIDA, HHS, SAMHSA, FDA, that have
to work together to figure out what we're going to
do with this problem. And we've got to figure out
from FDA if it's not an orphan drug -- so we can't
subsidize its development that way -- how are we
going to deal with the economic realities that Dr. Wermeling was talking about?

We could get Congress involved. Congress could pass a rider to the appropriations bill requiring that states who want to receive federal substance abuse funding have got to assure Congress within one year that they have developed legal mechanisms that assure that overdose reversal with naloxone is available to anybody in that state.

Medical education and training. The REMS is, I suppose, one model. As was pointed out today, we haven't even -- as Dr. Dasgupta pointed out, we haven't begun to think about incorporating the reversal element naloxone in training that way.

What about pain care? We're talking about the fact there are people using these drugs and maybe misusing them not because they want to have a really good time but because they are having a really bad time already and need pain care. What are we doing to make sure that we have more qualified pain care referrals to make when people need them? That seems to be a shortage profession,
and I think it's going to become a worse one. We face some risks.

As the state attorney generals and the DEA start to be confronted with this problem, they're going to use the tools they have. They're going to crack down on people, and we're going to be back to the days when we had fear among physicians of prescribing too many opioids. We have to worry again that we're going to go back to the days when cancer patients or people who just had broken legs, have been in a car crash, will come home with insufficient pain care.

So there are all those questions, which I think people are very aware of. I mean, Dr. Volkow's article, for example, was quite good on that.

But you can see the range of things. So in some sense, this meeting is about the need to pull those strings together and the need for leadership and -- just exactly what you were saying, Dr. Compton, sort of a more complex view. Research will be part of that, but action today will be part
of that.

And we really can't just have a piece. What we've got today is a world of pieces. And that is not going to stop this epidemic.

DR. LURIE: Let that be the last word.

(Applause.)

DR. LURIE: For our closing remarks, I'd like to introduce Sarah Wattenberg. She is the senior advisor for substance abuse policy in the Office of the Assistant Secretary for Health. She's also responsible for keeping Doug and Wilson and I in line and the behavioral health coordinating committee. And in that, I can assure you she's a failure.

Here she is.

Closing Remarks – Sarah Wattenberg

MS. WATTENBERG: Good afternoon, everyone.

I thought this was a great meeting today. And at times, it was hard. It was emotionally hard, I think, but I think it was good. And what I'm going to do is give that dry, boring and short closing to help bring down the heat, bring down the
heart rates, and really just review a little bit about what we've talked about today, and to just give my own personal impression, which is that we are all here today because we care deeply about this problem.

I think that that needs to be said. We all have different perspectives, but we're here because we want to figure out how to bring the perspectives together so that we can do something productive to address what we are seeing.

So I'm going to start by again reiterating thanks to FDA, NIDA, CDC and SAMHSA for joining together to make this meeting happen today. In particular, I want to thank Peter Lurie and Doug Throckmorton for their leadership, Mary Gross, Jan, Matt, wherever you all are, for coordinating logistics, making sure we had food, getting the PowerPoint presentations in and herding the cats. It's not easy to do that, and I think you did a great job.

One of the reasons why I want to sort of give yet thanks again to my federal partners is
because I want to underscore that this is not, in fact, an isolated event. For the past two years, through the Behavioral Health Coordinating Committee and the Prescription Drug Abuse Pharmaceutical Abuse Committee, these agencies actually have been coming together very regularly to talk about this problem, to see what we can do, do we have the right data, what we can do better, how can we improve. And this meeting today is partly a result of that.

So I want you to understand that you have our attention, all of you. And I also hear that you want us to do more, which is also okay.

So I want to thank all of our speakers, moderators, panelists and especially the public and the advocates in the advocacy organizations for coming today.

To the advocates, thank you for sharing your stories and your passion. I do feel that we have heard your sense of urgency today. And I don't think anyone will leave here today going untouched by your pain.
To the speakers, thank you for your excellent presentations and your reflections. You were articulate and thoughtful and at times brave in sharing your opinions. And I also heard you say that we needed to do more.

So to summarize today, we initiated a public discussion about whether to make naloxone more widely available outside the medical setting to reduce fatal overdoses. To appropriately contemplate that issue, we invited people to share all of the relevant scientific, regulatory, social, legal, ethical, and it seems like everything else information.

We heard about the use of naloxone in a variety of settings with different high-risk populations, different models of interventions, along with some of the potential risks and benefits associated with the interventions.

The FDA then provided some clear regulatory pathways, though perhaps burdensome, for expanding the use of naloxone should that be pursued.

Information was presented about new
formulation development, the over-the-counter process, the ethical issues related to studying naloxone in patients who cannot provide informed consent, issues related to the business case, and some of the cost and reimbursement issues.

Once the regulatory roadmap became clearer for how the broader use of naloxone could happen, our last panel opined on whether or not it should happen.

I am not going to recount the discussion for all the obvious reasons, but also because they just had it. But I will remark that it stimulated a range of opinions and passion about this topic. And I personally believe that the back and forth and the exchange was one that needed to be had. It's why we are here today. This is what we wanted. This is what we need to think about as we move forward.

So I am going to close the meeting today by just reminding everybody that the goal was not to answer the questions but rather to raise the issues, explore the risks and benefits, and better
understand potential pathways for moving forward.

And I think we did that.

Thank you for coming today.

(Applause.)

(Whereupon, at 5:30 p.m., the meeting was concluded.)