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6
7 Role of Naloxone in Opioid Overdose
8 Fatality Prevention
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P R O C E E D I N G S

(8:37 a.m.)

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,

1 about 20 percent, in the last decade or so. Opioid
2 analgesic deaths have risen along with this.

3 Prescription drug overdose deaths have increased
4 about threefold since 1999. And ever since 2003,
5 the number of overdose deaths from opioid
6 analgesics have actually exceeded the number of
7 such deaths from cocaine and heroin combined, a
8 fact that I think a lot of people in the public
9 don't fully appreciate. So we're really dealing
10 with a huge problem here, and the question is: what
11 can be done about it?

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

18 As I think everybody in this room knows, and
19 you will hear I'm sure in greater detail, naloxone
20 is an opioid receptor antagonist, which is
21 currently approved for use by injection only for
22 the reversal of opioid depression, for the

1 diagnosis of opioid overdose, and for adjunct use
2 in the treatment of septic shock.

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

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

17 To put this in context, I just want to point
18 to a couple of things. One is on the international
19 level. I want to point to the UN Commission on
20 Narcotic Drugs, which in 2012 released the
21 following statement: the Commission "encourages all
22 member states to include effective elements for the

1 prevention and treatment of drug overdose, in
2 particular opioid overdose, in national drug
3 policies where appropriate, and to share best
4 practices and information on the prevention and
5 treatment of drug overdose, in particular opioid
6 overdose, including the use of opioid receptor
7 antagonists such as naloxone," one of the longest
8 sentences I think I've ever had to read.

9 (Laughter.)

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

15 The drug czar's office has its own
16 prescription drug abuse plan, and that prescription
17 drug abuse plan says -- and I'm quoting
18 again -- that we should, "hold a public workshop to
19 discuss medical and social issues related to
20 naloxone use by nonmedical personnel," here we are,
21 "and provide guidance to researchers, community
22 groups, and the pharmaceutical industry on

1 potential routes to marketing approval for novel
2 naloxone formulations." So in a lot of ways, this
3 meeting is putting into effect something in the
4 ONDCP plan.

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

10 "On behalf of the White House Office of
11 National Drug Control Policy, I would like to
12 welcome you to this important public workshop. In
13 2010, the Obama administration's first drug
14 strategy was released. This strategy, as well as
15 subsequent strategies, recognizes the important
16 role naloxone can play in overcoming drug
17 overdoses.

18 "With more people dying from unintentional
19 drug overdoses than car accidents, it is vitally
20 important that we do what is necessary to prevent
21 drug abuse while also preventing drug overdoses and
22 getting people the treatment they need.

1 "Thank you for taking time to discuss this
2 issue, and I look forward to continuing this
3 important conversation."

4 So that's from Director Kerlikowske.

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

11 We have a morning and an afternoon. The
12 morning is really a scene setting kind of exercise.
13 We'll discuss who's at risk for opioid overdose,
14 what the epidemiology of overdose is. We'll
15 describe attempts by public health groups to
16 address overdoses in general. And then we'll talk
17 about naloxone and its particular characteristics
18 and how they affect the material that comes up
19 really in the afternoon session. And we'll have a
20 series of presentations that describe the
21 experience of different groups using naloxone in
22 nonmedical settings.

1 In the afternoon, we'll get to what, in a
2 way, is the meat and potatoes of the meeting.
3 We're going to talk about regulatory issues, what
4 it would take to get an intranasal form of naloxone
5 approved, what it would take to get a product
6 switched from prescription to over-the-counter
7 status. We'll have an industry perspective on why
8 they might or might not want to enter the market,
9 and we'll discuss the ethical issues that are
10 involved in the studying of these products.

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

18 After that, we'll have a final session on
19 social and legal concerns, which will begin with
20 lessons from other public health interventions,
21 where the question of behavioral disinhibition, if
22 you will, has been raised. And we'll hear about

1 the experience with the HPV vaccine, Gardasil. And
2 then we'll have a panel discussion, which we look
3 forward to being lively, in which all of these
4 issues will be battled back and forth for all of our
5 edification.

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

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

20 (Laughter.)

21 DR. LURIE: We do have ample breaks built
22 in. Kiosks will be set up outside the meeting room

1 where refreshments will be sold during breaks and
2 at lunch. There will be salads, sandwiches, other
3 refreshments when we break for lunch. The
4 bathrooms are out this door and to the right.

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

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

22 So in conclusion, I just want to say that

1 this effort today is part of many things that the
2 U.S. Government is doing about prescription drug
3 abuse and about overdoses in particular. And this
4 meeting will allow a discussion of various
5 potential uses of naloxone.

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

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

21 Okay. That concludes my opening remarks.

22 Doug, you're next.

Panel 1 - Moderator Bob Rappaport

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

1 public health strategies that have been employed to
2 address this problem.

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

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

17 We're on a very tight schedule today, as
18 Dr. Lurie said, with a packed agenda. So each of
19 the moderators, including myself, will be
20 attempting to keep the speakers to their allotted
21 times, and the question-and-answer session will be
22 limited to 10 minutes. So I apologize if I have to

1 cut you off. We'll try to find time for questions,
2 if possible, that weren't fitting into the allotted
3 times.

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

6 **Presentation - Len Paulozzi**

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

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

21 As was already mentioned, for a number of
22 years now, deaths involving opioid analgesics have

1 outnumbered deaths involving either heroin or
2 cocaine in the United States.

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

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

21 Moving on to risk factors, men are the
22 largest risk group for opioid overdose in the

1 United States, whether, it's the analgesics or
2 heroin. The analgesic bar is the center bar shown
3 in orange. Heroin is in yellow. The male rate is
4 twice that of the female, roughly, for the opioids
5 and about four times greater among men for heroin.

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

16 Rates really start to jump up in the 15 to
17 19 age group, particularly at age 18 is when kids
18 leave the home, go off to college, and we see the
19 largest increase when you look at it by single
20 years of age. There's something of a bulge growing
21 now in the people in their 20s, and after age 60,
22 rates drop off dramatically. When you get into

1 ages 65 plus, whether it's -- including suicides,
2 the rates are relatively low compared to people in
3 their 40s.

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

13 I show this slide really just to contrast it
14 with the overdose curve by age group. These are
15 opioid prescriptions per person by age group in the
16 U.S. in 2009 -- this is data that was published in
17 JAMA from Dr. Volkow of NIDA -- and really looked
18 at this way, people over age 60 get more
19 prescriptions per person than people in middle age.
20 So it's in contrast to, the peak in middle age,
21 it's really not a similar pattern in terms of usage
22 measured this way.

1 Rounding out the demographic variables, this
2 is race, ethnicity data from 2008 in the United
3 States, again, cocaine, opioid analgesics, and
4 heroin. For the opioid analgesics, the highest
5 rates are in non-Hispanic whites closely followed
6 by American Indians and Alaska natives. Hispanic
7 whites, blacks, Asian Pacific Islanders are much
8 lower. For heroin shown in yellow, the non-
9 Hispanic whites still have the highest rates with
10 Hispanic and blacks being slightly lower; American
11 Indians also having rates comparable to Hispanics
12 and blacks.

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

20 So if you look at these 16 states and you
21 restrict it just to U.S. whites, which that
22 restriction is because of the confounding between

1 race and urban residence, you can see that the
2 highest rates for drug overdose deaths are in
3 non-core, non-metro, the most rural counties over
4 the right side of the figure, for opioid
5 analgesics. It's not a stair step phenomenon, but,
6 in general, the non-metropolitan counties have
7 higher rates for opioid analgesics. In contrast,
8 the heroin rates are significantly higher in large,
9 central, metro counties and get progressively lower
10 as you proceed to non-metropolitan counties.

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

21 These are drug overdose deaths. See, these
22 are all drugs, but the bulk of them are going to be

1 related to either heroin or opioid analgesics. And
2 this is maybe related to the rural nature of the
3 states, maybe related to income factors. It's
4 unclear as to why we have these geographic
5 patterns.

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

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

1 a history of a previous overdose.

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

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

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

20 In West Virginia, actually, we were able to
21 compare the people who died or look at the rates by
22 residence in counties based on their poverty level

1 to basically look to see whether counties that had
2 higher percentages under the poverty level had
3 higher rates. And residents in counties with 22 to
4 39 percent of the population living in poverty,
5 which was the highest poverty level, had a
6 relatively high risk of 2.1 compared to residents
7 in a West Virginia county with the lowest level of
8 poverty, 9 to 16 percent.

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

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

20 A study of group health by Dunn in 2010
21 showed a substance abuse diagnosis in patients on
22 chronic opioid therapy had 2.6 relative risk.

1 These are developed by just combining the rates in
2 the study. They did not do the statistical
3 testing.

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

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

14 Finishing up these other personal
15 characteristics, lack of a prescription for the
16 involved drugs among overdose deaths has been a
17 common feature of a number of state studies. In
18 West Virginia, 63 percent did not have a
19 prescription in the state prescription drug
20 monitoring program for one or more of the
21 pharmaceuticals involved in their deaths. In Ohio,
22 25 percent did not have a prescription in the

1 previous three years in the state prescription
2 monitoring program. In Utah, unintentional opioid
3 deaths, 37 percent, again based on the state
4 prescription monitoring program.

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

11 And lastly, prescription history, there have
12 been a few studies in recent years looking at
13 prescription history of individuals oftentimes
14 using state prescription monitoring program data.
15 Again, the Ohio study found that one out of six
16 people who died of a prescription overdose had
17 filled prescriptions from an average of five
18 prescribers per year over the previous three years.
19 In the study we did in West Virginia, it was
20 similar, about 21 percent had filled prescriptions
21 from five or more prescribers in the preceding
22 year.

1 In a study we did more recently in the state
2 of New Mexico, these are crude odds ratios, just to
3 show that as the mean number of prescribers goes
4 up -- and multiple prescribers is what people often
5 use as the definition of, "doctor shopping." there
6 was a fairly steady increase in risk. And when you
7 get into people with 10, 15 or 20 or 30, you're
8 approaching 10 times the odds ratio or 10 times the
9 risk of dying of a drug overdose.

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

18 As a last measure, in a growing number of
19 studies about dosage, daily dosage usually
20 converted to morphine equivalence as a daily
21 dosage, measured in different ways and different
22 cut points. The first study probably was the study

1 by Dunn looking at people with chronic pain in the
2 Group Health Cooperative. They looked at people
3 with more than 100, a 100 or more morphine
4 milligram equivalence per day daily dosage,
5 compared them to people with no recent use of
6 opioids and found a relative risk of 8.8.

7 Braden looked at people with a dose of over
8 120 compared to people below the median dose, found
9 a small increase in risk, although it was
10 statistically significant of 1.08.

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

17 Another figure from the New Mexico study
18 again showing a steady increase with risk as you
19 increase in dosage. Although when you get up to
20 the very high dosage levels, there seem to be an
21 attenuation or a flattening of risk. It may be
22 that dosages over 500 milligrams per day of

1 morphine equivalent, people are not actually taking
2 all the drugs themselves. And they may be
3 distributing them to others. And perhaps that
4 explains why their risk is not going up at levels
5 of 1,000 or 2,000 morphine milligram equivalence
6 per day.

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

18 Personal characteristics included substance
19 abuse, history thereof; other mental health
20 diagnoses; nonmedical use of the prescription,
21 which might include nonmedical routes or use
22 without a prescription; and route of

1 administration. Prescription history risks are
2 multiple prescriptions, multiple prescribers and
3 high daily dosage.

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

12 Thank you.

13 (Applause.)

14 DR. RAPPAPORT: Thank you, Len.

15 Anybody interested in this field is familiar
16 with Len's work, but you may not be familiar with
17 his background. And since I neglected to give a
18 little bit of it before I introduced him, let me
19 just tell you. Len is a medical epidemiologist in
20 the Division of Unintentional Injury Prevention of
21 the National Center for Injury Prevention and
22 Control. And his area of concentration, as we all

1 know, is drug overdoses, especially those due to
2 prescription drugs.

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

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

16 Okay. Our next speaker is Nick Reuter.
17 Nick is a senior public health advisor in the
18 Center for Substance Abuse Services, the Division
19 of Pharmacological Therapy at SAMHSA. He is a
20 graduate of the University of Maryland and the
21 Johns Hopkins University School of Public Health.

22 Previously, Mr. Reuter served as a consumer

1 safety officer here at the FDA in the Office of
2 Health Affairs. And in these positions, he's been
3 responsible for coordinating and developing agency
4 positions in many areas, including those related to
5 drug abuse and drug control, as well as the
6 oversight of narcotic treatment programs.

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

13 **Presentation - Nicholas Reuter**

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

22 It fits nicely with SAMHSA's missions and

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

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

18 So I'm just going to paint a broad picture.
19 You'll hear later today some of the more specific
20 information about the various toolkits that are out
21 there and intervention techniques in more detail; a
22 little bit about naloxone distribution.

1 Since I work for the Center for Substance
2 Abuse Treatment within SAMHSA, I'm going to talk a
3 little bit about how treatment can fit into this
4 opioid overdose reduction initiative.

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

12 Around 1,000 deaths were reported between
13 2005 and 2007. Although it wasn't national in
14 nature, it was evident in 13 states. This epidemic
15 peaked in 2006 with the maximum number of cases of
16 150 cases, and it declined down in 2007. Most of
17 the issue was fentanyl sold on the street that was
18 being offered as either heroin or cocaine, and just
19 about all of it was being injected.

20 There was a clearly public health response
21 to this epidemic, and it was coupled with a law
22 enforcement reduction initiative as well. The

1 public health part of it included epidemiological
2 task forces that were formed in different states
3 and regions. And what these groups did was develop
4 alerts to providers, alerts to law enforcement
5 people. Information was provided to drug users.
6 And there was an intensified outreach to drug users
7 as part of this initiative.

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

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

19 The response also included a law enforcement
20 sort of supply reduction component where
21 non-pharmaceutical fentanyl was seized and
22 destroyed. Fentanyl clandestine labs were

1 identified by law enforcement and disrupted. DEA
2 published an immediate rule that controlled one of
3 the precursors used to make this illicit
4 non-pharmaceutical fentanyl.

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

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

22 There are some recommendations from that

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

12 It was mentioned earlier -- Dr. Paulozzi
13 talked about a recent MMWR article that chronicled
14 the naloxone distribution programs throughout the
15 U.S. And as of October 2010, there were 188 such
16 programs identified. And between 1996 and 2010,
17 these programs in 15 states provided naloxone to
18 53,000 people, resulting in over 10,000 drug
19 overdose reversals using naloxone.

20 The article also pointed out that many
21 states with high drug overdose rates do not have
22 overdose prevention programs that distribute

1 naloxone. And Dr. Paulozzi's slide showed this
2 very nicely. One of the highest rates of opioid
3 overdose in the U.S. is in the state of West
4 Virginia. And I didn't see a dot in there for a
5 naloxone distribution program in that state.

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

13 Just to summarize it, since 2003, they've
14 had a program to train and distribute naloxone.
15 And it's interesting the entities where they
16 distribute the naloxone: in needle exchange
17 programs, reentry programs for law enforcement,
18 which is a very interesting place to distribute
19 naloxone, when inmates are released and reducing
20 the risk of overdose, which is a little bit higher
21 than the general population. Some materials are
22 distributed at pain management clinics. I think

1 that's consistent with a lot of the overdose
2 prevention programs you'll hear about. Similarly,
3 methadone maintenance programs are a source of
4 distributing these overdose prevention materials.

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

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

21 In San Francisco, almost 2,000 providers
22 were trained and prescribed naloxone as part of

1 their prevention initiative. Eleven percent of the
2 participants used naloxone during an overdose
3 event, and 83 percent of those overdose responses
4 reported that naloxone successfully reversed the
5 overdose in those cases. So the message there is
6 that if you can conduct these trainings, naloxone
7 can be distributed, it can be used. It can reverse
8 opioid overdoses.

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

21 Also, in San Francisco, they did make an
22 attempt to look at, in addition to outcome, some of

1 the adverse events that were encountered with the
2 naloxone distribution. Serious adverse events were
3 rare, but there were in the publications some
4 reports of seizures, something we'll talk about a
5 little bit later.

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

12 I wanted to talk a little bit about
13 prescription opioid pain relievers. We heard the
14 statistics. The three classes with the highest
15 rates tripled from 1999 to 2006. I just wanted to
16 talk about methadone and single out methadone for
17 just a second, because methadone deaths rose more
18 rapidly than any other opioid analgesic between
19 1999 and 2006. But as Dr. Paulozzi reported, they
20 actually started to decrease and taper down or
21 trend down in 2008 and 2009. And this leads me to
22 just discuss some of the federal interventions that

1 went into place to address specific kinds of opioid
2 overdose issues.

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

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

17 So in the second bullet, that leads us to
18 physician continuing medical education. This is
19 something SAMHSA has supported for four or five
20 years now. We go into states and provide CME
21 education to physicians on appropriate prescribing
22 practices for opioids for pain relief, spend a lot

1 of time talking about methadone because of the
2 higher risks associated with methadone for pain
3 treatment. We also have a prescription drug
4 monitoring expansion initiative using the NASPER
5 program and the Harold Rogers grant program, all
6 components of the ONDCP strategy.

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

17 Something that affected, I think, the way
18 methadone is distributed for pain in this country
19 is DEA's successful effort to get the 40-milligram
20 methadone diskettes, which are labeled just for
21 addiction treatment but which were being
22 distributed extensively in pharmacies to be filled

1 by prescriptions for pain treatment -- actually not
2 distributed through pharmacies to be used in pain
3 treatment and dispensed by pharmacies in
4 prescription.

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

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

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

22 A couple years ago, we convened a group of

1 state officials, and the idea was to look at the
2 states that had the highest rates of opioid
3 overdoses and bring in states that had lower rates
4 of opioid overdoses, and try to find out on a state
5 level what may be the differences and why some
6 states have higher rates of overdose and some
7 states have lower rates of opioid overdose.

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

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

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

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

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

21 We also believe that OTPs have experiences
22 with opioid overdoses. If not directly in the

1 program itself, the patients know about them. The
2 patients have friends not in treatment, and they
3 have people in the community that they interact
4 with who are at risk for opioid overdoses. So
5 taken together, we thought that was the best
6 approach for getting an educational toolkit
7 available.

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

15 It talks about rescue breathing. This is
16 consistent with many of the other toolkits that are
17 out there, a big section on understanding how
18 naloxone works and how to administer naloxone. The
19 toolkit, as we're developing and issuing, is not
20 going to provide naloxone. Instead, it's going to
21 provide resources and information where people can
22 get naloxone.

1 We expect to have that toolkit released
2 maybe this afternoon for public review and comment,
3 maybe tomorrow, but soon. And we'd like to invite
4 the people in the group to take a look at it and
5 provide more input and comment. A few of the
6 people here in the front row helped us work on that
7 toolkit, and I think it's a very, very fine
8 product.

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

16 When we met with the states, they thought
17 this was a substantial shortcoming, that treatment
18 interventions' availability should be included in
19 these overdose reduction interventions. In the
20 U.S., we have methadone maintenance programs that
21 use the full opioid agonist, methadone. It is safe
22 and effective in both reducing withdrawal symptoms.

1 It's effective in blocking opioids' effects as
2 well.

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

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

15 The partial agonist buprenorphine is
16 available in office-based treatment settings. It's
17 been available since 2006. Currently, there are
18 22,000 physicians authorized in the U.S. to begin
19 this treatment. Those physicians are in emergency
20 departments. They're in public health treatment
21 programs. They are in every state of the country.
22 So that treatment capacity exists.

1 In 2010, 800,000 people received
2 buprenorphine prescriptions for addiction treatment
3 from physicians who had that authorization in all
4 those different settings. I would estimate that
5 there is around 500,000 people currently receiving
6 buprenorphine treatment through the office-based
7 physician program. There's a mono formulation of
8 buprenorphine, and there's a combination
9 formulation that contains naloxone, naloxone in
10 place to reduce the risk of intravenous abuse of
11 that formulation.

12 Finally, the treatment medication Vivitrol
13 in 2010 had its label modified to reflect its use
14 in preventing opioid relapse. It includes the
15 narcotic antagonist naltrexone in sustained release
16 30-day formulation.

17 So to sum things up, from our perspective at
18 SAMHSA, we clearly think that overdose risk
19 reduction programs have increased over the last
20 several decades. And they're in place, and they
21 have demonstrated substantial effectiveness in
22 reversing opioid overdoses. We think the public

1 health prevention approach has resulted in
2 thousands of overdose rescues.

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

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

17 I think from our panel, it was a little bit
18 mixed, that the naloxone was in place. It was a
19 successful rescue intervention. But what happened
20 next? Were there further -- was there more
21 intervention to reduce that risk further? And I'd
22 like to see those two things tied together.

1 Finally, I think we need to discuss today a
2 little bit more about future research needs: How
3 can this be safely and effectively be used? What
4 about the adverse effects associated with the use
5 of these products? Is that something that needs to
6 be the subject of future research so we can have an
7 informed decision about the way the naloxone
8 distribution programs advance from this day
9 forward?

10 Thank you.

11 (Applause.)

12 DR. RAPPAPORT: Thank you, Nick.

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

20 Dr. Terman received a Ph.D. in behavioral
21 neuroscience from UCLA and studied mechanisms of
22 endogenous pain inhibitory systems, including

1 interactions with tolerance to endogenous and
2 exogenous opioids.

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

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

14 **Presentation - Gregory Terman**

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

20 (Laughter.)

21 DR. TERMAN: I was asked to give a slide on
22 conflicts of interest that I have. And you should

1 know right up front that I have no known financial
2 interest in the drug naloxone nor companies that
3 make naloxone, nor companies that produce devices
4 to administer it. On the other hand, I've spent
5 more than 30 years performing behavioral
6 pharmacology research on opiates, and many of those
7 studies would not have been possible without
8 naloxone.

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

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

19 So I'm going to talk about the nuts and
20 bolts of naloxone. I'm going to divide it up into
21 three areas: specificity, toxicology and problems
22 with naloxone, which I will argue are largely an

1 unmasking of ongoing disease processes in the
2 patients that are receiving it or people who are
3 receiving it.

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

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

18 Whether or not people understood the
19 importance of that finding at the time is a little
20 before I can comment. But the latest version of
21 the book, pharmacology book, Goodman & Gilman,
22 talks about naloxone as a pure opioid antagonist,

1 talks about that you can get effects in giving it
2 IV, IM, subcutaneously, through an endotracheal
3 tube, so into the lung, and also intranasally.

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

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

17 In another related area of medical
18 investigation, when I was looking around to try and
19 decide about graduate school in the mid to late
20 '70s, I was enthralled by this Hughes and
21 Kosterlitz identification of two peptides in the
22 brain that had opioid agonist activity. These were

1 later called endorphins. But Leslie Iversen, in a
2 commentary that accompanied the publication of
3 these endorphins, said that a crucial item of
4 evidence was that the effects of morphine and of
5 the morphine-like compound in brain extracts could
6 be blocked by low concentrations of specific
7 morphine antagonists such as naloxone.

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

13 So if this drug is specific, what about its
14 toxicology? Well, so in rats, I didn't look too
15 far, but what I did see was a similar reversal of,
16 in this case, opiate-mediated stress analgesia with
17 100-fold change in the dose with no apparent
18 toxicities.

19 In people, the drug is packaged
20 .4 milligrams per milliliter, and the indicated
21 dose is .4 to .8 milligrams IV. In our hospital,
22 we use about 10 times less than that because in

1 post-op pain patients, it decreases the amount of
2 time when they don't have any pain relief. But if
3 you use 700 times as much as the indicated dose,
4 you will not see any adverse effects in
5 opiate-naive subjects who are not having pain.

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

10 (Laughter.)

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

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

20 So one of the things that's mostly likely to
21 happen -- and we've talked about it before -- is
22 acute withdrawal. If you unmask dependence with

1 naloxone, you will get withdrawal symptoms. Now,
2 it's important to realize that unlike, say,
3 benzodiazepine withdrawal, opiate withdrawal is not
4 a medical emergency. In fact, Farrell describes
5 withdrawal as moderate to severe flu-like illness,
6 subjectively severe but objectively mild.

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

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

19 Now, the concern in cardiovascular effects
20 probably again have to do with withdrawal,
21 catecholamine release, which actually probably
22 causes a number of the symptoms that we looked at

1 with withdrawal, including sweating and other
2 things. But tachycardia or other arrhythmias is
3 the concerning one. And this could synergize with
4 other drugs in the system, for example, cocaine
5 with cardiovascular sequelae, or even people with
6 preexisting cardiac disease may not be able to
7 tolerate a tachycardia and may develop myocardial
8 ischemia as a result.

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

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

21 In fact, it's also been reported that
22 naloxone has anti-arrhythmogenic effects. That has

1 been suggested as something that should be given
2 for arrhythmias in the emergency room, although I'm
3 not sure the level of evidence there is at the
4 moment for that.

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

12 In fact, naloxone-induced pulmonary edema
13 has been reported widely, and particularly in the
14 anesthesia literature. Review of the literature
15 probably suggests that the pulmonary edema is due
16 to negative pressure caused by acute airway
17 obstruction increasing the intrapulmonary pressures
18 and essentially sucking liquid into the alveoli and
19 causing pulmonary edema through that way. And
20 certainly, negative pressure pulmonary edema occurs
21 independent of whether opiates -- certainly
22 naloxone or even opiates are involved.

1 So I would suggest that most pulmonary edema
2 episodes are not so much the result of hypertension
3 but, in fact, are due to airway obstruction, again
4 a likely cause for giving the naloxone in the first
5 place.

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

13 The seizure concerns are around the
14 theoretical idea that naloxone may lower seizure
15 thresholds for patients with prior seizure
16 disorders or immediately after their seizures when
17 they're in the postictal period. And, in fact, in
18 the room next to me during my graduate school days
19 at UCLA, while I was working on the implications of
20 endorphins for pain, Hanan Frenk and others
21 were -- Yehuda Shavit -- were looking at the
22 effects of endorphins in modulating seizure

1 activity and finding that with seizures, endorphins
2 were released that kind of put a lid on the
3 excitability of the system to try and decrease
4 further seizures.

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

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

19 Finally, there's been some concern that
20 renarcotization might take place. The naloxone is
21 an hour half-life drug, as I mentioned. That's
22 shorter than most opiates, and including heroin,

1 where two to three hours tends to be the half-life.
2 The concern is if you give the naloxone and
3 patients are doing fine, will they run into
4 problems later when people aren't noticing because
5 the naloxone goes away.

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

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

22 So, in summary, naloxone -- despite having

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

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

21 (Laughter.)

22 DR. TERMAN: Now, realizing a picture is

1 worth a thousand words, I thought I would give you
2 a picture about naloxone. Here, we're giving nasal
3 naloxone to a rat who has, after animal care
4 approval, gotten an overdose of morphine
5 subcutaneously. And it's important for you to know
6 that you shouldn't really do this at home -

7 (Laughter.)

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

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

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

1 here.

2 (Laughter.)

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

6 (Applause.)

7 **Questions and Answers**

8 DR. RAPPAPORT: Thank you.

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

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

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

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

1 to focus efforts on?

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

8 DR. RAPPAPORT: Any other questions from the
9 panel?

10 Okay. At the microphones?

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

16 In the case of HIV among injection drug
17 users, ethnographic studies were able to identify
18 key points for intervention. And I don't think we
19 understand fully what's going on in prescription
20 opioid users and people who overdose, and how we
21 can best reach them, and how to intervene. And I
22 think ethnographic research would be very valuable.

1 DR. RAPPAPORT: Any comments on that?

2 (No response.)

3 DR. RAPPAPORT: Thank you.

4 Yes, sir?

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

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

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

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

21 DR. TERMAN: So all I can talk about is from
22 my own experience, where I've given naloxone

1 subcutaneous, now intranasally, IV. The answer is
2 that it all works pretty quick.

3 If you look at the Goodman and Gilman slide
4 about IV, it still takes a minute or two to start
5 working or to finish working, and so these are
6 pretty quick effects. And I'm not sure it would be
7 easy to get that data, whether over 30 seconds
8 versus over two minutes, wouldn't make much of a
9 difference in terms -- either way, I've seen these
10 effects regardless of whether it was over
11 30 seconds or over two minutes.

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

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

20 DR. WERMELING: Is it useful?

21 DR. TERMAN: -- and the answer is no,
22 definitely not. You don't have to. But there is

1 some evidence -- I think, or at least
2 anecdote -- that if you ventilate the patient, you
3 will decrease the number of seizures and
4 particularly arrhythmias. And that's likely -- I
5 mean, that makes a lot of sense if you think of
6 you're trying to reverse other causes that may add
7 together to cause a naloxone-associated adverse
8 event.

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

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

21 MS. WHEELER: Hi, my name is Eliza
22 Wheeler --

1 DR. TERMAN: Let me -- so get back to me at
2 the end of the day, okay?

3 (Laughter.)

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

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

19 DR. RAPPAPORT: Yes?

20 MS. WHEELER: Just a question for
21 Dr. Terman. So considering the potential risk of
22 unmasking these disease concerns that you talked

1 about after administering naloxone, would you ever
2 recommend not administering naloxone because of the
3 potential risk of those problems?

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

6 MS. Wheeler: Thank you.

7 DR. Terman: These are not risks that would
8 keep me from saving this patient.

9 MS. Wheeler: Thank you.

10 DR. Sommerville: Hi, Ken Sommerville from
11 Pfizer.

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

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

17 DR. Sommerville: No, the highest.

18 DR. Terman: In terms of the highest dose.
19 So as I showed, the toxicology is pretty forgiving.
20 There are reports of 700 times the recommended dose
21 with no adverse effects. So I would say
22 that -- you don't need to give that, though, and

1 that's why we give ten times less in the hospital
2 setting. But in that setting, we have people
3 around who are starting to control the airway, who
4 are able to inject another dose if that's
5 necessary. But the ceiling that you can give is
6 much higher than any need to give, as far as I can
7 tell, much higher.

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

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

15 DR. SOMMERVILLE: Right. Thanks.

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

22 DR. TERMAN: The population level. So it's

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

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

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

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

22 So the question is, what happens if they

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

11 DR. BELETSKY: Thank you.

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

16 (Whereupon, a recess was taken.)

17 **Panel 2 - Moderator Wilson Compton**

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

21 It's a pleasure to be with you this morning.
22 I am Wilson Compton. I'm with the National

1 Institute on Drug Abuse. And before I introduce
2 our panel, I want to take a moment to say a few
3 words on behalf of NIDA.

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

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

17 Dr. Lurie and Dr. Nora Volkow of NIDA are
18 co-chairs of a committee that's a subcommittee
19 looking at the issue of prescription drug abuse and
20 coordinating efforts across the department. And
21 this meeting in some ways is a reflection of that
22 collaboration and certainly reflects the

1 coordination that that subcommittee has provided to
2 all of our efforts.

3 Prescription drug abuse is a major theme and
4 topic for NIDA. We've been addressing these issues
5 through multiple mechanisms over the past at least
6 10 years since I've been at NIDA. And under
7 Dr. Volkow's leadership, we've had a particular
8 emphasis on this topic.

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

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

21 I would highlight for you some of our work
22 to change the way we educate physicians and other

1 healthcare providers in the United States to
2 provide a more balanced and nuanced approach to
3 treating pain. We think this may be one of the
4 ways to reduce the tremendous reliance, and in some
5 ways over-reliance, on narcotics as the approach to
6 treating pain, and in some ways we hope address
7 this epidemic of opioid overdoses by reducing the
8 pipeline of availability of prescription opioids.

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

18 In addition to that, we have two funded
19 randomized clinical trials that are looking at use
20 of naloxone for overdose prevention. You'll be
21 hearing in just a few minutes from Dr. El-Bassel
22 who has a randomized trial in an international

1 setting. And I'd also highlight Dr. Jody Rich's
2 study of prisoners who are being released in Rhode
3 Island, to look at the potential use of naloxone to
4 prevent overdose in that extremely high-risk
5 population.

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

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

1 populations we serve.

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

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

16 Dr. Binswanger.

17 **Presentation - Ingrid Binswanger**

18 DR. BINSWANGER: Hi. So I'll be talking
19 today. I have really three main goals. I want to
20 give an overview of naloxone for bystander use that
21 will help set up some of the other presentations
22 that come right after this one. And then I'll talk

1 about some of the work that we've done on high-risk
2 times for overdose mortality, particularly in
3 criminal justice settings.

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

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

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

20 So the rationale for naloxone for bystander
21 administration is that it helps prevent
22 complications of overdose through earlier

1 treatment, so before the paramedics get there, or
2 when fear of police inhibits calling 911 at all.
3 And we know from some of the qualitative work that
4 this is common, especially in heroin users and in
5 criminal justice populations.

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

13 It's generally distributed with the
14 education component that's on identifying
15 overdoses, administration, the need to call 911,
16 and rescue breathing. And I think it's very
17 important that the distribution of naloxone takes
18 place in conjunction with policy changes at the
19 state level to allow for 911 Good Samaritan laws.
20 This provides some immunity to bystanders who
21 witness an overdose and then call emergency
22 services so that they don't get arrested for having

1 paraphernalia or other -- prescription medications
2 without a prescription around.

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

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

19 I think it's important to stress that
20 naloxone should be part of a comprehensive
21 strategy, and we've already heard some of the
22 components of such a strategy to help prevent

1 overdose. And these include prescription drug
2 monitoring programs; prescription drug take-back
3 events, where we reduce the amount of prescriptions
4 that are in the home and potentially accessible to
5 youth, especially teenagers; safe opiate
6 prescribing education for physicians; expansion of
7 opiate agonist treatment like methadone and
8 buprenorphine; safe injection facilities. These
9 have been used in other countries successfully
10 where people can go inject heroin in an environment
11 where somebody may be able to recognize an overdose
12 and respond to it. And then also safe storage of
13 prescription opiates in the home, again to prevent
14 diversion to people in the family, such as
15 teenagers.

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

21 So there's been international studies and
22 also a recent meta-analysis looking at the risk of

1 death among former inmates. And these have all
2 pretty much shown the same findings. The risk of
3 death among former inmates from drug-related causes
4 is high compared to the general population, and
5 it's also high in the first two weeks after release
6 from prison.

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

18 The risk factor data comes from a nested
19 case control study within the cohort study, and
20 I'll just discuss a few findings from that. So the
21 population was basically all released inmates
22 during a four-and-a-half-year period from

1 Washington State Department of Corrections with a
2 sample size of over 30,000 people. We linked data
3 to the National Death Index to establish the deaths
4 and the causes of death, and we had comparison data
5 from CDC Wonder for the general population
6 estimates.

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

12 So the adjusted Washington state population
13 death rate adjusted for age, gender, and race is
14 with the red line. The columns represent the death
15 rates in the former inmates. And then in the first
16 two weeks after release from prison, the death rate
17 from all causes was 12.7 times higher than the
18 general population. Then it diminished somewhat to
19 a baseline that was around three and a half times
20 higher. For overdose deaths, this would actually be
21 much more dramatic with 127-fold increased risk in
22 the first two weeks.

1 So drug overdoses represented just under a
2 quarter of the deaths, so 103 deaths out of 433
3 deaths. I'll just note that the mean age of death
4 in this cohort was 41, so this is a very young
5 population, dying basically.

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

13 So these are some of the substances involved
14 in the deaths in our cohort. I just note that this
15 is in the Pacific Northwest where there's a lot of
16 methamphetamine and cocaine use. So it may be a
17 little bit more skewed towards those substances
18 than we might see in other parts of the country,
19 but opiates represented were involved in about
20 44 percent of all the deaths. And 27 of the
21 deaths, so about a quarter, had more than one drug
22 involved.

1 In terms of risk factors for overdose deaths
2 after release from prison, we found that so far in
3 our case control study that a documented history of
4 injection drug use in the prison medical chart or
5 the substance abuse chart was associated with a
6 substantial increased risk of both all-cause
7 mortality and overdose mortality.

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

13 We also looked at whether people had
14 received opiate prescriptions, thinking that maybe
15 this happened in some people who were on opiates
16 for pain while they were incarcerated; so if they
17 had been receiving opiate prescriptions for the
18 60 days before their release. And basically, we
19 found no association for that group. This may
20 change over time again. These data are from prior
21 to 2003, and this might change since then.

22 So I then want to just comment about the

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

9 For jails, this is tremendously larger. So
10 the number of people in jails at the year-end was
11 .8, but 13 million people interact with the jail
12 system, so are incarcerated and then released. So
13 this risk of death after release from incarceration
14 is particularly important for jails because it
15 affects so many people.

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

21 So this I think is pretty significant. The
22 blue bars here represent the rate of death per

1 100,000 person years. The first set is from drug-
2 related causes, the second set from homicide and
3 the third set from suicide. And the other bars
4 basically show that the risk of drug-related deaths
5 in former jail inmates is also higher than among
6 other New York City residents and among residents
7 in the poorest New York City neighborhoods. So
8 there's really something about this transition in
9 incarceration that's particularly significant.

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

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

21 We had 32 percent reporting a history of an
22 emergency department visit for an overdose. This

1 reflects a tremendous amount of health service
2 utilization that is costly that's associated with
3 these overdoses. Forty-four percent reported a
4 history of injection drug use, and 10 percent had
5 HIV.

6 When we asked people about whether they had
7 witnessed a heroin overdose and whether the person
8 lived or not, 46 percent said, yes, they had
9 witnessed a heroin overdose. At the last witnessed
10 overdose, did somebody, you or somebody else, call
11 911? Unfortunately, only 54 percent of the cases
12 did somebody call 911. This is why intranasal or
13 any other form of naloxone for bystander use is
14 very important because such a large proportion of
15 the cases, nobody calls 911.

16 Whether they were willing to receive
17 training to use Narcan for a witnessed overdose,
18 86 percent said yes. Whether they were willing to
19 give it if somebody they injected with overdosed,
20 90 percent of people said yes, they were willing to
21 give it. So they were more willing to give
22 naloxone than to call 911. People leaving jails

1 and prisons should be given Narcan, 76 percent of
2 the people said yes.

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

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

19 And what's very unfortunate about this case
20 is it took him several overdoses to understand this
21 concept of tolerance and then the associated risk.
22 This is why I think education that comes along with

1 naloxone distribution would be very helpful.

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

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

22 The other thing is the PONI program in Rhode

1 Island is also anticipating enrolling former
2 inmates or actually people hopefully before they
3 leave prison. And then also, the DOPE Project that
4 we've heard a little bit about has worked in
5 reentry centers. I think it is going to be
6 complicated to give naloxone to people before they
7 leave the prison, but that's probably the best time
8 to do it.

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

18 I think also the induction of treatment with
19 longer-acting opiates is also high risk, both for
20 methadone and buprenorphine and other long-acting
21 opiates. I think that this is an issue probably in
22 drug treatment and in pain management.

1 The reason that I think that this is
2 important is this data out of the United Kingdom.
3 This was a large study of people in opioid
4 substitution treatment in primary care. So
5 obviously, overall, being on treatment saved lives
6 or was associated with a lower risk of death, but
7 the first two weeks of treatment had somewhat of a
8 bump. That's the first arrow you see there in
9 terms of the risk of death. And then the first two
10 weeks off of treatment was also associated with an
11 increased risk, but considerably higher.

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

17 So I've just made some recommendations about
18 some of the populations. We've already discussed a
19 few of these: drug treatment clients, people with
20 prior overdoses, and so on. In prescription opiate
21 users, it might make sense to target naloxone to
22 people on high dose, people who are opiate naive,

1 so at the initiation of treatment, people on
2 concurrent sedating medication such as
3 benzodiazepines, people who use alcohol or who have
4 comorbid liver and respiratory disease. And I
5 should also just mention it's worth thinking about
6 people who have trouble accessing medical care,
7 very rural people or for other reasons can't access
8 care quickly.

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

16 The reason I mention primary care
17 specifically is because I work in a community
18 health center in Denver where we see many of these
19 patients who are at high risk for overdose. So I
20 pretty much see people in all of these risk groups
21 there. And I think if it was more available to me
22 to prescribe to my patients, I could probably get

1 access to some special populations that we've
2 already identified. I could also reach people who
3 don't themselves identify as drug users, so may not
4 go to a community-based organization to get
5 services but nonetheless are at risk.

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

19 So I'll just conclude with a couple
20 statements about that I think former inmates are
21 definitely an appropriate target population for
22 overdose education and increased access to

1 naloxone. It's definitely acceptable to the
2 population who is most likely to have it used on
3 them or to use it on other people. I think that's
4 very important and may get to some of the ethical
5 issues that we may discuss later today.

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

12 So thank you.

13 (Applause.)

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

16 I'm pleased to introduce our next speaker,
17 who will be Dr. Alex Walley from Boston University.
18 Dr. Walley is an assistant professor of internal
19 medicine at Boston University and will be telling
20 us about the naloxone distribution program in
21 Massachusetts, which I would suggest will show us
22 how the public health community in some ways is way

1 ahead of the research community and the regulatory
2 officials. So we wanted to learn from what's
3 happening in real-world settings, and Dr. Walley is
4 here to teach us about the Massachusetts story.

5 **Presentation - Alex Walley**

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

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

18 So this person had witnessed 20 overdoses in
19 his lifetime at the time that he was trained. And
20 in the last 30 days before he was trained, he used
21 heroin on 30 of those days. He used
22 benzodiazepines, a prescription pill likely without

1 a prescription, for 15 days, and he used cocaine or
2 crack for 15 days.

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

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

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

1 barrier.

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

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

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

19 The initial OEND programs started in Boston
20 and Cambridge in the years 2006 through 2007. You
21 can see them marked in pink. In 2007-2008, the
22 Massachusetts Department of Public Health expanded

1 this effort to the additional towns there. And you
2 can see that most of those towns are dark shaded.

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

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

14 So based on this difference between towns
15 where we implemented and towns where we did not
16 implement, we conducted this study called the
17 INPEDE OD study. And the objective there was to
18 determine the impact of opioid overdose education
19 with intranasal naloxone distribution programs on
20 fatal and nonfatal opioid overdose rates in
21 Massachusetts. And this study was funded by the
22 Center for Disease Control and Prevention.

1 So it's a quasi-experimental interrupted
2 time series, again, 19 Massachusetts cities and
3 towns with five or more opioid-related
4 unintentional or undetermined poison deaths in each
5 year from 2004 through 2006. And the setting was
6 these OEND programs that were implemented in some
7 of those towns. The outcome was fatal opioid
8 overdose per town population per year using
9 registry of vital records and statistics, basically
10 death certificates. And then our second outcome
11 was opioid-related emergency department or hospital
12 discharges per town population per year.

13 Our analysis approach was Poisson regression
14 which compared annual opioid-related overdose rates
15 among the cities and towns by OEND implementation.
16 This regression gives us natural interpretations as
17 rate ratios. We adjusted these models for city and
18 town population rates of age, gender, race,
19 ethnicity, poverty level, inpatient detox treatment
20 slots, the number of methadone treatment slots, the
21 number of state-funded buprenorphine treatment
22 slots. So Massachusetts has a relatively

1 aggressive program of funding buprenorphine
2 treatment in the community. And then prescription
3 to doctor shoppers, we used the prescription
4 monitoring program in Massachusetts to calculate a
5 rate of doctor shopping per town, and then adjusted
6 for that. And then the year to adjust for the
7 temporal trends in overdose rates, opioid overdose
8 rates.

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

17 So that's our reference group. And compared
18 to that, we looked at two other categories, so
19 those towns that had relatively low cumulative
20 enrollment, 1 to 150 people per 100,000 people in
21 uptown population and greater than 150 people
22 enrolled and treated per town population.

1 And you can see that in the adjusted
2 analyses, there was a substantial and statistically
3 significant reduction in the adjusted rate ratio.
4 So that's that .73 there for the enrollers with
5 lower enrollment, so that's a 27 percent reduction
6 in the overdose death rate in those towns. And
7 then in those with high rates, greater than 150
8 enrollments per 100,000, .5 was the rate ratio,
9 which is a 50 percent reduction in the rate in the
10 towns with high enrollment.

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

19 So the summary I wanted to stress here for
20 the INPEDE study is that fatal overdose rates were
21 decreased in Massachusetts cities and towns where
22 OEND was implemented, and the more enrollment or

1 the more implementation, the lower the reduction in
2 overdose rates. We did not see any clear impact on
3 acute care utilization such as ED or
4 hospitalization rates.

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

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

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

22 The components of our OEND program are very

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

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

1 events that come up.

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

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

16 The downsides are that this delivery method
17 is not FDA approved. There's been no large
18 randomized controlled trial. There's assembly
19 that's required for our kit, and it's subject to
20 breakage. It's a high cost for each kit, not
21 relative to an EpiPen, by the way. It's actually
22 much cheaper than that. But for a program that

1 doesn't have a lot of external funding or doesn't
2 have insurance coverage, it's \$30 per kit.

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

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

20 We have almost 13,000 individuals in
21 Massachusetts who have been enrolled and trained,
22 and we're enrolling at a rate of 300 per month, so

1 that's 10 people per day. We documented 1300
2 rescues since the beginning of the program, and our
3 current rate of rescue documentation is 30 per
4 month or 1 per day.

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

18 So I just want to highlight here the
19 difference between the light blue and the neon
20 green here. The light blue are the people who are
21 either actively using drugs or they're in
22 treatment, whereas the neon green are the nonusers.

1 They're usually families or parents or staff
2 members who work with people who are at risk for
3 opioid overdose. And you can see at the community
4 meetings, the vast majority -- and this is one of
5 our fastest growing sites. The vast majority of
6 the people we enrolled are actually nonusers.
7 These are parents, family, and friends.

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

17 Among the half that have had an overdose, 44
18 percent have received naloxone themselves before
19 they were trained. High-risk times like inpatient
20 detox or being incarcerated are common. And among
21 all the people that we train, if you're in the user
22 group, 7 and a half percent of them return to us

1 and report that they use the naloxone for an
2 overdose. That's a number needed to treat 15.
3 Among the nonusers, mostly parents and family, two
4 percent of them return to us and report an
5 overdose. And so we have the nonusers actually
6 using naloxone to reverse overdoses.

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

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

20 So when people come back, this is to report
21 their overdose, what do they say happened? Not
22 their overdose, the overdose that they reversed

1 using naloxone, their overdose rescue. What else
2 had they done besides deliver naloxone?

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

15 What about adverse events? So among the
16 1300 overdose reports that we've documented, seven
17 of them were deaths. And I can tell you that
18 having reviewed each one of these, in each case,
19 these were people who were dead when the response
20 came about. So the person was already dead. They
21 didn't have any response to the naloxone because
22 their heart wasn't beating any more.

1 Overdose requiring three or more doses, so
2 this does happen. And so this scenario is really
3 when -- because we only give two doses in the kit.
4 It's usually the person gives two doses, and then
5 they've called 911, and the ambulance comes, and
6 they give more naloxone. So that does happen.

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

13 Precipitated withdrawal I think happens more
14 commonly than what we see, but this is what has
15 been reported on our reports, very low rate of
16 .3 percent.

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

22 Then negative interactions with public

1 safety. So about a quarter of the time, the
2 interaction when you call 911 is a negative one.
3 That means three-quarters of the time it's either
4 neutral or positive.

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

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

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

22 So I think from our experience here in

1 Massachusetts, we can say that intranasal works in
2 the real world, and it's popular. We've really
3 been able to draw in a diverse group of
4 stakeholders to be invested in this. It could be
5 improved, however, with a one-step affordable
6 FDA-approved intranasal delivery device.

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

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

21 Prescription status is a barrier when you're
22 talking about wide distribution outside of medical

1 settings.

2 Fear of police is a barrier to help seeking,
3 and that's been demonstrated in multiple studies.
4 And we don't have a good Samaritan law in
5 Massachusetts. And I think while that is not the
6 only answer, that I think is helpful in getting
7 better interaction with the emergency medical
8 system.

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

11 (Applause.)

12 DR. COMPTON: Thank you, Dr. Walley.

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

18 Dr. El-Bassel will be presenting to us on an
19 unusual project taking place in Central Asia to
20 show that these kind of projects can benefit from
21 information gleaned from international settings as
22 well as the United States.

Presentation - Nabila El-Bassel

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

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

6 For you, having been in the region, as you
7 see, Kazakhstan is Central Asia. It has borders
8 with Russia, China, Iran, and Afghanistan. And I
9 will highlight Afghanistan given that Afghanistan
10 is the largest producer of opium and 35 percent of
11 the opium production or hemp production from
12 Afghanistan, it goes through Central Asia.

13 Kazakhstan by itself, if you look at the red
14 lines, has 10 drug trafficking routes of heroin to
15 other countries from Afghanistan. So the access to
16 drug use and drugs from Afghanistan to this region
17 increase clearly drug use and also increase the
18 cost -- reduce the cost of drugs which increase
19 overdose.

20 This is a map that published recently by the
21 Lancet, showing that there are 250,000 registered
22 IDUs in Central Asia. And I am saying registered

1 because there are many more that are not
2 registered.

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

11 As I mentioned earlier, the geographic
12 proximity to Afghanistan increases the drug use but
13 also decreases the purity of drugs, which increase
14 overdose. What we see in Kazakhstan, based on
15 several reports, the IDUs mix heroin with other
16 drugs and alcohol, which increase the overdose.
17 There is a high rate of incarceration and
18 discrimination among drug users, which also
19 increase the risk of experiencing, overdose which
20 we have seen also in the United States. The issue
21 of high risk of HIV and HCV also compromises the
22 immune system of the drug users, which increase the

1 risk of overdose.

2 Discrimination against drug users in the
3 region is huge. Fear of the police prevent drug
4 users from calling the police during an event of
5 overdose. Also, it prevents their social network
6 to call the police. And in many cases, in many,
7 many cases, when they call the ambulance, the
8 ambulance brings the police. And in many cases,
9 the drug users and the people who witness the
10 overdose, they are arrested and put in jail. And
11 also in many cases, drug users are taken into detox
12 and put in detox for maybe a few months. And then
13 they go out, and again, they go through the same
14 process. So this leads -- not only the drug users
15 but all people who witness drug use will not call
16 the emergency services to deal with these issues.
17 Also, there is lack of naloxone in ambulances and
18 in hospitals.

19 Another problem among drug users that
20 increases overdose is the ineffective methods that
21 the drug users use, injecting saline solution,
22 taking a shower, or shaking the person. These are

1 strategies the drug users use to deal with
2 overdose. Again, I want to highlight that there is
3 low quality of medical care related to overdose in
4 emergency services. And in many cases, the medical
5 services provide primarily CardiaMin to treat
6 overdose.

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

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

1 distribution of naloxone.

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

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

17 This is a map that was published by the Open
18 Society Foundations recently showing the peer-based
19 naloxone administration. And you see the dot
20 lines, there are very countries, low and middle
21 countries, that have access to naloxone,
22 unfortunately.

1 So the second part of my talk is Project
2 Renaissance, which I'm very, very excited to talk
3 about it. This is a randomized control trial.
4 It's the first trial that has been done in the
5 region. The intervention, it incorporates HIV
6 prevention with naloxone prevention. And I want to
7 tell you that it's very important to integrate HIV
8 and naloxone because in some regions in Central
9 Asia, the prevalence rate of HIV range between 20
10 to 25 percent.

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

18 Why we combine again HIV with overdose, we
19 know that overdose is the leading cause of death
20 among injection drug users living with HIV. HIV
21 infections increases where there is drug overdose,
22 and access to naloxone, in fact, is found to

1 increase engagement in HIV treatment and care.

2 This is the clinical trial we used. As you
3 see here, we screened people. We screened around
4 966 individuals. And we did the baseline and
5 overall randomized at 300 couples, 600 injection
6 drug users in two arms. We have data about the
7 600, but I will talk today about the 600 IDUs.

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

16 These are the lists of the core components
17 of the intervention that primarily related to
18 overdose, and we're going to talk about
19 intervention on HIV. As you see here, we did a
20 educational piece, education about causes of opiate
21 overdose, how to avoid overdose. And what I'd like
22 to highlight in these core components is that we

1 talk a lot about how you can work with your social
2 network, how you can work with your family to help
3 you to live and how to use naloxone.

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

12 If you look at here the description of the
13 population, they are young, 35 average age. The
14 majority are Russian, which is typical in the
15 region, and the majority are married. The history
16 of incarceration is quite high. And if you see
17 here, in terms of the HIV prevalence rate,
18 26 percent, but if you only look at the IDUs, the
19 prevalence increases to 28 percent. HCV is a huge
20 problem among this population.

21 Injecting heroin. And here, as you see,
22 76 percent injected heroin, and they are using

1 other type of drugs. And we are seeing increase in
2 methamphetamines, and binge drinking is a huge
3 problem in the region.

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

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

20 We also asked them what do they do when they
21 use drugs, and many of the heroin users say they
22 use alcohol while they're high on heroin, which

1 increases the overdose. And they mix drugs with
2 heroin more than a third of the time. And here, as
3 you see, when we ask what do you mix with heroin,
4 many of them say that they mix Demerol or Benadryl.

5 We asked if they ever overdose, and
6 74 percent of the population, the 458, said they
7 ever overdose. And in the past six months -- we
8 are not asking historically, but in the past six
9 months, we see 23 percent overdosed. And we ask
10 the question if they knew people, if they
11 overdosed, and more than 50 percent said yes. And
12 if they knew people who died from overdose in the
13 past six months, 26 percent of them, they said they
14 know people who died from overdose.

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

20 We were interested in comparing people who
21 overdose and who did not overdose in the past six
22 months. Now, you see in this figure -- and we used

1 random effects model because when talking about
2 couples and to control for dependency, we used the
3 random effects model.

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

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

19 During this study, 89 percent reversal
20 happened from baseline to six months. We haven't
21 finished the study yet, but this is at the six
22 months. Seventy-four reversal, which is

1 83 percent, occurred where the study participant
2 administered the naloxone to their study partners
3 or others in their network. And 15 reversals,
4 17 percent, occurred where someone administered
5 naloxone to the study partners.

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

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

22 We also were interested if there is a

1 reduction, overdose reduction, from baseline to six
2 months. We're also delighted to say that there is
3 a significant reduction from baseline to six
4 months, 18 to -- so we are delighted to see this
5 kind of finding.

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

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

21 So in conclusion, I'd like to say that
22 training IDUs and their partner to administer

1 naloxone, it's feasible. It can be done. It is
2 safe. It can prevent fatal overdose among not only
3 people who inject drugs but also their networks.

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

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

20 So the good news, we see significant
21 decreases in the rates of overdose, injection
22 heroin use, and sharing syringes and cookers among

1 IDUs participants from baseline to six months. We
2 also see that obtaining naloxone kit was not
3 associated with reporting injection drug use or
4 overdose at six months. However, we know that
5 although the voucher system helped to link some
6 IDUs to the primary care, still it is a barrier for
7 them to go to primary care because of
8 discrimination, because of oppression, because of
9 registration of drug users.

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

19 So for us, we think that given all these
20 barriers, we believe that in future studies, we
21 will hopefully be able to distribute the naloxone
22 during the study, but also we were hoping that we

1 can provide easy access over-the-counter, where
2 they can get it and survive. So we're excited very
3 much that we are introducing naloxone into the
4 region, and we're showing that naloxone can work.
5 And it saves lives and empowers drug users to seek
6 drug treatment and HIV treatment, which is really
7 an important issue.

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

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

21 This is a memory that I have from the start
22 of the study when we sat with the minister of

1 health and Republican AIDS Centre in the region to
2 talk about naloxone. And we were challenged and
3 continued to be challenged, but luckily they became
4 partners with us in this study.

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

15 Thank you very much.

16 (Applause.)

17 **Questions and Answers**

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

19 Now we have the opportunity to entertain
20 questions from the other members of the panel of
21 our three speakers and then from the members of the
22 audience. If you'll please come up to the

1 microphone and introduce yourselves when called.

2 Any questions from our panel for the
3 speakers?

4 (No response.)

5 DR. COMPTON: Well, I actually have a
6 question for Dr. El-Bassel, one sort of very basic
7 question.

8 What was the formulation of the naloxone that
9 was distributed? Was it injection or intranasal?

10 DR. EL-BASSEL: It was injection. Nasal is
11 not there yet.

12 DR. COMPTON: Thank you.

13 All right. Let's start up with --

14 DR. SOMOZA: Hi, I'm Gene Somoza from the
15 University of Cincinnati and the Cincinnati VA
16 Medical Center. This is for Dr. Walley.

17 I'm wondering if you can describe some of
18 the challenges. For example, was the Massachusetts
19 State Medical Board okay with this, of giving
20 prescriptions to people that weren't sick, those
21 kind of things? Were they okay with that? Or
22 maybe they just don't even know about it.

1 I mean, we're having trouble in Ohio trying
2 to do something like you've done already.

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

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

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

19 So we have about 13,000 individual
20 bystanders who have been trained. It's about over
21 35,000 units of naloxone that's been distributed,
22 and that's all under that standing order.

1 But I have to say, we are trying to make
2 prescription naloxone more available because I
3 think there's a clear rationale for it, but there
4 are barriers to that. And it's getting it at the
5 pharmacy. That's not easy to do. It's getting
6 insurance to pay for it. And then the big one
7 really is getting doctors or prescribers to
8 prescribe.

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

12 DR. SOMOZA: Thank you very much.

13 DR. COMPTON: Next question?

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

18 I'd like to know a little bit about the
19 particulars of the training that these users and
20 nonusers are receiving so that they can administer
21 the medication appropriately, and how intensive
22 that is, and what kinds of materials you're

1 providing to them so that they have something for
2 reference -- I'm assuming they've got stuff like
3 that -- in consideration of what over-the-counter
4 possibilities may be ultimately.

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

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

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

21 And the training really depends at
22 least -- you saw the different sites where we train

1 people. The trainings look different at different
2 sites, honestly. A community meeting, it's
3 typically a half hour training that's didactic with
4 opportunities, and then a demonstration in front of
5 a group with opportunities to ask questions;
6 whereas a training at a syringe access program is
7 more likely to be one-on-one. And it really begins
8 with an assessment of the person, the potential
9 bystander's knowledge, so you know how much
10 training you have to deliver. And then that
11 training is adapted at that point.

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

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

1 help arrives.

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

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

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

19 So the barriers, I mean we've had some
20 cases, very few. We'll have a homeless person with
21 mental illness who really can't perform the
22 training. That happens very, very rarely. And

1 other than that, the people who come to us to be
2 trained, we haven't seen that many problems. It's
3 more implementing in different environments.

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

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

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

1 relapses and remits.

2 DR. LEONARD-SEGAL: Thank you.

3 DR. COMPTON: Question from the front?

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

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

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

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

1 broadly applied.

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

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

20 So I like the model. It's worked really
21 well, although I think -- we still call ourselves a
22 pilot, which makes me nervous because we're still a

1 pilot, which means that -- and so even in
2 Massachusetts, I think we need to integrate this
3 into the public health code or through the drug
4 control regulations, or have it legislated so it's
5 a permanent program.

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

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

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

19 Dr. El-Bassel, I am wondering if in some of
20 your qualitative data you've had experiences
21 parallel to mine. Where would you say that the
22 drug users you've seen in Kazakhstan prioritize

1 overdose versus HIV and hepatitis C?

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

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

1 the study itself, and injected him, and he
2 survived.

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

12 DR. STANCLIFF: Thank you.

13 DR. COMPTON: Dr. Throckmorton.

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

19 Did you have evidence -- do you have any
20 data on entry into treatment? So were people that
21 received the intervention, say, more likely to
22 receive treatment, or anything like that?

1 DR. EL-BASSEL: We do have data.
2 Unfortunately, we haven't analyzed the data yet,
3 but we have qualitative data saying that they want
4 to be in the treatment. They want to go because
5 they want to access this kit, and they wanted us to
6 give them the kit more and more. In fact, we're
7 limited how much of the study we can give it, and
8 the primary care doesn't have a lot. So we heard
9 qualitatively that they start going to primary care
10 more than before. And hopefully, by the end of the
11 study, we'll have more data to quantify the
12 percentage of people who access care because of
13 naloxone.

14 DR. COMPTON: Next question?

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

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

1 we're educating.

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

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

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

22 And I think that's a legitimate concern. It

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

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

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

1 conducted.

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

10 DR. BINSWANGER: Well, I'll just speak to
11 that first. I think that's a critical need because
12 I think we really have to engage insurance
13 companies in terms of their willingness to pay for
14 overdose counseling and also -- so counseling and
15 practice, so you can bill for counseling for
16 certain conditions. And this would be a nice way
17 of advocating for increased counseling around
18 substance abuse treatment generally, substance
19 abuse in general, and overdose prevention. And
20 then I think another reason is so that we could
21 potentially bill for the medications as well as the
22 delivery systems that are required.

1 So I think there's a big role for finding
2 ways to understand the health service use patterns
3 and the costs associated with overdose in terms of
4 just being able to engage health systems,
5 healthcare payers, Medicaid, public health systems,
6 as well as Kaiser and other large HMO-type of
7 settings where they have an interest in preventive
8 care.

9 DR. COMPTON: Thank you.

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

17 And then the issue of nonfatal overdose
18 is -- well, I'll just tell you. In OEND, we train
19 people to utilize. In fact, we train them to call
20 911. That's what we train them to do. So the
21 intervention on the one hand explicitly increases
22 health services utilization.

1 On the other hand, there's also a strong
2 prevention message as part of OEND, and we're
3 hoping that we're eliminating some of the need
4 for -- we're eliminating the overdose in the first
5 place. So we're preventing the overdose as well
6 with the knowledge that we're passing on. So in
7 that case, we would be reducing high cost
8 utilization.

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

16 DR. COMPTON: Thank you.

17 DR. EL-BASSEL: One of our goals in Central
18 Asia is to educate the medical staff and health
19 services staff about naloxone. And what we have
20 been doing is training around 200, so far, of
21 doctors from different settings, and from trust
22 points, the staff about naloxone. They have no

1 clue, and that's really our first priority in the
2 region.

3 DR. COMPTON: Thank very much.

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

6 (Applause.)

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

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

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

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

1 adhere to schedule. Thanks.

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

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21 A F T E R N O O N S E S S I O N

22 (1:00 p.m.)

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

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

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

18 **Panel 3 - Moderator Douglas Throckmorton**

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

22 First, several people have asked about the

1 availability of slides. Let me just say we're
2 working through making sure that the speakers agree
3 to have the slides posted publicly, and we're
4 working through obscure federal regulations related
5 to access and important things like that.

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

15 So with that, let's transition just a bit.
16 This morning we heard about the complex challenge,
17 the progressive tragedy of overdose deaths due to
18 prescription drugs as well as other opioids and the
19 various states and local efforts that are going on
20 to try to address those things. Many of those
21 efforts obviously are very encouraging, and there's
22 a lot of interest in them.

1 Now, it's time to transition to discussion
2 of drug development. This might be titled "Why the
3 Heck am I at the FDA?"

4 (Laughter.)

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

15 Second, given the enormity of this, the
16 enormity of the tragedy, the thousands of deaths,
17 and the suggestions that have been made that the
18 state and local efforts, the pilots, if you will,
19 are bearing fruit and need to be considered to be
20 broadened -- whether it's broadening in the way of
21 new formulations that are easier to use, intranasal
22 or the like, or broadened in terms of over-the-

1 counter status or something like that -- those
2 kinds of activities are regulatory in nature, and
3 they come to the FDA.

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

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

22 To the extent that the FDA can assist with

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

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

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

19 We're going to hear from the business side
20 of things, some discussion of what it would take to
21 build a business case for a new formulation that
22 was approved and available for use. And then we're

1 going to end with some important discussions about
2 some of the ethics around trials in this area.

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

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

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

21 She is a neurologist. She's been in the
22 division that's developed pain medicines for

1 several years. She has been in the analgesics
2 department specifically for around 13 years at the
3 FDA. Prior to that, she did her work at the
4 university of -- the Upstate Medical Center in
5 Syracuse as well as her neurology training at SUNY.

6 And, Sharon, thank you for talking with us.
7 I look forward to the discussion.

8 **Presentation - Sharon Hertz**

9 DR. HERTZ: Thanks, Doug.

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

16 In very broad terms, you can bring a new
17 drug application in for review by the FDA under two
18 regulatory pathways. In a 505(b)(1), this type of
19 application is one in which the applicant provides
20 all of the information based on work that they've
21 conducted or that's been conducted for them. And
22 in contrast, a 505(b)(2) is an application for a

1 drug, which the necessary investigations relied
2 upon by the applicant for approval were not
3 conducted by that applicant or for which the
4 applicant has not obtained a right of reference.

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

13 So we've heard a bit about naloxone. I'll
14 go very briefly over what it's currently approved
15 for and some of its labeling. It's, as we know,
16 indicated for complete or partial reversal of
17 narcotic depression. The labeling describes the
18 need for continued surveillance and repeated doses
19 of naloxone under this period of observation since
20 the duration may be shorter than the duration of
21 the narcotics that led to the overdose. And it's
22 important to note that, of course, it's not

1 effective against respiratory depression due to
2 non-opioid drugs. And, in fact, even
3 buprenorphine-induced respiratory depression may be
4 incomplete because of the pharmacology of that
5 drug.

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

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

19 So when we think about a new product being
20 developed for treating opioid overdose, we have a
21 few key questions that need to be answered. The
22 first is how does the new -- a new naloxone

1 product -- how does the bioavailability of the new
2 naloxone compared to the approved product? If the
3 relative exposure, the systemic exposure,
4 bioavailability is low, then we have to wonder
5 whether or not there will be adequate efficacy.
6 And if it's high, we in general will question
7 whether there are any implications for the safety
8 profile. And I think we heard earlier that in this
9 instance, it's not too much of a concern.

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

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

1 it been modified in any way?

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

16 Nonclinical data, the amount required will
17 depend on the route of the planned application for
18 a 505(b)(2) application where there are plans to
19 rely on the agency's previous findings for
20 naloxone. In general, we may only need some local
21 tolerance. Generally, that would be in two
22 species. But if clinical monitoring of the local

1 tissues during any clinical studies is considered
2 acceptable based on the novel route, there may not
3 be any requirement for nonclinical studies. So the
4 answer on this one is it depends.

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

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

19 The first step is to look at the relative
20 bioavailability. And we like to see that in at
21 least two doses compared to the approved naloxone
22 by an approved route of administration, preferably

1 IM or IV. And the idea, of course, is to target
2 the plasma naloxone levels to be detectable and
3 comparable and present for a meaningful duration
4 relative to the approved product. And then dose
5 selection can be based on a variety of assumptions
6 of different levels of absolute bioavailability of
7 the intranasal naloxone.

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

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

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

1 can't be confident that there would be efficacy.

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

4 First, we have to consider the patient population.

5 These are events generally occurring out in the
6 community. The people involved in the study may be
7 first responders, possibly emergency department.

8 There have been some discussions about using a
9 perioperative population. And there have been some
10 other clinical settings that have been discussed
11 that might offer the opportunity to administer the
12 product to patients in an overdose situation.

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

20 There are some populations where you could
21 consider getting informed consent ahead of the
22 study, for instance, in a perioperative population,

1 but there are pros and cons for all of these.

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

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

13 How much safety data does an applicant, a
14 company, need? And again, that depends. It
15 depends on how the PK profile of the new product
16 compares to the approved product. So, in general,
17 we would like to get some experience with this
18 product in actual use for a couple of reasons. It
19 helps give us some of the safety data, and then it
20 also gives us additional data about the usability
21 of the product. Generally speaking, some safety
22 data will be necessary. We're probably talking a

1 few hundred patients as a minimum in a product
2 that's got good relative bioavailability compared
3 to the approved naloxone.

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

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

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

17 (Applause.)

18 DR. THROCKMORTON: Thanks, Sharon, very
19 much.

20 Continuing the theme of regulatory pathways,
21 I turn to over-the-counter development. So this is
22 not specific to intranasal formulation. It could

1 be whatever formulation of a product you had that's
2 approved that you want to make available in an
3 over-the-counter setting.

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

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

17 Thanks very much, Andrea.

18 **Presentation - Andrea Leonard-Segal**

19 DR. LEONARD-SEGAL: Good afternoon.

20 I hope we're going to have a little fun with
21 this because over-the-counter drug development is
22 actually a very interesting area. We get to

1 hypothesize a lot about things. We forge new
2 territory. And certainly, considering naloxone as
3 an over-the-counter drug is forging new territory.

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

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

18 I'll talk a little bit about OTC drug
19 labeling, which is unique, and we'll consider how
20 naloxone could become an over-the-counter drug.
21 And then we'll talk about a few other issues that I
22 think we would need to be thinking about.

1 So first, regulations. The Durham Humphrey
2 Amendment to the Food, Drug and Cosmetic Act
3 formally differentiates prescription from
4 nonprescription drugs. Now, this act was passed in
5 1951, and around that time, the world was a
6 nonprescription world. So the way this amendment
7 comes forth, it almost looks as though we're
8 carving out this little niche for prescription
9 drugs.

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

20 Now, the Code of Federal Regulations,
21 another regulation manual, describes the procedure
22 by which drugs that had been limited to

1 prescription use shall be exempted from
2 prescription dispensing requirements. Now, what
3 does that mean? That means it tells us what we
4 need to know about a drug to switch it from
5 prescription to over-the-counter.

6 So how can drugs be marketed in the United
7 States? Currently, there are two marketing options
8 for drugs, prescription and over-the-counter.
9 Behind the counter is not a marketing venue in the
10 United States. It exists in Europe and in other
11 countries and involves a pharmacist being able to
12 make a determination to give a medicine to a
13 patient who is seeking some help without the input
14 of a physician. We don't have that here.

15 So the law has been interpreted so that dual
16 marketing of the same active ingredient in products
17 that are both prescription and over-the-counter can
18 only occur when a clinically meaningful -- and
19 that's very important -- when a clinically
20 meaningful difference exists between the two that
21 makes the prescription product safe only under
22 supervision of a physician or other licensed

1 practitioner. In other words, a drug cannot be
2 marketed both Rx and OTC for the same indication,
3 population, and conditions of use.

4 So how might the law apply to naloxone?
5 Well, I have two questions that I'm going to pose,
6 and I don't know the answer to them. Would a
7 clinically meaningful difference exist between an
8 OTC naloxone and prescription naloxone so the
9 current prescription products would remain
10 prescription after the OTC switch? Would those
11 conditions allow dual marketing?

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

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

21 We have the drug facts label in the OTC
22 world. Any of you who go into the drugstore and

1 you buy a box of acetaminophen or some kind of an
2 over-the-counter laxative, if you look at the back
3 of the box, you're going to see the drug facts
4 label. And this label has its own regulations. It
5 has to follow certain standardized formats. And
6 this formatting is intended to provide clarity and
7 consistency to consumers so that they know what to
8 expect from over-the-counter labels and where to
9 find the most important information. And these
10 labels have been tested in consumer studies, and
11 they appear to do pretty well.

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

20 Here's the skeleton of the drug facts label,
21 and all of these different elements are described
22 in the regulations. So think about this and say,

1 can we make people understand naloxone with this
2 label?

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

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

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

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

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

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

18 Dr. Hertz just talked about some of the
19 aspects of bioequivalence and maybe other efficacy
20 issues that might be involved for naloxone. We
21 would be working with a group that Dr. Hertz works
22 with to establish the efficacy of a new formulation

1 for over-the-counter switch. If we were going to
2 switch a current formulation, then new efficacy
3 data probably would not be needed.

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

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

20 So let's think a little more about naloxone
21 because we're hypothesizing. We already did talk a
22 little bit about efficacy, so I won't go there.

1 But for safety, the switch of the approved
2 prescription product would be supported by current
3 safety database, which would be clinical studies
4 and post-marketing. However, if there were a new
5 formulation, we would need new clinical safety
6 data, say, if there were a topical formulation or
7 intranasal formulation. And if the product were
8 more bioavailable than the reference to which it
9 was compared, it probably would be wise to market
10 it first by prescription to acquire a
11 post-marketing safety database to support OTC use.

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

22 For naloxone, we would need to understand

1 the potential for conversation into an opioid
2 agonist that could be abused. We would want to
3 know about that.

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

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

19 So the first of these four studies, the
20 label comprehension study, is the first step in
21 predicting consumer behavior. Can the consumer
22 understand the label? We want to know this. If

1 not, we know that it's not likely that they're
2 going to use the product properly. However, the
3 converse is not necessarily true. We know from
4 past experience that even when people understand
5 the label, it doesn't necessarily predict that they
6 will use the product properly.

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

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

18 For naloxone, I think we probably would need
19 one. Listening to Dr. Walley's talk about the fact
20 that there is a lot of training needed even to
21 administer the nasal formulation because of some
22 manipulations that need to be done with the product

1 ahead of time, I think that might need to be tested
2 for instructions. Certainly, we would want to
3 assess if consumers could properly prepare or use a
4 syringe.

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

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

21 However, for naloxone, data will be needed
22 to assess whether the individual administering the

1 drug could properly diagnose the opioid overdose
2 and determine that it is appropriate to give
3 naloxone based upon the information in the drug
4 facts label.

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

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

18 So we know that people can go into a
19 pharmacy and pick up several boxes of aspirin. And
20 so we would not want to falsely limit access in an
21 actual-use study if it would not be representative
22 of what would occur once the drug is approved.

1 There is limited study investigator contact to
2 avoid introducing bias into the study. Actual use
3 data would be needed to support an over-the-counter
4 application for naloxone.

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

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

22 Now, just thinking about naloxone, there are

1 other things that come to mind when I think about
2 it as an OTC possible product. Some of these are
3 needle safety for the injectable formulation. We'd
4 have to think about that. We'd have to think about
5 the impact of the injectable no longer being a
6 prescription drug if one of those laws said it
7 can't be.

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

15 But this is something that is also very
16 important to know. FDA does not control over-the-
17 counter drug advertising. It does control
18 prescription drug advertising. The Federal Trade
19 Commission regulates OTC drug advertising. So if
20 naloxone goes over-the-counter -- and the rules are
21 different than probably how we would like to think
22 about doing things over here. So you need to think

1 about what a TV ad for naloxone might look like.
2 We would not have control over that here.

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

11 Thank you very much.

12 (Applause.)

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

16 (Laughter.)

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

22 Dan Wermeling is the professor of pharmacy

1 at the University of Kentucky College of Pharmacy.
2 He received his Pharm.D. from the University of
3 Kentucky as well and is the founder of a company
4 AntiOp, Inc.

5 Dan, thank you very much for coming.

6 **Presentation - Dan Wermeling**

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

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

1 feasibility overall.

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

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

16 And so we then have to think about that
17 context and that label, and then visualize what the
18 new product look like, and can we say naloxone
19 hydrochloride nasal spray is indicated for. And so
20 we have to then basically introduce and transpose
21 these notions to understand if it's possible or
22 not.

1 We could also think broadly about different
2 kinds of transmembrane routes. Now, I do a lot of
3 work in intranasal delivery, but there are all
4 kinds of other companies that look at all these
5 different routes technologically either for
6 formulation capability or that they have device
7 technology that allows or enables administration.

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

17 So some of these you could see right away
18 might not be all that useful, like rectal, for
19 example. We have emergency products with rectal
20 diazepam gel, but that's not really highly
21 accepted. Other things like endotracheal are
22 pretty challenging to think about of instilling

1 drugs to the lung. That's not something simple.
2 And some of these others have all their various
3 considerations about what might optimize them or
4 not.

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

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

22 In general, powders can work, but it adds an

1 additional step. It's nice if the drug is in
2 solution because that's how drugs get absorbed.
3 The molecule can cross a membrane if it's in
4 solution. If you have to have a powder dissolve,
5 then it doesn't work as fast. So aqueous is
6 probably better.

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

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

1 And so it has to be durable.

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

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

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

22 But we still have to define clinical

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

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

20 We need to understand the pKA. This tells
21 us about some basic chemistry about how it
22 solubilizes in water. And so this drug will be

1 dissolvable in water, which is great. We can
2 understand ionization from this, meaning that drugs
3 cross membranes when they're in their un-ionized
4 state. If they're ionized, then they're harder to
5 get across. The challenge here with opioids is
6 that they're also unstable if you raise the pH. So
7 you have to have a low pH to keep it stable in
8 solution.

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

17 We can also look at the chemical structure
18 to understand them, and the chemical structures
19 fit, again, general nasal paradigms, and so that
20 works nicely. And the general core structures are
21 all the same. And it's just one side chain in
22 general that creates the difference in its

1 pharmacologic activity but doesn't have a lot of
2 influence on the chemistry.

3 The biopharmaceutics of these other drugs
4 are known. Hydromorphone was a product that I was
5 involved with at a prior company and has been
6 published, and so it has a bioavailability of about
7 50 to 60 percent. If you give 2 milligrams, you'll
8 get a peak of around 3.5 nanograms. And a Tmax,
9 how long it takes to get the maximum concentration,
10 of 20 minutes, so it explains the slope of
11 absorption.

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

17 Butorphanol is a marketed drug. It's Stadol
18 nasal spray. You can look it up on the package
19 inserts or in the labeling available on the
20 website, and you can see that it does also have
21 very excellent bioavailability of 60 to 70 percent,
22 Cmaxes of 5.5 nanograms per mL, and is absorbed a

1 little bit faster. And that's because it has a
2 higher Log P. So butorphanol nasal spray, all
3 these drugs have very similar core chemical
4 structures and very basic, similar chemistry and
5 formulations.

6 So then if we look at how these things
7 perform in terms of biopharmaceutics -- I've pulled
8 these charts from some of the papers. The left one
9 is hydromorphone, and the top bar shows an IV
10 versus two different nasal doses. And so you can
11 see how IV achieves very high rapid concentrations
12 after an injection. And then there is somewhat of
13 a dose proportionate exposure from 1 versus 2
14 milligrams of hydromorphone. And so you could say
15 1 and 2 milligrams hydromorphone, and 1 and 2
16 milligrams naloxone, maybe these profiles are going
17 to look somewhat similar. And so that might be a
18 good marker.

19 The butorphanol does a similar kind of
20 approach where we can see that 1 and 2 milligrams
21 provides about 4 to 5 nanograms per mL peak
22 concentrations. It's those proportionate. And so

1 this is again a fairly good marker. And
2 naltrexone, again, this is an expanded scale, but
3 it shows that you can get again very rapid
4 bioavailability of the other antagonist.

5 And lastly, the closest example I can find
6 of giving naloxone nasally is in a paper that was a
7 drug abuse liability study performed actually at
8 the University of Kentucky by one of our
9 colleagues, who crushed suboxone tablets and let
10 subjects snort, if you will, suboxone powder. And
11 so then a half a milligram in one group and
12 2 milligram naloxone powder was administered
13 nasally. Just think of in the movies like cocaine
14 straws, right, that kind of concept.

15 And so what we see here is a Cmax of about
16 1.6 nanograms per mL, Tmax of 20 minutes, which is
17 about what I would expect, and a relatively low
18 bioavailability of 30 percent, sort of mid-range.
19 And I believe that part of that relationship again
20 is that this is powder. Right? So we have a
21 dissolution step that has to occur before the cilia
22 in the nasal cavities sweep the drug away. The

1 drug is not bioavailable orally, so if it's swept
2 and you swallow, it's lost.

3 So why is this? This last one is sort of a
4 very good clue about what might happen with
5 2 milligrams of nasal powder with a peak at 1.6 and
6 a bioavailability of 30 percent.

7 So then you can go back and look at other
8 studies where pharmacokinetics of naloxone has been
9 published -- the most recent one is Dowling in
10 2006 -- and you can see there are two charts there
11 of 0.8 milligrams IV and 0.8 milligrams
12 intramuscular, which might be the route of
13 administration of greatest interest for comparison.

14 And so what you can then at the bottom chart
15 is that 0.8 milligrams IM, which is a generally
16 clinically relevant dose, provides a peak of around
17 1.7, 1.6 nanograms per mL in about 15 to
18 20 minutes. And so this might compare something
19 close to what an intranasal administration might
20 look like if you were thinking back to this. So
21 there might be some relationship then between IM
22 and intranasal delivery from these two studies.

1 The link that I use is really that
2 0.8 milligrams IM is known to be clinically
3 effective. Right? So ambulances and clinics and
4 other places, injection centers, are able to use
5 this. But what we don't know is the exposure from
6 an optimized nasal formulation. The injection used
7 with the MAD device is about 10 times more dilute
8 than what is typically formulated for a nasal spray
9 product.

10 If you had an Afrin nasal sprayer or Flonase
11 or whatever, that delivers 100 microliters, one-
12 tenth of an ml per activation, because that's about
13 the volume that the nose can actually physically
14 handle without drug either going this way or this
15 way. It's not going to stay. It's going to run.
16 And so the effective dose of giving 2 milligrams
17 with a MAD device isn't effectively 2 milligrams.
18 We just don't know what that is. Nobody knows what
19 the exposure of that means, either.

20 So we don't know what the exposure looks
21 like from an optimized nasal formulation or the
22 exposure from the current off-label practice.

1 However, there is a lot of clinical practice going
2 on off label. And this is from, I believe, Karl
3 Sporer at UCSF for the intranasal naloxone protocol
4 for their EMS services in San Francisco. And so
5 you'll see that they have a standard of care
6 written that the 2 milligram syringe with the MAD
7 device can be used to reverse opioid overdose in
8 the field, pre-hospital. And the paper suggests
9 that this works about 70 to 80 percent of the time
10 in the patients that they come across.

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

20 Then there's another paper in Denver where
21 this also started with the MAD device, and Denver
22 EMS services compared 2 milligrams intranasal using

1 the MAD system with 1 to 2 milligrams of IV
2 naloxone. And their main outcome interests were
3 Glasgow Coma Score, which is a measure of cognitive
4 function and how well people can interact with you.
5 And so a higher score of 15 means you're normal,
6 and a lower score means that you're impaired.

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

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

21 And so if you look at the right side of this
22 chart, you'll see that the drug-to-clinical

1 response time does take a little bit longer for
2 nasal delivery, 13 minutes versus nine minutes.
3 But if you account for drug administration time,
4 the five minutes you might need to actually to get
5 the IV in, then the outcome times tend to be
6 equivalent. And so you're not really losing
7 anything hopefully to time-to-clinical response by
8 using nasal delivery in pre-hospital setting.

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

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

1 So nasal delivery has expired.

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

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

18 If you had to include children in your plan,
19 then you got an additional six months. And if you
20 convert and do additional research to get OTC
21 status, you will get another three years. So you
22 can see where the whole series of sequences of

1 research requirements, you might get up to six and
2 a half years.

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

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

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

21 One other element to think about, because
22 I've heard a lot of training mentioned here as an

1 issue, and that is, for every prescription, it's
2 required for a pharmacist to offer counseling on
3 every product. This is not required in an OTC
4 setting.

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

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

19 This expanded access about no prescribing as
20 an additional market to sell more units is unknown.
21 It's untested as a market. And it's unknown
22 whether prescribers of pain products, which is the

1 largest population of all, in the millions versus
2 hundreds of thousands -- will prescribers embrace
3 the kinds of practices that you espouse today,
4 these harm reduction principles? That's an
5 unknown. I don't know to a great extent how the
6 pain management world has been approached with
7 these topics.

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

18 And then lastly, healthcare finance is
19 uncertain. I'm hearing a lot of calls for over-
20 the-counter status, but if I look at the amount of
21 money that has to go in versus trying to get money
22 out to reimburse for the costs and the risks

1 associated with investing in such a product that
2 may cost 20 or \$30 million to do, will that money
3 come back? Can you entice capital into this
4 setting? It's a real interesting question, one I'm
5 just starting to engage in.

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

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

21 Right now, to my sense, it's pre-hospital,
22 but that's hugely expensive. I went and costed

1 a -- wrote a protocol, sent it to a CRO for a
2 500-patient safety study, and the price came back
3 as \$10 million for a single trial, \$10 million.
4 That's a serious number. So the development is
5 contextual across these different uses.

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

14 AUDIENCE MEMBER: Morphine.

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

17 Development and marketing then, feasibility
18 is a real question and planning for this. The
19 considerations and the regulatory structure that
20 was explained are really pretty standard. I
21 brought five different products for development to
22 Dr. Hertz's division over 12 years, and they're

1 very consistent in explaining what is required to
2 demonstrate safety and efficacy in chemistry for a
3 new drug product, even if it's a reformulation of
4 something that's very well known. The standards
5 are the same, and the public demands in general
6 that those standards be met.

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

16 Thank you for your time.

17 (Applause.)

18 DR. THROCKMORTON: Thanks, Dan, very much.

19 The last speaker before we have a break and
20 then we move to the public speaking period is Skip
21 Nelson, who comes from the Office of Pediatrics at
22 the at the Office of the Commissioner level at the

1 FDA, but is also, more importantly, one of our
2 ethicists, and one of the people that we turn to
3 when we have trials that raise challenges regarding
4 assessment of patients, enrollment of patients,
5 informed consent, and the like. And he's going to
6 be talking to you about some of those issues.

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

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

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

18 Skip, thank you very much.

19 **Presentation - Robert Nelson**

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

22 So with the prior presentations, I think

1 I'll be able to go through some of my slides more
2 quickly to stay within my allotted time. And I
3 want to just sort of highlight some issues,
4 depending on the kinds of clinical development
5 challenges that are in the pathway for getting
6 naloxone on board.

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

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

1 overdose from illicit opiates.

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

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

17 So the question is, well, who are the study
18 subjects if you're going to do a clinical trial?
19 The point is the person who's receiving the
20 naloxone is the study subject. Now, depending on
21 your research question, the person you're training
22 to give it may or may not be a study subject, but

1 the person who's getting it is the recipient of the
2 investigational product.

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

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

19 Well, if you need an efficacy study and
20 you're doing that in those who are at risk from
21 prescription drug overdose, that as well could
22 probably be done with fairly standard procedures

1 because they have a family. That family could be
2 administering it to them, but you've got consent
3 from them to do that, and at least probably been
4 able to train their family under that.

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

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

17 Are you going to tell someone, I've given
18 you a drug that could save your life, but don't
19 save the life of your buddy if you see them get an
20 overdose because that would be against the
21 regulations. I mean, I would hope they wouldn't
22 follow your advice on that.

1 And the bottom line is, if you include those
2 witnessed overdoses and you don't have consent from
3 everyone that that person may come into contact
4 with, which would be an operational nightmare,
5 basically, you're in the setting of needing to do
6 what's called an exception from informed consent.
7 I'm going to walk you through those regulations.

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

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

20 So first of all, it's conducted in -- it's a
21 study subjects who cannot provide informed consent.
22 And obviously, if someone is acutely overdosed,

1 they cannot provide informed consent. You also
2 have to have a therapeutic window where the product
3 has to be administered before you can get informed
4 consent. Obviously, giving naloxone to someone who
5 is in acute overdose I think meets that therapeutic
6 window requirement.

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

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

19 The other thing is available treatments must
20 be unproven or unsatisfactory, and I think you
21 could make an argument that in the field,
22 intranasal naloxone is better, that IM naloxone may

1 be unsatisfactory unless there's an auto-injector.
2 So you get into the situation of saying even though
3 naloxone is approved and has been used by
4 paramedics, if we want to move it into a setting
5 where it's being used by the community, in fact, at
6 risk themselves, that that would be an
7 unsatisfactory alternative to just say here, here's
8 the IM naloxone, although I believe that's been
9 used in one program.

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

19 And again, the intervention must hold out a
20 prospect of drug benefit. Well, I think that's
21 fairly evident that this intervention would. We
22 have plenty of clinical efficacy data in the hands

1 of paramedics that it would. So presumably,
2 putting it into someone else's hands would also
3 have that prospect and that the risks would be
4 reasonable, and it appears to do that.

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

17 So as you can tell from my presentation, I
18 would argue that an efficacy study or an actual-use
19 study of the use of IN naloxone would, in fact,
20 meet the criteria for an exception from informed
21 consent, provided that community consultation and
22 public disclosure are conducted. One caveat, this

1 approach is not permitted for prisoners. So that's
2 a population where this approach would not apply.

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

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

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

22 So I personally didn't get a sense that this

1 would be a hard bar to meet because it's been met
2 in many communities that have done that kind of
3 work anyway. Well, you'd have to do it again for
4 the trial. You can't just rely on what you did a
5 few years ago.

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

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

21 Some people have used random digit dialing
22 telephone surveys or surveys. I think that's all

1 right, but you've got to have that two-way
2 communication. This is really not meant to be a
3 poll. That's not what community consultation is
4 meant to be. So random digit dialing to just find
5 out how many people would go into the trial isn't
6 community consultation. That needs two-way
7 communication. One-way communication is public
8 disclosure.

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

19 How many here have CPR training?

20 (Show of hands.)

21 DR. NELSON: All right. How many here have
22 ever used a defibrillator?

1 (Show of hands.)

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

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

18 They had two groups. So there were the
19 volunteer people who basically received the
20 training, but then there were the people who
21 actually suffered a cardiac arrest. Now, you don't
22 know who that's going to be. So the one, they had

1 informed consent from. So that's the people that
2 would go out with the naloxone. That was easy.
3 The people who had the arrest, that's hard. Aunt
4 Millie is over for Thanksgiving dinner and suffers
5 a cardiac arrest. Well, she wasn't in that
6 building. She didn't get no consent, et cetera.
7 So they did various aspects of community
8 consultation.

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

14 So what bothers me about this is given that
15 using naloxone for witnessed events may have a
16 greater public health impact, and including such
17 events may actually make a clinical trial both more
18 feasible and relevant, what's the ethical
19 justification of excluding administration of IM
20 naloxone to non-consenting subject simply to avoid
21 the ethical requirement of consulting with the IDU
22 community?

1 What I'm suggesting is that from a public
2 health perspective, you could argue that to design
3 a study simply to avoid the need to do community
4 consultation could be criticized as being
5 unethical.

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

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

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

20 An efficacy study or an actual-use study
21 requires an IND unless all of the exemption
22 criteria -- and I didn't list them under 312, but

1 one of them is, say, that you're not using a study
2 population where the risk of using it would be
3 considered any different than its current approved
4 use. And I would argue at least that if you're
5 going into vulnerable populations, that you should
6 have an IND to do that.

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

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

21 I saw one innovative publication where they
22 looked at the number of deaths that occurred after

1 12 hours of receiving naloxone, and then someone
2 refused to be transported by the paramedics to the
3 hospital. And they showed that there were no
4 deaths within that 12-hour period, arguing that
5 just because I then refused to go to the hospital,
6 I wouldn't walk down the street and then die
7 because the naloxone has worn off.

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

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

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

22 Thank you.

1 (Applause.)

2 **Questions and Answers**

3 DR. LURIE: Doug, could I just ask a couple
4 of, I think, quick questions and then -- I don't
5 want to take away from the public questioners.

6 Sharon, I just want to make sure that I've
7 got these take home messages correct. It's true,
8 right, that it's entirely possible that no animal
9 studies would be necessary. It's at least possible
10 that that's the case, right?

11 DR. HERTZ: Yes, that's true.

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

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

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

1 size per arm might be?

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

11 DR. LURIE: Per arm?

12 DR. HERTZ: No.

13 DR. LURIE: For the whole study?

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

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

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

20 DR. LURIE: Gotcha. Okay.

21 A question for Andrea is, the data that
22 people have collected in the field over the years,

1 it's conceivable at least that some of that data
2 could satisfy some of your requirements, right? I
3 mean, it could be submitted as part of a package,
4 or do you need fresh data?

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

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

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

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

21 So there are different aspects to safety.
22 If it somehow were topical, we'd be interested in

1 dermal safety studies. There are a variety of
2 different kinds of things that we didn't talk about
3 because we're not really discussing formulation
4 specific things.

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

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

21 I did want to make one other comment,
22 though, if I could, on the animal stuff. Depending

1 on the formulation, I agree with Sharon totally on
2 naloxone, but if there were excipients that were
3 not qualified in a new formulation -- and that
4 means that they're new or they have never been used
5 in the quantity that they're used in this product;
6 in other words, they exceed previous -- there might
7 be some qualification of inactive ingredients that
8 would require some animal information.

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

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

19 DR. THROCKMORTON: Other panel members?
20 Skip?

21 DR. NELSON: Just one quick on the -- my
22 reading of the literature was that most of the

1 programs had a component of training. And so that
2 wouldn't really be the OTC model where there's a
3 clinician under appropriate state law or local
4 regulations are distributing naloxone with a
5 training component about the use of naloxone. It's
6 very different than the OTC.

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

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

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

1 label.

2 DR. THROCKMORTON: Let's move to the
3 questions.

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

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

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

1 insulins are not available that way.

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

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

19 DR. THROCKMORTON: Next?

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

22 I just had two quick questions. One was, in

1 the OTC discussion, there was a reference to other
2 considerations, including whether this would
3 encourage opioid misuse or discourage 911 calls.
4 And I think that there's a body of experience out
5 in the field that's been discussed already today
6 documented in the MMWR article.

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

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

20 MR. RAYMOND: And similarly, in the context
21 of a potential intranasal formulation, as we've
22 heard, there's a lot of experience in the field

1 right now with both community-based programs and
2 fire departments' first responders using unapproved
3 off-label intranasal formulation.

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

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

1 be the first application that comes in.

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

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

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

21 And so when I listed the key questions,
22 anything that's out there already, it does not have

1 to be generated by the applicant. So existing
2 information out there will be reviewed in the
3 context of any new product that comes forward.

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

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

22 In terms of us actively seeking companies to

1 do this, I don't know that we really have --

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

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

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

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

21 So there's no way sort of a priori we
22 can -- I mean, there's so many variables here that

1 it will be very hard for us to come out with a
2 position paper saying because we have this
3 information, this is the exact thing you need to
4 do. And that's why my comments about what's
5 necessary included "it depends," because it will
6 always depend on how similar or different, how
7 innovative, if there's novel excipients; everything
8 depends on the individual situation.

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

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

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

21 DR. THROCKMORTON: I'll take my prerogative.
22 I'll make a short comment, and then if there's

1 other conversation, we can talk about this at the
2 break.

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

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

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

22 DR. SOMOZA: I'm Gene Somoza from the

1 University of Cincinnati and the VA Medical Center
2 there in Cincinnati. I just want to make a comment
3 about the fact that several speakers have spoken
4 about what's ethical and unethical in all of this.
5 And when I try to put this whole day together, it
6 seems to me that the most ethical decision that
7 could be made today is to expand what Dr. Walley
8 talked about this morning, also, the Lazarus
9 program that's similarly going in North Carolina,
10 and what's going on in San Francisco to the rest of
11 the country.

12 For one thing, we're talking about thousands
13 of people that are going to die this year and more
14 next year. And we can already use the drug that's
15 already available and can give it intranasally or
16 IM or IV or subcutaneous. What else do we want?

17 I think to come up with a new product that's
18 going to take a lot of time and a lot of money,
19 this is totally crazy, from my perspective, when we
20 have something that works and is very safe already.
21 And it seems to me the best thing is to expand
22 these programs. And while we're doing that, as

1 we're treating the people that are going to be
2 otherwise dying, we can go on -- same thing with
3 over-the-counter. Apparently, even over-the-
4 counter takes a long time.

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

9 And also from the perspective of the cost,
10 \$5 for a vial of 0.4 milligrams of naloxone is not
11 that bad. This is for people that are spending
12 hundreds of dollars to get their twice daily heroin
13 dose. And if they can't afford it, I'm sure their
14 family members can afford it. At least in Ohio, we
15 had a hugely --

16 DR. THROCKMORTON: If you could --

17 DR. SOMOZA: What's that?

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

21 Do you have anything last -- if not, let's
22 let someone else have a comment.

1 DR. SOMOZA: Okay. That's fine. Thanks.

2 DR. THROCKMORTON: Thank you.

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

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

18 DR. LEONARD-SEGAL: Yes, I do. There was a
19 part, what we call the Part 15 hearing, which as an
20 attorney, you probably are well familiar with,
21 where FDA listened to lots of different people from
22 different stakeholder groups talk to us about the

1 pros and cons of OTC products with conditions of
2 safe use. It would be sort of a different kind of
3 a paradigm, which would still be over-the-counter,
4 not behind the counter. And we heard lots of
5 interesting talks on that. And actually, someone
6 did talk about naloxone during that presentation.

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

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

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

20 DR. BELETSKY: Okay.

21 DR. DASGUPTA: Thanks. Dr. Hertz, a
22 question for you.

1 Can you expand a little bit on what the
2 justification is for -- if there was a formulation
3 that was bioequivalent to IM, what the
4 justification is for the actual-use studies? And
5 specifically, with the -- and not for OTC but for a
6 prescription. And specifically in the context of
7 the more recent labeling for suboxone sublingual
8 films are very similar -- the safety and efficacy
9 data in the label are largely drawn from solid oral
10 dosing form -- or the sublingual dissolving tablet.

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

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

21 So, for instance, we have asked for FMEA,
22 failure mode evaluation, examinations for

1 instructions just to make sure. Because the last
2 thing we want is for a physician to prescribe this
3 naloxone product, it goes home with a
4 patient -- let's say it's a pain patient. There's
5 an accidental exposure in the home. Somebody grabs
6 this, and then they can't figure out how to use it.
7 I mean, that's not helping anyone.

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

16 So depending on what it is, that will
17 describe how much information we think is
18 necessary. Frankly, how do you write the
19 instructions? I mean, it seems so self-evident
20 until you see things in their initial forms that
21 are quite bad. And if you actually give it to a
22 population that's not been working on it for the

1 last three years, they can't interpret the
2 instructions, and that's when it has to be
3 modified. So that's the kind of information we
4 look for.

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

13 DR. THROCKMORTON: Thanks, Sharon.

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

18 (Whereupon, a recess was taken.)

19 **Open Public Hearing**

20 DR. LURIE: Okay, everybody. It's time to
21 start the open public session, and this is the
22 point where we at FDA and the other sponsoring

1 agencies get a chance to hear from you. So we're
2 really looking forward to this part. We look
3 forward to a diversity of opinion.

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

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

22 So on my list, Leo Beletsky is first, and

1 he's a lawyer from Northeastern. So, Leo.

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

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

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

19 Second, naloxone's prescription status is a
20 regulatory bottleneck. This drug should be
21 available over-the-counter, but its purchase could
22 be predicated on computer-assisted training at the

1 point of sale under, for example, the safe use OTC
2 program, which we just discussed.

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

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

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

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

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

20 Thank you.

21 DR. LURIE: Okay. Next.

22 MS. BELL: My name is Alice Bell. I've run

1 the overdose prevention project in Pittsburgh,
2 Pennsylvania since its beginning 10 years ago.
3 Since 2005, close to 800 people have received
4 naloxone through our syringe exchange. We've
5 documented 621 successful rescues, and other
6 speakers today echo my own experience hearing
7 hundreds of reports from people who have used
8 naloxone to save a life or had their own life
9 saved.

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

15 Two HIV clinics, a free clinic, and a
16 traditional family practice are adopting this
17 protocol. Two methadone programs offer naloxone
18 prescriptions. One hospital emergency department
19 plans to offer take home naloxone to patients at
20 risk. One community pharmacy encourages physicians
21 to prescribe naloxone when opioids are prescribed
22 and provides training on opioid safety and naloxone

1 administration to patients.

2 But these remain small-scale efforts in the
3 face of burgeoning deaths. And this progress is
4 already being reversed. This week the nurse at one
5 clinic told me they can't get naloxone anywhere in
6 the U.S. There's a national shortage. At the
7 syringe exchange, facing multifold increases in
8 price, I imagine a face I will look at when I have
9 to say, "We don't have enough naloxone for you. We
10 can't afford enough for everyone who needs it."

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

21 I come here today to speak for them.
22 Surely, in this room, we have the expertise,

1 practical experience, regulatory and administrative
2 power to make this life-saving medication quickly
3 accessible to those in desperate need.

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

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

21 When our OD program started in '96, CRA was
22 paying less than \$2 for a 10 cc vial of naloxone.

1 Competition was the only thing keeping the price of
2 this life-saving medicine low. Today, there is
3 only one manufacturer of naloxone, and the price
4 has increased eight to tenfold. What was less than
5 \$2 in the last '90s now lists for \$35. OD
6 prevention efforts will at best be greatly
7 curtailed because of this high price.

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

17 Thank you.

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

1 naloxone needs to be removed.

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

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

15 In 2011, North Carolina Harm Reduction
16 Coalition trained over 3,000 people, mostly
17 incarcerated people and people at drug detox
18 centers, to recognize and prevent drug overdoses.
19 Whenever I do a training, half the room will raise
20 their hands saying they've personally witnessed a
21 drug overdose or know someone who has lost their
22 life to a drug overdose.

1 I hear lots of stories such as Stan. Stan
2 lost his friend Will who was using "oxy" to manage
3 chronic pain. Will restarted his use after a brief
4 stay in jail and drug detox due to his inability to
5 manage his chronic pain. Will didn't know that you
6 could lose your tolerance to drugs when you have
7 not used for a while. When he got out of detox, he
8 took his regular dose of "oxy" and overdosed. Stan
9 was present and not able to reverse the overdose
10 because he was afraid to call 911 due to fear of
11 arrest and because he did not have access to
12 prescription naloxone. Stan watched his friend
13 die.

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

18 In North Carolina, our program does not have
19 access to a costly prescriber who can issue
20 prescriptions whenever we do trainings. This
21 roadblock has made us unable to provide naloxone to
22 the majority of the people we train.

1 Naloxone is a life-saving drug and the most
2 effective tool in stopping drug overdose deaths.
3 Without easy over-the-counter use to access
4 naloxone, we're going to see many, many more people
5 die.

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

10 This here is a picture of my three sons. My
11 oldest son Danny is in the middle with his arms
12 around his brothers. Danny died five years ago
13 from an accidental heroin overdose, and he was only
14 20 years old. Words cannot describe the pain or
15 the hole that has been left in our family without
16 him.

17 His drug use began at the age of 16 with
18 marijuana and quickly progressed to Vicodin and
19 oxycodone. By the age of 19, he was using heroin
20 only because it was cheaper. He battled his
21 addiction for three and a half years, and as his
22 family, we did everything we could to try and stop

1 it, including expensive out-of-state rehabs and
2 professional interventions.

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

9 I was afraid for him, and I knew that this
10 was a very high-risk time period for him. But I
11 didn't know what to do. With eight months of
12 sobriety under his belt and only two weeks left on
13 this tether, Danny confided in me that he was
14 beginning to relapse mentally. He was terrified.
15 "I don't want to die, Mom. I need treatment."
16 Danny was white knuckling it, as they say in the
17 program.

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

22 "No, Mom. It's okay. I love you."

1 Those were his last words to me. Danny
2 left, and he went and he passed his drug test.
3 Then he went into Detroit to buy heroin, and he
4 used with two other using friends in a local
5 grocery store restroom. And when things went
6 wrong, his friends ran, and they did not call 911.
7 My son died alone on a bathroom floor. And on the
8 other side of that door was a store full of people,
9 a pharmacy, and a major hospital less than a mile
10 away.

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

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

22 MS. LYNCH: My name is Pam Lynch, and for 13

1 years, I have worked advocating for naloxone
2 distribution and programming starting with Dan Bigg
3 in Chicago, since in New York, New Jersey and
4 Michigan.

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

16 Nick G. is an 18-year-old that I met at the
17 drug treatment facility where I work, from Midland,
18 Michigan, who has buried five friends in the last
19 two years from overdose, the most recently of which
20 was March 20th. Nick himself has overdosed three
21 times and continues to medicate his emotions with
22 substances. Nick doesn't have much hope. No

1 amount of jail time will change Nick's investment
2 in life or death. Naloxone can buy Nick and the
3 Greek grandmother who loves him another chance
4 until someday he may care enough about living.

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

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

22 Of one thing I'm confident, if we leave here

1 today, if it was your child, mother, brother,
2 sister, you want naloxone in the house, whether by
3 needle or intranasal device. Ethical? I don't
4 think so.

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

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

9 (Laughter.)

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

14 Please start.

15 DR. DASGUPTA: Good afternoon. My name is
16 Nab Dasgupta, and I'm a pharmacoepidemiologist at
17 UNC and cofounder of Project Lazarus in North
18 Carolina. We've heard reference to the current
19 naloxone shortage. The main manufacturer of
20 naloxone in the U.S., Hospira, has been unreliable
21 and unable to even tell the public when naloxone
22 will be regularly available in the United States

1 again.

2 On at least two occasions in the last
3 15 years or so, the agency has allowed importation
4 of naloxone from foreign countries. The
5 irresponsible monopoly in the naloxone market is
6 contributing to preventable overdose deaths. Some
7 of the overdose prevention programs in this room
8 are about to run out of or already have run out of
9 naloxone. For what other disease condition would
10 we allow the supply of the antidote to lapse in the
11 middle of the epidemic that we heard about this
12 morning?

13 FDA should be encouraged to take more
14 aggressive action to address the shortage. To that
15 end, we have compiled a list of over 50 naloxone
16 manufacturers worldwide, including major U.S.
17 companies that sell naloxone in Western Europe for
18 less than 50 cents a vial, but not in the United
19 States, where it goes for \$9, \$10 for the generic
20 intramuscular, and it's approaching \$20 for the
21 intranasal. By comparison, the street price for a
22 milligram of oxycodone is 80 cents.

1 While costs are not usually the agency's
2 focus, there is precedent for federal agencies to
3 coordinate the supply and stock of critical
4 medications, notably antidotes for nerve agents and
5 influenza vaccine.

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

15 Further, the public health agencies that
16 have had success in reversing overdoses have not
17 been recognized as stakeholders to contribute to
18 long-acting opioid REMS. Today's meeting
19 represents a coalescing of the political will and
20 scientific gravitas that has been lacking. Now
21 it's time to have better representation from civil
22 society as well.

1 MR. RAYMOND: Whitney Englander had to step
2 out. I'm Daniel Raymond. She asked me to present
3 her statement for her. She's the government
4 relations manager of the Harm Reduction Coalition
5 and will submit her full statement to the record.
6 But she wanted to be very clear that she would not
7 be here at all if not for the fact that somebody
8 had been able to revive her with naloxone eight
9 years ago.

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

18 And we are grateful. However, we also need
19 more. I think that you hear in our voices the
20 sense of urgency around this epidemic. Just on
21 Monday, I lost a friend of mine to overdose. Many
22 of us have lost friends, family, loved ones, and

1 we're looking to the federal government to share
2 our sense of urgency because we've all thought,
3 what more can we do, what else can we do.

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

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

19 Thank you.

20 MS. DUNCAN: My name is Marianna Kate
21 Duncan. In September 2009, we lost our only child,
22 Nicholas, to an accidental heroin overdose. He was

1 25 years old. Despite Nick's struggles with
2 alcohol and drug use, he established and maintained
3 a productive role in society. For the last five
4 years of his life, Nick was a teaching assistant
5 with preschool autistic children. He was seriously
6 conscientious about his work, rarely missed a day,
7 and he was well loved by the students and well
8 respected by the staff.

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

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

20 At the time of his death, he was surrounded
21 by friends that were not using heroin and had no
22 idea how to deal with an overdose. By the time

1 they recognized he was having respiratory distress
2 and could not be resuscitated, they called 911.
3 Unfortunately, the rescue came too late. Nick
4 suffered brain death and was removed from life
5 support four days later.

6 Nick did not have to die from an overdose.
7 Had these friends been provided with information
8 about overdose prevention, recognition and
9 treatment, or had they had access to naloxone, Nick
10 would still be with us today.

11 It is my hope that in the future, other
12 parents and anyone that has association with a
13 heroin user can gain easy access to this crucial
14 information and whatever might be available to them
15 in recognition and treatment of overdose.

16 In our case, it is too late. Our future is
17 forever changed. This does not have to be the sad
18 reality for everyone.

19 DR. JONES: I am Steve Jones, a retired
20 staff member of the Centers for Disease Control and
21 Prevention. I want to speak today about the nearly
22 unique status of Italy, where naloxone is not a

1 prescription medication. Some copies of this flier
2 summarizing the status of naloxone in Italy and
3 including pictures of the packages of the
4 medication have been distributed. See me, if you
5 didn't get a copy, after the talk.

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

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

21 We have made some effort so far to find more
22 information about the distribution and any problems

1 associated with this status. So far, we have
2 anecdotal reports of no problems related to the
3 non-prescription status of naloxone. We are
4 planning to ask the Italian equivalent of the FDA
5 for data on naloxone distribution and any adverse
6 events.

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

10 Thank you.

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

19 In this extremely conservative model, only
20 three lives would be saved for every 2,000 people
21 who receive naloxone, resulting in an incremental
22 cost of \$400 per quality adjusted life year gained

1 similar to checking blood pressure to screen for
2 hypertension. Maximizing the price of naloxone
3 under current circumstances would increase that to
4 \$900.

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

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

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

20 Thank you.

21 MR. HENEGHAN: I'm Chris Heneghan. I work
22 as the director of the Windham Harm Reduction

1 Coalition. My agency operates a syringe exchange
2 program in a rural county in northeast Connecticut.

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

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

16 The American Heart Association reports that
17 only 21 percent of Americans feel confident they
18 could perform CPR during an emergency. Even if an
19 individual on site during an opioid overdose is
20 confident with their ability to perform CPR,
21 rescuer fatigue can occur in as quickly as two
22 minutes or five breath cycles.

1 Research shows in all cases of opioid
2 overdose, it makes intuitive sense to reduce the
3 time it takes to administer naloxone by getting it
4 into the hands of those best positioned to respond
5 rapidly. Naloxone provides a 30- to 90-minute
6 window of opportunity to call 911 and get someone
7 to the emergency room. This action can sometimes
8 make the difference for getting someone into
9 treatment and getting their lives back on track.

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

17 My agency cannot afford to employ a
18 prescriber to provide naloxone to our clients. If
19 naloxone is relabeled as a non-prescription
20 product, we can afford to purchase it and train our
21 outreach workers to distribute it through our
22 syringe exchange program.

1 This cost-effective reduction in mortality
2 of the population most at risk cannot be achieved
3 without your support. Please ensure the FDA is a
4 leader in preventing further deaths, in fighting
5 this epidemic by facilitating rapid approval for
6 the relabeling of naloxone as a non-prescription
7 product.

8 Thank you.

9 DR. LURIE: Great. Thank you, everybody.

10 Dr. Dasgupta, I'll take that list, if you
11 don't mind. Thank you very much.

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

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

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

20 MS. RALSTON: My name is Megan Ralston. I
21 live in Los Angeles. I work for the Drug Policy
22 Alliance. I have written extensively and have been

1 fortunate to have been quoted and interviewed
2 extensively about the urgent need for expanded
3 access to naloxone and other overdose fatality
4 prevention programs.

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

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

21 The majority of the parents and surviving
22 spouses and family members I speak with aren't just

1 dealing with the trauma of losing their loved one
2 but dealing with the added grief of discovering the
3 existence of naloxone only after the death of their
4 loved one.

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

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

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

22 MS. ODENHAL: My name is Marilee Odenhal

1 from Freeport, Illinois. I am here on behalf of my
2 son and my family.

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

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

15 Ian died of overdose three days after his
16 28th birthday. He died four days before he was to
17 be baptized at his church. He died too young.

18 The FDA considers matters in scientific
19 terms. Well, scientific fact is that naloxone
20 could have saved Ian's life. I live with the
21 certain knowledge that had my son suffered from
22 cancer, doctors would have exhausted their skills

1 and tried every possible drug to save his life.
2 But no doctor ever mentioned naloxone to me. I
3 never even heard the word until four months after
4 Ian's death, and that from harm reductionist.

5 Why naloxone hasn't been touted on every
6 media outlet and shouted from every rooftop, I will
7 never understand. It makes me livid. I have the
8 rest of my life to live without Ian, and I cannot
9 describe that kind of loss to you. Most of us have
10 children, and none of us thinks they will die of
11 overdose. But it happens every single day to
12 families just like yours and mine.

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

16 MS. PETERSON: Good afternoon. My name is
17 Joanne Peterson. I'm from the organization Learn
18 to Cope in Massachusetts. Today, we have seven
19 chapters across the state and nearly 3,000 parents
20 registered to our website, all parents, siblings,
21 grandparents with sons and daughters that are
22 addicted to prescription opiates and/or heroin.

1 I feel very fortunate today. My son is
2 alive and well and in recovery, and I also feel
3 very fortunate to be from the state of
4 Massachusetts where we do have this pilot program.

5 We see people, parents and grandparents,
6 save their kids' lives. Back in November, we had
7 14 parents trained through the Massachusetts
8 Department of Public Health's Bureau of Substance
9 Abuse pilot for Narcan. And we started
10 distributing it at every chapter every week at
11 every meeting. We started distributing it in
12 December, and in two weeks, we had a mom save a
13 daughter and a father save a son.

14 Back in 2007, long before we had that, we
15 lost nine kids in seven weeks. And that's when
16 Narcan started to become available, and ever since
17 then, we've been very lucky to have access to it.
18 And my heart goes out to the families that do not
19 have access to it that have kids or loved ones that
20 are addicted to these terrible drugs. Nobody
21 should suffer the pain of losing a child or even
22 witness an overdose--its trauma, its pain-- and

1 it's something that they will live with for the
2 rest of their lives.

3 I only hope that Narcan will be available
4 around the country. I hope that it will be easily
5 administered in an easier to obtain container
6 that's easily sprayed. I can't imagine any reason
7 why we wouldn't have it, especially with this
8 epidemic and the way these opioids are just flooded
9 all over the streets and in homes. It's a must.

10 MS. MCQUIE: Hi, my name is Hillary McQuie.
11 I'm the California director of the Harm Reduction
12 Coalition. The Harm Reduction Coalition runs two
13 community-based overdose prevention programs, one
14 in California, the DOPE Project that you heard
15 about earlier, and one in New York.

16 But today I want to talk about the issues
17 that we come across doing technical assistance and
18 networking with overdose prevention programs
19 throughout the country and the kind of shortages
20 and access problems that people are
21 having: increasing prices, which you've heard
22 about already; supply shortages which are extreme;

1 the lack of overdose prevention projects in most
2 regions of the country; and finally, the lack of
3 funding for existing programs.

4 The programs that you heard about today,
5 such as the one in Massachusetts, the extension of
6 those is rare. Usually, the programs are quite
7 small. Often, there's no dedicated staff. Often,
8 there's no paid staff. It's just another activity
9 that a syringe exchange program adds on, and they
10 have no dedicated funding.

11 There's very few of those 188 programs that
12 have any funding whatsoever, and there is no real
13 funding stream for this kind of work. It doesn't
14 seem to fit anywhere. Nobody wants it really to
15 fit somewhere.

16 So I was very happy to see SAMHSA here today
17 because I completely agree that there needs to be
18 integration between treatment and overdose
19 prevention and harm reduction. When people are
20 leaving treatment, they should be given referrals
21 for harm reduction. And when people are coming to
22 harm reduction, they should be given referrals for

1 treatment. And not just referrals like here's a
2 list of places; referrals like here's some slots
3 that we have, some program that funds these kind of
4 linkages to make them more formal, because just
5 talking about it without funding it really doesn't
6 do the trick.

7 I think what the FDA can do is support this
8 in terms of your negotiations with other federal
9 agencies and, again, approve the foreign
10 manufacturers and perhaps educate physicians that
11 they can prescribe now without any problems.

12 DR. DOMBROWSKI: Good afternoon. My name is
13 John Dombrowski. I'm a physician. I'm an
14 anesthesiologist specializing in pain medicine at
15 the Washington Pain Center. I'm the chair of the
16 American Society of Anesthesiologists'
17 communications committee. I'm also a member of the
18 committee on pain medicine.

19 Now, opioid-related deaths have reached
20 epidemic proportions, and the means of avoiding
21 deaths related to respiratory depression need to be
22 improved on, on multiple fronts. Prior to

1 prescribing naloxone, it's been imperative that
2 physicians educate patients, as well as patients'
3 friends or family members about naloxone.

4 Education should include how to recognize
5 opioid overdose, how to administer naloxone, the
6 importance of calling 911 immediately after
7 administering naloxone, how to administer rescue
8 breathing, and information on the shelf life of
9 naloxone.

10 We recognize that the side effects of
11 naloxone, such as negative pressure, pulmonary
12 edema, or extreme high blood pressure can be
13 severe. However, naloxone is a patient safety
14 tool, and these side effects are treatable and
15 preferable to an opioid-related death.

16 For this reason, the American Society of
17 Anesthesiologists sees the importance in patient
18 access to naloxone. The ASA, however, has a
19 serious concern about making naloxone available
20 over-the-counter. A physician who evaluates a
21 patient, determines opiates are medically
22 indicated, and counsels and educates the patients

1 about opiates should also be involved in counseling
2 and education, educating the patients about
3 naloxone and prescribing the medication.

4 Naloxone is not the only step in combating
5 the misuse and abuse of these prescription drugs.
6 However, it is an important safety tool for those
7 taking opiates.

8 We thank the FDA for considering whether
9 naloxone should be made more accessible to patients
10 outside conventional medical settings.

11 MS. WHEELER: Hi. My name is Eliza Wheeler.
12 I run the DOPE Project in San Francisco. We've
13 been distributing naloxone to drug users since 2003
14 and have had over 600 reports of lives saved.

15 I've provided access to naloxone for over
16 10 years in both San Francisco and Massachusetts.
17 I have literally heard hundreds of stories of
18 people using naloxone to save someone's life. I
19 myself have used it four times, and I'm here to
20 tell you that it's not rocket science and that
21 those four people are still alive today.

22 Using naloxone during an overdose is easy,

1 and it's also an intensely powerful experience.
2 Many people say that it makes them feel different,
3 like a good person to have been able to save a
4 friend's life. Sometimes the act of saving someone
5 is actually what's life changing for people.

6 I've heard parents say that they let out a
7 sigh of relief as soon as they got that naloxone
8 kit into their hands and that it gave them some
9 peace to know that if their child overdosed and
10 they happened to be there, they would know what to
11 do.

12 For the same amount of time that I've been
13 distributing naloxone, I've been hearing all of the
14 criticisms and concerns about what we do. What's
15 happening here today is clearly a shift in that
16 which I am grateful for, and thank you. But,
17 frankly, I'm also really sick of hearing about how
18 there's not evidence that this can work and that
19 people can't recognize an overdose, they can't use
20 naloxone, they can't put it together, they don't
21 know how to use a needle, it might not be safe, it
22 might increase or encourage their drug use, it

1 sends the wrong message, they won't call 911. It
2 gets a little tiresome to keep having to hear this
3 when we see the evidence in front of us every day.

4 So I encourage you to move forward in any
5 way you can to make this easier, and I'm here for
6 Brian, Ariel, Billy, Tim, and Paul, who didn't make
7 it.

8 DR. LURIE: Thank you, everybody.

9 I think we can get everybody who remains on
10 the last panel. Roxanne Soucier, Sharon Stancliff,
11 Jo Sotheran, Azzi Momen, Steve Lankenau, Thomas
12 McNally, and Gary Langis.

13 MS. SOUCIER: Hello, my name is Roxanne
14 Soucier, and I'm a consultant with the Open Society
15 Foundations. We support naloxone programs in
16 Russia, Vietnam, Thailand, Georgia, China, and
17 Central Asia. Though far away from this room, the
18 FDA's decisions about naloxone have impacts in
19 these settings, too.

20 In all of the places we work, drug users
21 report that seeking emergency services is often
22 unrealistic. People live in remote and mountainous

1 areas. Ambulances charge fees. They refuse to go
2 to drug hot spots, or if they do, police come with
3 them. In some countries, registration by police as
4 a drug user means years in forced labor camps.

5 Because of these factors, to insist that
6 naloxone must only be available through emergency
7 services and hospitals is to insist that people
8 die. Instead, we support programs that train
9 laypeople in naloxone administration and make the
10 medicine available. In most of these countries,
11 naloxone is less than \$2 a dose.

12 Drug users witness overdoses frequently, so
13 are well positioned to respond. In one city in
14 China, 90 percent of drug users reported witnessing
15 an overdose. Through the programs we support, more
16 than 680 reversals have been documented to date.
17 In China, drug user groups have formed overdose
18 rescue squads where trained responders with
19 naloxone arrived quickly on motorbikes.

20 I would like to close with a quote from one
21 of these participants. "I had another overdose
22 earlier this year, and again my friends called the

1 overdose rescue team for help. They didn't blame
2 me but asked me with great care what I felt. It
3 was easy to talk to them. They introduced naloxone
4 to me and shared their knowledge on drug abuse
5 prevention and treatment. Now I take part in their
6 harm reduction activities. Now that I know what
7 they do, I trust them.

8 "I called the outreach workers right away
9 when my companions had an overdose. I saw how they
10 used naloxone to save my friends and its magic
11 effect. In the past, we helped each other using
12 stupid methods like kicking and slapping.
13 Sometimes a person wouldn't recover and would be
14 lost forever. Now I know these actions are
15 dangerous.

16 "As addicts, we don't trust others easily.
17 We are afraid to be arrested and sent to the drug
18 detention center if others report us to the
19 authorities. But the outreach workers keep our
20 secrets and help us from the goodness of their
21 hearts."

22 DR. STANCLIFF: I'm Sharon Stancliff, the

1 medical director of the Harm Reduction Coalition,
2 and I oversee the SCOOP Project, the sister to the
3 DOPE Project, in New York.

4 This SCOOP Project, we have dispensed,
5 prescriber to person, something over 8,000 naloxone
6 kits in the past six or seven years. Our biggest
7 barrier in New York is about having a licensed
8 person on site at a needle exchange offering this.
9 Right now, two prescribers cover eight syringe
10 exchanges with multiple sites. So we're there a
11 fraction of the time that people are seeing that
12 the clients are there.

13 Syringe exchange, I can give them all the
14 needles they need to prevent HIV, but I can't
15 legally hand them this life-saving vial unless
16 you're right here. It just doesn't make a lot of
17 sense.

18 Thinking of the vial, I'm talking about
19 over-the-counter -- and I don't want us to forget
20 about the intramuscular form. This is not so
21 scary. We've had a lot of success using this.

22 Two things. New York City, we offer a

1 choice of the intranasal or the intramuscular. We
2 have a lot of illicit drug users that are like,
3 yeah, that's fine, that's what I want. But I also
4 see people that are afraid of needles initially say
5 this just looks really simple, and somebody can
6 figure it out just by looking at it. I think I
7 want the intramuscular one.

8 We've also helped something over 60
9 agencies -- whether in New York, we worked a little
10 in Vietnam with them -- in setting up programs.
11 And outside of New York City and New York State,
12 only the intramuscular is available.

13 We're doing it with Daytop Village, a
14 therapeutic community. We're giving this out in
15 abstinence-based programs. So I think in this
16 process, we need not to forget that the
17 intramuscular has already been through a lot of
18 steps, and we need to do that maybe while we're
19 working on the other stuff.

20 Thank you.

21 MS. SOTHERAN: Hello. I'm Jo Sotheran. I'm
22 a long-term board member of the National Alliance

1 for Methadone Advocates, sometimes known as NAMA
2 Recovery. We're a recovery community organization
3 dominated by the methadone patients who exist
4 within the silence and stigma of the addiction
5 treatment clinic system.

6 The country's 300,000 patients have a unique
7 perspective on naloxone because both naloxone and
8 methadone are life-saving medications. A lot of
9 patients say that methadone treatment just plain
10 saved their lives. So we know that the very
11 availability of a pharmacological intervention
12 matters.

13 Methadone patients also know a lot about
14 overdoses because they can occur before, during,
15 and after treatment. Usually, the period before
16 treatment is one of out of control drug use with a
17 lot of risks. Although being in methadone
18 treatment decreases overdose risk very sharply,
19 some deaths do occur even so, usually in the early
20 induction period when the appropriate dosing level
21 is being established and there is still common
22 polysubstance use.

1 Finally, patients who leave treatment -- and
2 there are many of them -- often relapse rather
3 quickly into drug use and go back to the risks.
4 Many patients have seen overdoses, some have lost
5 partners and friends, and some have survived
6 overdoses themselves. As a result, they understand
7 the danger of overdoses, and they often want to
8 help others like themselves.

9 Fatal overdoses among people both in and out
10 of treatment could be reduced if naloxone were
11 available in settings that are connected to the
12 community of people who can actually most
13 effectively use it. Methadone programs can be an
14 excellent platform for distributing naloxone just
15 as for many other health interventions. And the
16 patients and those close to them could use it in
17 their own communities.

18 But for reasons that Sharon alluded to,
19 mostly including the limited clinic workforce and
20 funding, despite the fact that many programs want
21 to have this, a major barrier is the prescribing
22 requirement. If that could be reduced, many more

1 could have access to yet a second life-saving
2 medication. And we would ask any help you can give
3 in helping us with this.

4 Thank you very much.

5 MR. MCNALLY: My name is Thomas McNally, and
6 I'm a board member and volunteer of the Windham
7 Harm Reduction Coalition in Windham, Connecticut.
8 I come before you today to speak for my friends who
9 cannot be here.

10 My friend Timmy, who is dual-diagnosed with
11 mental illness and drug dependence, had been in and
12 out of treatment in mental wards often. Tim came
13 out of his last away time and overdosed on heroin
14 injection, injecting the amount he was using prior
15 to being in treatment in a treatment facility. Tim
16 was found dead in a restroom. I have known Tim for
17 years, and I will miss him.

18 Jason is a young man who is an opiate
19 dependent. Traveling to the capital city with his
20 girlfriend, Jason got a much stronger bag of heroin
21 than he was getting locally. And after injecting
22 his usual dose, he overdosed and became

1 unresponsive. Thankfully, his girlfriend had
2 naloxone with her and was able to administer the
3 naloxone until assistance arrived. Jason related
4 this episode to me during a visit to our agency.

5 My last story is about a young man, Chris,
6 who died of an overdose of methadone. He was found
7 dead in his room after working during the day. We
8 don't know how this happened, and we hope somebody
9 was with him at the time. Unfortunately, Chris did
10 not know about the problems with methadone and was
11 not aware of naloxone. Chris was my grandson.

12 Epinephrine pens are available to persons
13 with insect allergies. They save lives. Naloxone
14 also saves lives, and the death of just one person
15 because of the lack of an antidote has an impact on
16 many others, including the person's family, friends
17 and community.

18 I ask that you allow naloxone to be made
19 available to those whose very lives depend upon it
20 and having naloxone easily accessible without
21 creating additional obstacles to our
22 opiate-dependent citizens.

1 Thank you.

2 MS. MOMEN: Hi. I'm Azzi Momen from the
3 Open Society Foundation, where we support
4 community-based naloxone distribution worldwide.
5 Internationally, naloxone distribution is
6 increasing thanks to low-cost naloxone and donors
7 like the Global Fund. I'm pleased to note that the
8 U.S. government through PEPFAR has also agreed to
9 support these programs. And in countries like
10 Kyrgyzstan and Tajikistan, USAID has provided
11 ongoing technical support to NGOs and medical
12 professionals on implementing naloxone programs.

13 Because naloxone is something that drug
14 users want access to, these programs attract drug
15 users into existing health services. They
16 strengthen the bond between clients and healthcare
17 providers and increase the uptake of other critical
18 healthcare interventions like needle exchange and
19 HIV testing and treatment. In Russia, for example,
20 the NGO Tomsk Anti-AIDS attracted 900 new clients
21 when they started the naloxone program. That's
22 representing an increase of 60 percent.

1 The bottom line, naloxone saves lives,
2 especially when it's given to those who are most
3 likely to witness an overdose and respond first.
4 And that means other drug users, their families and
5 friends.

6 These programs give people like my colleague
7 Twan (ph) from Vietnam a sense of pride and purpose
8 to life. Since Twan cannot be here, I'd like to
9 read his testimonial to you now.

10 "I was also a drug user, and I witnessed
11 many painful overdose deaths. My best friend died
12 of an overdose right in my arms. That was an
13 unforgettable moment, and it helped me want to live
14 and start over. I've stopped using drugs. And I'm
15 currently the leader of a peer support group for
16 drug users in Ho Chi Minh City, implementing a
17 naloxone response program.

18 "Being able to save lives is the most
19 meaningful thing we have ever done in our lives.
20 And the residents where we work have seen us in a
21 different light, knowing the good things that we're
22 doing.

1 "I want to pass on something that a drug
2 user said when he was revived. He said to me,
3 'Maybe I won't be able to quit using drugs after
4 this, but now I know that there's someone who cares
5 about me. And that will be my motivation to
6 live.'"

7 Thank you.

8 DR. LANKENAU: Good afternoon. My name is
9 Steve Lankenau. I'm an associate professor in the
10 School of Public Health at Drexel University and
11 also principal investigator who conducts research
12 on substance misuse.

13 My comments, which are in support of
14 expanding access to naloxone, are based on current
15 evaluations of naloxone prescription programs
16 offered by community-based organizations in Los
17 Angeles and Philadelphia. The L.A. study is
18 supported by a grant from NIDA.

19 Programs in both cities target injection
20 drug users. Our studies which recruited 150 IDUs
21 across both sites for in-depth qualitative
22 interviews compared to two groups of IDUs, those

1 who had received naloxone prescriptions and those
2 who had never received naloxone prescriptions.

3 In both L.A. and Philadelphia, IDUs reported
4 successfully administering naloxone to reverse
5 recently witnessed overdoses. Reversals often
6 occurred in public places by both housed and
7 homeless IDUs.

8 Despite these successes, IDUs frequently did
9 not have naloxone with them when they witnessed an
10 overdose. Two typical reasons reported were
11 naloxone was confiscated by police, and IDUs did
12 not feel comfortable carrying naloxone in the event
13 of being stopped by police. Similarly, some
14 untrained IDUs reported discomfort with the idea of
15 carrying naloxone on them as their reason for not
16 gaining a prescription.

17 While naloxone is not a controlled
18 substance, changing its status to over-the-counter
19 could reduce concerns among IDUs, particularly
20 those who are homeless or who have ongoing criminal
21 justice involvement, about carrying it with them
22 and lessening the chances of naloxone being viewed

1 suspiciously or confiscated by police. These
2 changes could increase the likelihood of IDUs
3 having naloxone on them when overdoses occur.

4 Furthermore, during our research, it was
5 much easier locating IDUs who had never received
6 doses of naloxone compared to those who had.
7 Expanding access and availability of naloxone may
8 reverse this dynamic, which in turn may help reduce
9 deaths due to opioid overdose in communities across
10 the country.

11 Lastly, expanding federal funding for
12 research on naloxone prescription programs is
13 necessary so that policy changes are based upon
14 well-designed scientific studies.

15 Thank you.

16 MR. LANGIS: Gary Langis. I've been working
17 on several overdose prevention projects in
18 Massachusetts over the years, and I'm here to talk
19 about Josh.

20 I was on an outreach route one night -- one
21 afternoon, and I came across a house. And people
22 called me into the house because there was a

1 gentleman overdosing. I walked into the house, and
2 I met Josh. And Josh was ash gray, blue, not
3 responsive, and I pulled him to the floor, and I
4 started to do rescue breathing. I didn't know
5 Josh, didn't know if he was going to use the next
6 day. I had no clue who he was.

7 I went through the rescue breathing,
8 administered Narcan, brought him back, and he
9 didn't call 911. He didn't want to call 911.
10 Well, I stayed in touch with the people in the
11 house all during the day for the next six hours,
12 and I didn't see Josh for a couple of months.

13 He came walking into my office one day, and
14 he looked really healthy and wonderful. And he
15 said -- I said, "How you doing?" I said, "Jeez,
16 you look great."

17 He said, "Yeah. You know, the next day I
18 went into treatment after my overdose, and I'm
19 doing volunteer work over at Cambridge Cares About
20 AIDS."

21 This is two months later, and I kept track
22 with him. And Josh ended up working at the

1 exchange, training people in Narcan, testifying at
2 the statehouse at our celebration of our 500th
3 reversal.

4 We don't know what the outcome is going to
5 be. I don't know if he's going to use. I don't
6 know if he's going to get into treatment. But you
7 know what? It's a life. Every life is precious,
8 and I have to remember that.

9 Listening to Susan and Marilee and Marianna,
10 I know what it's like to lose a child. And the
11 first thing I thought when I lost my child -- he
12 took his life -- was I never want another parent to
13 go through this. And I know. I've talked to many
14 parents, and that's what they say. And I didn't
15 want Josh's parents to go through this.

16 Thank you.

17 DR. LURIE: Thank you everybody for some
18 very moving testimony about, really -- it puts a
19 human face on the problem we're dealing with today.

20 (Applause.)

21 DR. LURIE: I also want to particularly
22 thank this device here in the middle, which I'm

1 going to ask to borrow to limit my children's
2 videogame time from now on because it seems rather
3 effective.

4 We'll get back at 4:00 exactly, if that's
5 okay. And then we'll get into the very final
6 session, so 4:00, please.

7 It's been pointed out to me, sorry. I
8 thought we had a break scheduled here, so let me
9 retract. Sorry about that.

10 Let's bring Greg Zimet up instead. Sorry.
11 I misread the schedule.

12 Greg, can you come up?

13 (Pause.)

14 **Panel 4- Moderator Peter Lurie**

15 DR. LURIE: Sorry for the confusion there,
16 my mistake.

17 So in trying to put together this
18 meeting -- and sorry for the confusion about there
19 not actually being a break. In trying to put this
20 meeting together, one of the things we thought
21 about was the concern that the availability of
22 naloxone in some greater fashion might have a

1 disinhibitory effect upon people's behavior in
2 terms of increasing drug use. And this is
3 something we've heard before in a number of
4 different settings. We've heard it in needle
5 exchange. We've heard it with contraceptive pills.
6 We've heard it with Plan B. We've heard it in a
7 number of different areas.

8 And so we thought that it would be helpful
9 to bring along somebody who has actually looked on
10 the data on this question, not with respect to
11 naloxone, of course. But I searched the country,
12 and I came up with Greg Zimet, who is a clinical
13 psychologist in the department of pediatrics in
14 Indiana University School of Medicine.

15 He's interested in the application of social
16 science and biomedical approaches for prevention
17 and detection of sexually transmitted diseases.
18 And most of his research, or much of it, relates to
19 attitudes and behaviors related to STDs, and in
20 particular to HPV vaccination, the vaccine
21 Gardasil.

22 So he's going to go through that experience

1 and some other related experience as well. Thanks.

2 Greg.

3 **Presentation - Gregory Zimet**

4 DR. ZIMET: Thank you, Peter.

5 I'm very pleased to be here and hope that
6 you find this information relevant. I think you
7 will.

8 So briefly, what I'm going to cover here is
9 first to talk a little bit about the theory behind
10 disinhibition, or the worries about disinhibition
11 or risk compensation. And then I'm going to review
12 in some detail, but quickly, the application of
13 these issues to HPV vaccination. And then look at
14 the evidence for disinhibition or risk compensation
15 with respect to HPV vaccination; briefly talk about
16 other behaviors as well, and then end with some
17 recommendations, some summary and recommendations.

18 So when you look at the theory behind risk
19 compensation and disinhibition, the theory sort of
20 suggests that individuals have an inherent set
21 point that determines their willingness to take
22 risks. So that it follows then that interventions

1 that reduce risk will result in persons increasing
2 their risk-taking behaviors to maintain their set
3 point.

4 The theory -- and if you look at some of the
5 literature and how it's applied -- sort of implies
6 that there's this universal trait that applies to
7 all persons across all situations. And I'm going
8 to call that into question actually.

9 But first, with respect to HPV vaccination,
10 there have been two major issues that have been
11 discussed, largely covered in the media. And the
12 first is sexual disinhibition. And this is the
13 concern that HPV vaccination will be seen as
14 protection against sexually transmitted infections
15 in general, not just HPV, and that HPV vaccination
16 would somehow be interpreted as permission to
17 engage in unsafe sexual behaviors. And the result
18 of this, then the concern is that it would lead to
19 earlier initiation of sex, decreased use of
20 condoms, and perhaps an increase in the number of
21 sexual partners.

22 That's been where the major focus has been,

1 but there's been a little bit of discussion as well
2 that young women who get HPV vaccine years later
3 will feel protected against cervical cancer, and
4 therefore will not -- their participation in
5 cervical cancer screening, Pap testing, will
6 decrease.

7 So I think the first question I want to
8 quickly address, in terms of evidence, are parents
9 really concerned about this because you would think
10 with all of the exposure in the media that this
11 would be something on every parent's mind.

12 So across multiple research studies, what we
13 have found is that worries about sexual
14 disinhibition are sometimes associated with
15 opposition to HPV vaccination. And these are just
16 correlations, and we certainly find significant
17 statistical correlations. But a very different
18 question, and I think a relevant question, is: are
19 many parents actually really concerned about
20 disinhibition?

21 The fact is few parents express this
22 concern. When you look at research on reasons for

1 non-vaccination that are surveys of parents and
2 interviews with parents, the main kinds of reasons
3 brought up is that the physician or healthcare
4 provider didn't recommend vaccination, the parents
5 had worries about vaccine safety - unsubstantiated
6 I might add -- and concerns that the vaccine is too
7 new.

8 Here's just an example of one study. This
9 is out of British Columbia in Canada. This was a
10 survey of nearly 2,000 parents. In this study, as
11 you can see from the graph, about 65 percent of the
12 parents had their daughters receive the first dose
13 of vaccine, and about 35 percent or almost 700 of
14 the parents declined to have their daughters
15 vaccinated. This is unusually low for Canada,
16 actually. Most of the other provinces, it's much
17 higher.

18 But the parents who declined vaccination
19 were asked to indicate the reasons for the
20 decision. And here you see a breakdown of their
21 reasons. And they were allowed to endorse as many
22 reasons as they wanted to, which is why the

1 percentages add up to over 100.

2 So you can see that over 40 percent of the
3 parents indicated that they wanted to wait until
4 their daughter was older. So this isn't really
5 opposition to vaccination at all.

6 A little over 40 percent had safety
7 concerns. A little over 20 percent said they
8 didn't have enough information. Somewhat over
9 10 percent thought their daughters were not at
10 risk. Maybe 7 percent or so said the vaccine was
11 too new. And then less than 5 percent brought up
12 sexual disinhibition as a reason for non-
13 vaccination, which is about the same percentage
14 that brought up the belief that HPV vaccine was a
15 conspiracy of the pharmaceutical industry.

16 So is there actual evidence for
17 disinhibition after HPV vaccination? I'm going to
18 review a few articles. I have to start by saying
19 that this is a question that is almost impossible
20 to answer definitively, but we begin to get a sense
21 of it from these research studies.

22 This is a study that Nicole Liddon from the

1 CDC published earlier this year. It's a survey of
2 over 1200 women, 15 to 24 years of age. Nicole
3 found no association of vaccination with initiation
4 of sex or with receipt of sexual reproductive
5 healthcare. Sexually active women who had been
6 vaccinated reported actually more consistent condom
7 use than those who were not vaccinated. Findings
8 were limited in this case by the cross-sectional
9 design, again, which is the problem with all of
10 these studies. You can't randomize people to
11 receive vaccine or not receive vaccine.

12 In another study that I was a co-author on,
13 Tanya Mullins published earlier this year. This
14 was research with about 339 young women, 13 to
15 21 years of age, who were surveyed after the
16 receipt of the first vaccine dose.

17 Now, it was interesting when the media
18 reported on this because you got two different
19 perspectives. So about half of the stories said
20 that 24 percent of the young women perceived
21 themselves to be at less risk for STIs other than
22 HPV, and this was touted as a real concern. But to

1 my mind, the most important statistic here is that
2 nearly 100 percent endorsed the need to continue to
3 practice safe sex behaviors. And those who didn't
4 endorse that were actually less knowledgeable about
5 HPV vaccine and reported less mother-daughter
6 communication. So to my mind, the findings are
7 actually encouraging and actually suggest that what
8 we need is more communication.

9 Again, it's a cross-sectional study. It's
10 retrospective, so those are limitations. But it
11 begins to give us a picture that disinhibition,
12 risk compensation doesn't seem to be much of an
13 issue.

14 Two additional studies I was involved with,
15 one was published earlier this year, the other
16 hopefully will be accepted for publication soon.
17 We recruited 75 female adolescents from our urban
18 health clinics, 14 to 17 years of age. They
19 self-reported their HPV vaccination status. And in
20 the Stupiansky study, we compared that to medical
21 records as the gold standard for vaccination
22 status.

1 In the Cummings study, from a previous
2 study, we matched these 75 to 150 young women who
3 were recruited prior to HPV vaccine licensure and
4 compared them on a number of different measures.

5 So in terms of self-report versus medical
6 record, if you look on your left, you'll see these
7 are the young women who had been vaccinated
8 according to medical record. And what you see is
9 that about 45 percent didn't remember. So 30 out
10 of the 66 who were vaccinated said that they had
11 not received HPV vaccine. On the right side is the
12 eight young women who had been vaccinated, and all
13 of them accurately reported that they had not
14 received vaccine.

15 So I think the important point here is
16 nearly half of these girls who had been vaccinated
17 couldn't remember. So for them, to assume that any
18 disinhibition is possible for an event that they
19 couldn't remember seems silly.

20 This is the pre-vaccine to post-vaccine
21 comparison. This shows on the left the number of
22 sexual partners in the prior two months. And what

1 you see is that the post-vaccine group actually
2 reported fewer sexual partners. It was not
3 statistically different but certainly not more. On
4 the right side, you see the number of unprotected
5 sexual events in the previous two months, and this
6 means -- in our twisted lingo, what this means is
7 the post-vaccine group actually used condoms more
8 frequently than the pre-vaccine group. And this
9 was statistically significant, again, in the
10 opposite direction of the sexual disinhibition idea
11 or risk compensation idea. We also found no
12 differences in diagnosis of gonorrhea or chlamydia
13 between the two groups.

14 So with respect to Pap testing and the
15 concern that somehow vaccination will lead to
16 decreased Pap testing sometime in the future, we
17 have no evidence. And we won't have -- I don't
18 know if we'll ever have evidence, but we certainly
19 won't for quite a while. We probably will never
20 have adequate evidence because the guidelines for
21 Pap testing will keep evolving over the next 10 to
22 15 years as they've recently changed, actually.

1 What about other research on sexual
2 behavior? The empirical evidence is somewhat
3 mixed, but I think the important point here is from
4 a review study that involved mathematical modeling
5 that Steven Pinkerton from Wisconsin did.

6 What he found is that it's possible that
7 some risk compensation may occur with condom
8 promotion programs. But it generally does not
9 neutralize the beneficial effects of increased
10 condom use stimulated by the programs. And I think
11 this is a very important point to think about.

12 So which means ultimately the condom
13 promotion programs increase protection, and
14 therefore did not increase risk for infection from
15 STI or HIV. It actually decreased those risks.

16 There's also research on protective
17 equipment in childhood injuries, and this involved
18 slightly less than 400 children, 8 to 18. They had
19 an injury while participating in an activity that
20 could have involved the use of protective
21 equipment. And by protective equipment, I mean a
22 bicycle helmet or a wrist guard, something like

1 that. And they looked at users and nonusers of
2 protective equipment, and they found no evidence
3 that the use of protective equipment led to greater
4 risk taking behavior or greater severity of injury.

5 Other domains, this is risk compensation
6 area has been looked at with respect to a lot of
7 areas, not just health but actually many, many
8 different areas. And some of the questions are,
9 does requirement for seatbelt use lead to reckless
10 driving? Does the use of ski helmets reduce head
11 injuries? Does the use of bicycle helmets lead car
12 drivers to drive more closely to bicyclists? Which
13 may sound strange, but there is a study that seemed
14 to suggest that when drivers see a bicyclist with a
15 helmet, they'll drive closer to them. And then do
16 antilock brakes lead drivers to brake later?

17 So the research evidence overall is somewhat
18 mixed, but I think the problem is that research is
19 really, really difficult to carry out in ways that
20 you get very clear cut results.

21 So in summary, although concerns about
22 sexual disinhibition predict the opposition to

1 vaccination, few parents express such concerns.
2 Parents rarely mentioned decreased Pap testing as a
3 worry. There's no evidence for sexual
4 disinhibition after HPV vaccination, and there are
5 no studies yet on the effect on Pap testing.

6 Risk compensation, in summary, is clearly
7 not universal, and it's not inevitable. And it's
8 likely dependent on the prevention strategy that
9 one is looking at, whether it's vaccination,
10 wearing helmets, flossing, et cetera.

11 The target of the strategy, whether you're
12 talking about prevention of HPV, HIV, sports
13 injuries, individual characteristics, there are
14 going to be some individuals who are very
15 impulsive, and it may be that they're more prone to
16 risk compensation. And so you have to consider the
17 larger social context. Condom use, for instance,
18 occurs in the context of romantic relationships,
19 and it's often not individually determined.

20 And I think again -- I really want to
21 emphasize -- the increase in risk behavior -- and I
22 put risk behavior in quotes -- may not lead to

1 increases in adverse outcome; that a lot of these
2 areas of health promotion or injury prevention,
3 even if there is a certain degree of risk
4 compensation, it doesn't negate the positive
5 effects.

6 So I would say the question should never be
7 and should not be to vaccinate or not to vaccinate.
8 I think it's ethically questionable to withhold
9 vaccine or often other preventive measures because
10 of unproven fears about disinhibition and risk
11 compensation. Research is important. We want to
12 know when risk compensation may be more likely to
13 occur and with whom but not to withhold treatment
14 or prevention from those individuals.

15 Focus should be on how to deliver vaccine
16 most effectively and how to best communicate about
17 the benefits and possible risks associated with HPV
18 vaccination.

19 Thank you.

20 (Applause.)

21 DR. LURIE: I think that was a model of
22 clarity, so I'm going to assume that there aren't

1 any questions unless someone has a clarifying one.

2 (No response.)

3 **Panel Discussion**

4 DR. LURIE: And not seeing one, I think I'd
5 like to move on to the next group, which is our
6 panel discussion. And here in this, we will
7 consider a number of issues -- or we certainly hope
8 we do -- that go beyond some things that FDA has
9 concern or jurisdiction about. It's things that
10 the government more generally might be more
11 concerned about, including cost, ethical issues,
12 what have you, things beyond FDA, though.

13 We hope and expect that we'll have a free-
14 ranging and even -- what's the word -- adversarial
15 conversation, if that's what it takes, because it's
16 important to bring out the complexity and the
17 difficulties of the issues involved here. So we've
18 selected a panel that we think will do a good job
19 for us in this respect, and here they are.

20 I've asked them to take three minutes to
21 reflect upon what they've heard so far during the
22 day, react to anything that seems particularly to

1 merit that. And then once they've done that, then
2 we'll go to an open discussion between them,
3 including --

4 Greg, you're still at the table? Good.

5 And finally, there will be a short
6 opportunity for questions from the audience as
7 well.

8 So why don't we start with Ed Boyer. And by
9 the way, it's three minutes for the opening
10 statement, as it were, not really an opening
11 statement, but a reflection and summary of what
12 you've so far heard.

13 DR. BOYER: I was going to say a
14 three-minute introduction of myself might be a bit
15 long.

16 I'm Ed Boyer. I'm a medical toxicologist,
17 and I practice at University of Massachusetts,
18 where I'm chief of the Division of Medical
19 Toxicology and at Children's Hospital Boston. For
20 those of you who don't know what a medical
21 toxicologist is, our area of practice is poisonings
22 and overdoses. So I don't prescribe opiates to

1 anybody, but I give naloxone to the folks. I'm an
2 emergency physician primarily.

3 And I guess my thoughts on this thing today,
4 one of the things that struck me was how rapidly
5 the distinction between opiate and opioid got
6 blurred very, very rapidly. And I think that
7 pharmacologically, that's kind of an irresponsible
8 thing to do for the most part.

9 The reason is opioid analgesics, either
10 because of their pharmacokinetic properties or
11 because of their formulations, often have
12 long-acting properties, which dramatically exceed
13 that of single-dose naloxone.

14 So does naloxone reverse heroin overdose?
15 Does it reverse opiate overdose? Yes, it does.
16 Does it truncate opiate overdose? I think the data
17 is pretty clear. Yes, it does, because only a
18 minority of individuals who overdose on heroin
19 require a second dose to maintain respiratory
20 effort.

21 Does naloxone reverse opioid analgesic
22 toxicity? Yes. Does it truncate it? And I think

1 the answer there is a pretty clear no for most
2 cases.

3 So when I put that in the context of should
4 this be available to everybody, heroin addicts,
5 yes, I think it should be. I mean, if I were a
6 scientific purist -- and I'm sensitive to the "Oh,
7 for gosh sakes; quit talking about the need for
8 more data." But if I were a scientific purist, I
9 would say the data is pretty good, but rigorous
10 data, in all honesty, is lacking.

11 To say that about opioid analgesics, to say
12 that it can save lives, I think that might actually
13 be a questionable if not dangerous clinical
14 assertion. And I think that that does require
15 better data than what we have right now. And there
16 are places that clearly can do that sort of thing,
17 but that hasn't happened yet to, I think, the
18 extent it needs to occur.

19 This has implications in other things as
20 well. If you move into an over-the-counter
21 medication, we know that over-the-counter
22 medications are relatively safe things, and that

1 means that they can be misused a little bit more
2 with a little bit less penalty than prescription
3 drugs.

4 So I'm just worried -- work as I do in a
5 pediatric facility, what would it mean if a kid is
6 exposed to an opioid analgesic? We know that kids
7 have delayed onset of toxicity. We know they have
8 longer onset of toxicity. And if somebody walks up
9 and treats them and doesn't do the right thing,
10 like call 911 and bring them into an emergency
11 department or a healthcare facility right away, I'm
12 afraid that you're going to see increased mortality
13 in highly susceptible populations.

14 Those are my initial thoughts, and I'll just
15 start there.

16 DR. BRASON: My name is Fred Brason, and I'm
17 one of the founders and head up Project Lazarus, a
18 comprehensive community approach to address the
19 opioid overdoses that have been occurring
20 specifically in North Carolina and now elsewhere.
21 And I also am project director for the North
22 Carolina Community Care Network case management

1 system for Medicaid for their chronic pain
2 initiative, addressing chronic pain and the
3 prescribing of opioids and, unfortunately, the
4 overdoses within the Medicaid system.

5 With that, a couple of comments that I do
6 have, and what I'm hearing today, and what I know
7 from what we've been doing in North Carolina, is
8 the epidemic amount of opioid overdoses that have
9 been occurring, both from those individuals who
10 clearly have had addiction problems and issues but
11 also clearly with those who were simply patients
12 who unfortunately misused their medication, either
13 by taking more because they had more pain or not,
14 realizing that the benzodiazepine or something else
15 with that was going to have the adverse effect of
16 an overdose -- so our project has been to reach the
17 prescribing population as well as the general
18 public in our communities for that education, so
19 that they could also have the rescue component of
20 naloxone for those times when someone might slip
21 into that overdose mode. And hopefully, the
22 education would allow them to be able to administer

1 and save those lives.

2 So what I'm hearing today and what I had
3 been hearing is that naloxone, yes, it does reverse
4 overdose. Yes, it does provide an education moment
5 between the person who's doing the training or the
6 person who has administered. And the person wakes
7 up, and there's that opportunity to address the
8 issues and what happened and what occurred, and
9 then hopefully get that individual into treatment
10 and into help.

11 So it does all of those things, which to us
12 is the perfect remedy for the epidemic status that
13 we're currently in, especially with the opioid
14 prescriptions that are occurring in our
15 communities, both for those individuals who
16 definitely need that medication, we want to ensure
17 that they do not have an access to care problem by
18 removing those opioids, but at the same time,
19 making sure that a patient is safe and that those
20 individuals do not have easy access to
21 prescriptions that aren't theirs.

22 But in so doing, we've got to cover the

1 whole gamut as far as the education component from
2 the addiction and problems in that community as
3 well as simply the patient, no matter age, in that.
4 So it's the issue of having it available, having it
5 in the right device, and having the education
6 component to all aspects of our entire population,
7 our entire society because we have gone into a
8 cultural society issue with this overall, and it
9 needs to be addressed.

10 So in North Carolina, everybody is on board.
11 The entire state hospital system, state medical
12 system, and our opiate treatment programs have now
13 decided that they are going to co-prescribe
14 naloxone to those patients who are new enrollees
15 into treatment.

16 I can tell you that in February in Wilkes
17 County, we had our documented utilization of
18 naloxone where a sibling saved the life of another
19 sibling. And that sibling within four days was in
20 treatment and getting help because they decided at
21 26 years of age, they did not want to die that way.
22 That was reached because of a community-based

1 project, and that's where we need to be.

2 We talked about the Indian Health Services
3 earlier today; it was mentioned. And we are now
4 initiating Project Lazarus and the naloxone
5 component to the Indian -- the Koala Boundary
6 Eastern Band of Cherokee Indians.

7 We heard today that the average overdose was
8 around 40 years old. The Koala Boundary is 18 to
9 24 and well exceeding state averages for overdoses.
10 I do not want to meet with them next month to do
11 the training to the medical staff -- the suboxone
12 buprenorphine program and pharmacy and those in the
13 emergency department -- and tell them that here is
14 your training, here's how to do it and to tell them
15 that naloxone is not available to save the lives of
16 those on the Indian reservation.

17 Thank you.

18 MR. BURRIS: Hello, everybody. I'm Scott
19 Burris. I'm a lawyer, and I've been working on the
20 law related to naloxone and harm reduction for a
21 long, long time. And certainly, the law is all
22 over here as we've heard. I think it's important

1 to mention that there's a lot that can be done at
2 the state level to cope with the fact that naloxone
3 is a prescription drug and to make it more
4 available, given the rules we have at the state
5 level. And we're seeing that happening. So that's
6 a bright spot, and it shows the work that local and
7 state level advocates and public health people have
8 done.

9 Of course, I also think that we've heard
10 today about a host of very hard regulatory burdens
11 that stand in the way of wider access to naloxone,
12 and that it's much harder for advocates to deal
13 with.

14 I was almost getting depressed by that as I
15 listened this morning. It's such a big burden, and
16 it was going to be such a big advocacy challenge.
17 Then I realized -- actually I've been working with
18 people who have taken responsibility for naloxone
19 access themselves, and they have gone out on the
20 streets and made overdose prevention happen.

21 But really, it's not their responsibility
22 anymore. I think the panel previous to this one

1 really handed responsibility off to you people in
2 the government. And I think to some extent
3 rightfully so.

4 When I think about whether you're going to
5 rise to that challenge and how you should rise to
6 that challenge, I reflect on some of my own
7 experiences first as a kid growing up in Wisconsin
8 in the '60s. I still essentially lived in the New
9 Deal. Hard to believe when you think about
10 Wisconsin today, but back then it was a time -- it
11 was a place where we expected that government was
12 going to help solve problems, and that government
13 could be effective, and that government would rise
14 to challenges when faced with challenges.

15 And then, of course working in the AIDS
16 epidemic, I saw government rising to challenges,
17 this agency rising to challenges. Of course, also
18 sometimes being pushed by consumers to rise to
19 challenges. But still we had some success stories.
20 And I think the question before us now is whether
21 we're going to have a success story here, and that
22 lies in your hands.

1 We know we have a drug. We know how it
2 works. We know it's generally effective for the
3 use to which it's being put. We know that the
4 nasal formulation has been successfully used by a
5 variety of different providers over many years. We
6 have very few stories of disasters. We really
7 don't have any stories of disasters. We have some
8 concerns and some anecdotes, and we certainly have
9 reason to continue to do research.

10 But what we don't have now I think is reason
11 to wait five, six, seven, eight years for a
12 solution to this problem. Maybe it isn't OTC
13 status right away, but we could throw money at this
14 problem. Hillary talked about the fact that
15 naloxone programs now are working on a shoestring.
16 We could provide a lot of shoestrings, as Phil
17 Coffin says, in a way that would be very cost
18 effective.

19 We could have stronger encouragement and
20 coordination from the federal government to states
21 to encourage them to make the legal changes they
22 need to make to allow naloxone programs to go

1 forward, albeit with licensed prescribers, at least
2 with licensed prescribers in a less intense role.

3 What we can't do is walk away from here and
4 wait a decade for real change. And this is a great
5 first step. I think this was a really great
6 learning experience we had today, and it was great
7 to see the involvement from the really key federal
8 agencies. But I want you guys to walk out of this
9 room with the responsibility on your shoulders.

10 DR. MADRAS: Hello. My name is Bertha
11 Madras. I am a professor of psychobiology in the
12 department of psychiatry at Harvard Medical School.
13 And I formerly was the deputy director for Demand
14 Reduction for prevention, intervention and
15 treatment in the White House Office of National
16 Drug Control Policy.

17 I have seen substance users. I have seen
18 the addicted in stories, in manuscripts, in
19 scientific meetings. I have seen it all, and I'm
20 delighted that this meeting has occurred today
21 because I think this is a very crucial and
22 important convening of stakeholders in it.

1 This topic with regard how to address
2 overdose covers every single spectrum of human
3 endeavor. It covers the science. It covers
4 biomedicine. It covers public policy, social
5 policy, ethics, morality, legal issues, just as
6 every other substance abuse problem does. It is
7 one of the few areas in science that spans all the
8 domains of human activity.

9 My overview with regard to this issue is my
10 foremost principle is to save lives. That is
11 number one. And this meeting is an FDA regulatory
12 meeting that responds to the large increase in
13 opioid overdose. The regulatory issues are clear.
14 The biological rationale is clear. Naloxone is a
15 pure new opioid receptor antagonist. Over
16 activity, these receptors leads to respiratory
17 failure, possible death, and naloxone can surmount
18 the agonist activity of opioids to rescue people.

19 But we should -- and I encourage operating
20 within the constraints of sound FDA regulations
21 because we've seen when states try to take control
22 of these regulatory mechanisms. And I trust the

1 FDA as the ultimate resource with regard to sound
2 scientific approval of drugs.

3 Unlike EpiPens for bee stings, we have to
4 assume that the majority of overdoses are among
5 people that have substance use disorders, and that
6 leads to my secondary principle. And my secondary
7 principle is that you have to save more than a life
8 after an overdose crisis. You have to try to
9 prevent a recurrence or save a person from a
10 lifetime of addiction, from depression, or from
11 noncompliance with pain medications because lives
12 are truly in danger here. It is not like an EpiPen
13 where you can simply rescue a person because by
14 happenstance they have a bee sting.

15 In recent studies in Norway, one-third of
16 all patients with substance abuse poisonings
17 reported previous suicide attempts, and one-third
18 of suicide attempts reported daily substance use.

19 So with regard to how to address this, let's
20 look at some of the constraints and some of the
21 guidance that we have from the United States
22 Preventative Services Task Force. They look at

1 preventative services with regard to morbidity and
2 mortality, not only mortality, not only saving
3 lives with also quality of life and sickness.

4 Very little has been discussed about
5 addiction here and the quality of life. And what
6 we haven't heard is patient education. We've heard
7 of three programs from Dr. Binswanger, Dr. Walley,
8 Dr. El-Bassel, but we have not -- we have only
9 skirted the issue of after the rescue, what is
10 being done. And I think that should be formulated
11 as part of guidance with regard to Narcan rescue.

12 We've heard of no interventions, no SBIRT,
13 no counseling, no data on referral to treatment.
14 We know that Narcan can assist. We know that it is
15 critical, but the elephant in the room is that the
16 people who overdose are in grave danger. And that
17 is not being addressed at all, and I would like to
18 see that part of the dialogue.

19 I will now defer to the clock and allow my
20 colleague to continue.

21 DR. BARTOSZEK: Hello, everybody. My name
22 is Dr. Mike Bartoszek. I'm board certified in

1 anesthesiology and pain management, and I'm the
2 chief of the interventional wing in the pain clinic
3 at Fort Bragg, North Carolina. And I have to say
4 first that the views that I express are those of
5 our clinic at Fort Bragg, not necessarily the views
6 of the Army or the DoD as a whole as I talk today.

7 Just so you get a background of where I come
8 from and what we're doing down at Fort Bragg, we've
9 had a problem with chronic pain for a long time at
10 Fort Bragg. And after 10 years of war, we've added
11 comorbid conditions like post-traumatic stress,
12 traumatic brain injury, anxiety and depression, and
13 all of the polypharmacy that's come from that.

14 And that has resulted in sort of an
15 unexpected, unacceptable high rate of overdose and
16 death in our highest-risk patients. And so we at
17 Fort Bragg recognized that problem, and we've
18 emphasized many of the sort of standardized risk
19 reduction principles such as the sole provider
20 programs, prescription monitoring, year-end drug
21 monitoring, and then emphasized non-opioid pain
22 treatments like interventional care, psychological

1 care, alternative therapies like acupuncture.

2 But to that, we've also added the naloxone
3 piece. And we began collaborating with Fred from
4 Project Lazarus, and we came up with a broadened
5 program of patient, family, and community
6 education, in addition to naloxone, prescribing,
7 for our highest-risk patients.

8 We began this sort of robust education
9 program with an emphasis on the risks of overdose
10 and also the indications and the instructions for a
11 naloxone rescue. And since we've been doing that
12 in our highest-risk patients, what we've noticed is
13 we've had absolutely zero naloxone reversals at
14 all.

15 We've also had zero overdoses and zero
16 deaths at Fort Bragg in the past one year since
17 we've been doing all this. And I think that from
18 what I've heard today -- I've heard a lot about
19 naloxone reversals -- the point I think we've seen,
20 and what I'd like to emphasize, is the prevention
21 piece.

22 For us, it's almost like when I prescribe

1 the naloxone for the patients and their family and
2 support system, there's the education, but then
3 there's that actual moment where you give them the
4 naloxone. And there's that realization of how
5 important this is and how serious this is in their
6 eyes. And it's not just the soldiers' families.
7 It's the soldiers' unit that is not about to let
8 one of their own fall victim to their medication.

9 And so I think what we've found and what I
10 emphasize from what I've heard here today is really
11 the teaching and the prevention that we can be
12 doing. It's not necessarily the rescue. The
13 rescue is secondary prevention. I think it's the
14 primary prevention of education and actually
15 prescribing naloxone that we've seen the effect of
16 at Fort Bragg.

17 We have 50,000 soldiers there on active
18 duty. We've studied this, or at least piloted this
19 in about 500 or so. And we're about to roll it out
20 to the entire Fort Bragg community through our
21 primary care clinics. And we've come up with I
22 think a cost effective way to risk stratify

1 patients so that we treat with naloxone or educate
2 only the high-risk chronic pain patients who raise
3 red flags for problematic use and kind of leave
4 alone the thousands of people who get opioid
5 prescriptions who take them as prescribed for a
6 medical indication.

7 So we're looking for research money to sort
8 of study that and try and get some good outcomes
9 from our program at Fort Bragg.

10 DR. LURIE: Great. Thank you very much.

11 So I think perhaps I heard less disagreement
12 than I heard a variety of perspectives. So that's
13 very helpful, I think.

14 I think what I'd like to do next is to give
15 each of you a chance to ask questions of each
16 other, whoever wants to go first. If you have a
17 question of other panelists, if you have a question
18 of another panelist, you can ask it for all or
19 ideally, to one person.

20 MR. BURRIS: This is for you, Dr. Madras.
21 Maybe it's a disagreement. Maybe it's just a
22 clarification. But I didn't hear that naloxone

1 reversal programs are not addressing substance
2 abuse disorders. What I heard is that people are
3 drawn in. One of the advantages of a naloxone
4 program is that it draws more people in to get an
5 opportunity for treatment and to get a referral for
6 treatment.

7 So it sounds to me, what I heard you -- the
8 only way I can understand what you said is that we
9 should be -- that naloxone programs should be
10 designed to provide substance abuse treatment or
11 substance abuse intervention at the time of
12 reversal. Even EMTs don't do that.

13 Can you clarify?

14 DR. MADRAS: Yes, I'd be delighted to
15 clarify.

16 There were two things that I looked at the
17 data on the slides that were presented, and I was
18 curious about how many people had actually entered
19 treatment post analoxone rescue, how many people
20 had had secondary, tertiary, quaternary overdose
21 events after the fact.

22 We did not see one of the slides, which I

1 did receive earlier, and that was from Dr. Walley,
2 showing that drug use had essentially not gone
3 down. It had gone up from benzodiazepines. So
4 there seemed to have been a very constrained view
5 of how to present the data, and that is the fact
6 that this rescues lives.

7 I understand that there is an opportunity to
8 engage in treatment. I'm far more interested in
9 outcomes rather than opportunities.

10 DR. LURIE: Would anybody like respond to
11 that?

12 I think that what Dr. Madras is suggesting
13 here is a research agenda that relates to -- I know
14 that in other areas analogous to this, there were
15 data about numbers of referrals to treatment,
16 perhaps the outcomes of treatment. And I think
17 it's a fair point that we heard a little bit less
18 about that than we heard maybe in the needle
19 exchange literature. So I think that's a challenge
20 to people to try to put that together.

21 And I think the other methodological
22 challenge you seem to be putting forth is that you

1 want an, in effect, I guess you can call it
2 prospective data on how a person who is reversed
3 does subsequently. Not a tallying of overdoses,
4 but whether that person who is reversed later
5 overdoses. I think that's -- is that fair?

6 DR. MADRAS: When I was serving at ONDCP,
7 the Narcan issue came up because I had organized a
8 fentanyl meeting to try to gather as many
9 stakeholders as possible to try to avert and
10 prevent the disaster of fentanyl overdoses in
11 Detroit and Chicago and Philadelphia and other
12 cities.

13 And we heard presentations on naloxone, and
14 during that time, I was very curious to see whether
15 or not the rescue would give rise to improvements
16 in outcomes. To me, outcomes means trying to get
17 on medications, trying to get people to reduce the
18 drug use, reduce risky behaviors, whether or not
19 they would re-overdose in a period of time and
20 whether or not these rescues would reduce the
21 number of secondary and tertiary overdoses.

22 So when we heard that there were a thousand

1 rescues at the time, I asked staff to find out the
2 nature of the data. And they called the source of
3 the data, and they were told that they had called
4 needle exchange programs throughout the country.
5 And they had said, well, we had 100 here, 100
6 there, 100 there.

7 And I said, "What was the nature of the
8 rescue? Was it an opioid, an opiate? Was it a
9 synthetic opioid, a derivative of morphine? And
10 what were the longitudinal follow-ups?"

11 And there was no data, and it disturbed me
12 because, as I said, I do think that people who are
13 rescued from an overdose should be treated the same
14 way as a suicide attempt or anyone who is in danger
15 of their lives. And there needs to be follow-up.
16 There needs to be an intervention. There needs to
17 be a sense of the sacredness of their lives beyond
18 saving their lives.

19 DR. LURIE: Dr. Boyer.

20 DR. BOYER: I see Alex standing at the back.
21 I know I've seen your talk a couple of times, and I
22 just don't remember the slide.

1 Does it say that there was no change in
2 utilization rates or no increase in utilization or
3 acute hospitalization, whatever it was? And if
4 that -- if I'm remembering the slide correctly,
5 does that mean that people were not coming into the
6 emergency department after? Is that the
7 implication?

8 DR. WALLEY: Would you say the last part of
9 your question? I just missed that part.

10 DR. BOYER: Jeez, I don't know if I remember
11 it.

12 (Laughter.)

13 DR. BOYER: Let's answer the first part
14 first.

15 DR. WALLEY: Okay. So I think you asked
16 about emergency department and hospital
17 utilization. And almost any way we model it, our
18 independent variable is implementation, so the
19 number of people for whom we have a documented OEND
20 enrollment. There's basically no association with
21 either -- there's no increase or decrease in ED or
22 hospital utilization.

1 DR. BOYER: Does that imply that people are
2 not calling 911 after a reversal?

3 DR. WALLEY: So I talked a little bit about
4 it this morning. I think there's two -- I do think
5 there's two things going on. Number one is that we
6 are explicitly training people to call 911, and so
7 some people who otherwise would not have called
8 911, I believe actually are. And then at the same
9 time, we're also training people to prevent
10 overdoses in the first place. And so those people
11 would not go to the emergency room at all.

12 So we're doing two things with OEND, that
13 one would increase utilization by encouraging
14 people to call 911, and the other thing, other,
15 would decrease utilization by preventing the
16 overdose in the first place.

17 So that's how I speculate that
18 interpretation. But what's interesting is we see a
19 substantial reduction in death rates in places
20 where we implemented. So that is -- I think
21 that's --

22 DR. BOYER: So we can't interpret the data,

1 but who cares, people are surviving?

2 DR. WALLEY: Pardon me?

3 DR. BOYER: We can't necessarily interpret
4 the data, but who cares, people are surviving
5 better now?

6 DR. WALLEY: No, no.

7 DR. BOYER: People are alive --

8 DR. WALLEY: I did give you an
9 interpretation of the data.

10 DR. BOYER: I mean, the ED utilization rate
11 data --

12 DR. WALLEY: No, I gave you an
13 interpretation of it. I mean -- do you have
14 another interpretation of it?

15 DR. BOYER: Well, I just -- it sounds like
16 there's a bidirectional opportunity here. Either
17 people are not overdosing, therefore, they're not
18 coming in, or they're overdosing and not going.

19 DR. WALLEY: That is for the non-fatal
20 measure of overdose --

21 DR. BOYER: It seems like there's so many
22 contributors that haven't winnowed out --

1 DR. WALLEY: -- which is ED
2 utilization -- excuse me. I'm sorry. I'll let you
3 finish.

4 DR. BOYER: No, no, I --

5 DR. WALLEY: So that's for the non-fatal
6 overdose measure, which is ED and hospital
7 utilization. That's the best proxy for non-fatal
8 overdose that we could come up with.

9 But fatal opioid-related overdose, that's a
10 hard outcome, and I don't -- there's no -- I mean,
11 there's no ambiguity about how to interpret that.
12 It's there.

13 I think Dr. Madras was referring to another
14 issue, though, which was whether -- and I didn't
15 show this slide, but I hope it's available to
16 people who have access to the slide set after, and
17 I hope it's included.

18 So we are a program that is funded as a
19 program, not as a research study. I think I
20 mentioned that. It's a public health program. We
21 do not have systematic follow-up. The people who
22 come back to us, report their overdose, it's

1 self-reported. And those come back, and it's
2 really convenience sample. I would love to get
3 funding for a prospective trial -- or not a trial,
4 a prospective cohort study to systematically follow
5 up people who we enroll, but we don't have access
6 to that.

7 There's an accident that happens. Because
8 we're a large system, we require each program site
9 to enroll people newly if they come to a new site.
10 So, for example, if you're enrolled in New Bedford
11 and then you go to Lynn and say I was enrolled in
12 New Bedford, give me my refill, we don't allow
13 that. We actually require Lynn to enroll that
14 person.

15 So what that means is in 380 cases, we've
16 gotten two points in time where we have enrollment
17 information. And with that enrollment information,
18 we have their 30-day drug use history. And so what
19 we've done on that slide is looked at whether that
20 30-day drug use history, the number of days they've
21 used, goes up on the second enrollment compared to
22 the first enrollment, goes down, or stays the same.

1 And essentially, there's no change in the drug use
2 information except with benzodiazepines, which I
3 think is an area that we need to continue to look
4 at it.

5 But the important aspect of that is I think
6 it addresses what Dr. Zimet was talking about.
7 It's one of these imperfect studies that looks at
8 whether there's an enabilitation of higher risk by
9 the intervention. And we see no evidence of that
10 for opioids, which is in biological terms, that is
11 the use that would be enabled by naloxone, not
12 benzodiazepines. In fact, we counsel people not to
13 use benzodiazepines.

14 So I do think that's a concerning finding,
15 but it does support the concerns I think that
16 Dr. Madras is bringing up. Her concern now has
17 shifted from enabling worse drug use to the fact
18 that we're not aggressively promoting treatment.
19 And I mean, we're doing the best we can with what
20 we've got.

21 I mean, I don't -- you've heard the
22 testimony from parents. They are doing everything

1 they can. They just want a little naloxone to help
2 them as well. It's not like they're not going to
3 refer their kids to treatment just because they
4 have naloxone.

5 The natural history of addiction is
6 recovery. That's the miracle, right? The natural
7 history of addiction is for people to get better.
8 Now, treatment is helpful in that, but it's not
9 necessary. Actually, most people who get better
10 from addiction do it without treatment.

11 (Applause.)

12 DR. LURIE: Let's give Fred a chance to
13 comment.

14 DR. SZALAVITZ: I just want to --

15 DR. LURIE: I'm sorry. I see you. Let me
16 just give Fred a chance because he --

17 DR. BRASON: I just want to respond to this
18 whole dialogue because as Project Lazarus, we're
19 not a naloxone program. We're not just a
20 standalone trying to reach individuals on the
21 street and dispensing that way. Our whole goal was
22 to introduce naloxone into mainstream medical care

1 as best practice for those individuals who are at
2 risk for an overdose because of their opioid
3 medication.

4 And a whole list of the factors -- because
5 of comorbid conditions and going to the inmate
6 being released from prison, we've heard all about
7 that -- we reach all of the segments with that.
8 But in doing what we're doing, we are heightening
9 treatment for everybody who wants to have
10 treatment. And those of you who are out there
11 working with individuals, if somebody doesn't want
12 treatment, they are not going to get it. But we
13 certainly have that -- treatment facilities rise to
14 the occasion to meet that.

15 But in the context of the medical community
16 and with naloxone and overdose education, we are
17 introducing that into SBIRT as a brief intervention
18 so that those individuals will have that
19 opportunity. We are introducing it into general
20 medical practice that when the physician sees an
21 at-risk category, boom, they get a naloxone script
22 and they get education both for themselves and

1 their family. That will open the doors more to
2 treatment, we hope. We have seen that. There's
3 evidence of that.

4 But it's also going to reverse the deaths.
5 It is going to lower that amount as Alex Walley has
6 already seen. So there will be that hard outcome,
7 but at the same time, it becomes common within our
8 society and in our communities that naloxone is an
9 antidote to an overdose and can be used for heroin.
10 It can be used for opioid medications and should be
11 readily available to those who need it at the time
12 of the overdose. And then all the factors within
13 the community rising up to meet the need after the
14 overdose, so that that individual does have the
15 opportunity and does have the avenue for the help.

16 That's kind of the crux of our program
17 because it's comprehensive, addressing all of those
18 issues, making naloxone just common, and that's
19 what we're after.

20 DR. LURIE: Let's take a question or a
21 comment from the --

22 MS. SZALAVITZ: Yes, I would just like to

1 say --

2 DR. LURIE: -- and now this can go to the
3 microphone I think at this point.

4 **Questions and Answers**

5 MS. SZALAVITZ: Oh, sorry. I would just
6 like to ask why naloxone is being held to a higher
7 standard. If this was a drug for cancer, we
8 wouldn't ask it to cure AIDS as well.

9 I am myself a former IV drug user who was
10 saved by information about needle exchange. And we
11 were having the same exact debate that we had
12 20 years ago when I first got into recovery about
13 is this going to enable people. And I'm just
14 really curious, like how can we say to a mother
15 who's lost a child, we don't want this available
16 because it might not work or because it doesn't
17 cure the addiction?

18 I just would like the panel to address this.

19 DR. MADRAS: First of all, I would like
20 emphasize that not once in my comments did I say
21 that naloxone should not be made available. And
22 you've misinterpreted what I said, so I regret

1 that, or I did not explain it clearly. I clearly
2 said the most important principle of all is to save
3 the life of anyone who is an overdose crisis.

4 I also said that the life that is saved also
5 requires secondary intervention because unlike
6 cancer, this is a biobehavioral disease, which
7 could lead to further death. It could lead to
8 death. It could lead to a lifetime of addiction.
9 And therefore, the rescue should be phase 1 of at
10 least a two-phase project.

11 That's what I'm trying to say. I never once
12 implied that naloxone should not be made available.

13 MS. SZALAVITZ: I thought your position used
14 to be --

15 DR. MADRAS: Pardon?

16 DR. LURIE: Can you identify yourself,
17 please?

18 MS. SZALAVITZ: Didn't you used to oppose
19 it?

20 DR. MADRAS: That was a profound, profound
21 misinterpretation of some of my statements. I
22 always said it should always be available. It

1 should be made available to people who are in need
2 of overdose rescue, but it should be made available
3 under circumstances that are also going to help the
4 person recover.

5 DR. LURIE: Let's take another comment.

6 Can you identify yourself before your
7 comment or question?

8 MS. BERGER: I'm Carol Berger. I'm with the
9 Chicago Recovery Alliance.

10 I really appreciate the discussion around
11 treatment. I think treatment is really important,
12 but I feel a little saddened by the presence of
13 still pervasive stigma in some of the comments in
14 this room. And I feel like if this was a
15 discussion about other diseases that also have
16 behavioral components, like the discussion about
17 making defibrillators available in the hallway, I
18 wonder how much of that discussion was nuanced
19 with, well, we need to make sure as soon as we
20 intervene and do something with that; that's
21 phase 1. And then this person needs to go and have
22 other intervention to address the behavioral

1 components that might have caused their heart
2 attack.

3 I feel like with addiction we're always
4 doing this. It's different. It's different.
5 We're making it different. This isn't different.
6 This is a life-saving medication that we have that
7 people should have access to.

8 We should also have treatment, but that's
9 not what this discussion is about. This discussion
10 is just simply about saving lives and making the
11 medication more available to save more lives,
12 something we've been doing in Chicago for a long
13 time. We're very, very proud of and that we can do
14 a much better job with. And we're really just
15 asking for help in making this diffused to more and
16 more people so that there are less deaths.

17 Thank you.

18 (Applause.)

19 DR. LURIE: Dr. Bartoszek, you had a
20 comment.

21 Dr. Bartoszek had a comment, I think.

22 DR. BARTOSZEK: I'll just respond real quick

1 to what she said. I don't think what she's saying
2 is that we shouldn't reverse the -- or the ID
3 analogy. If someone is defibrillated, they then go
4 to the cardiologist to have an evaluation and maybe
5 something implanted, or whatever it is that caused
6 the problem is treated.

7 And so I think the same thing with naloxone
8 for this problem, that if you have a reversal, then
9 you're then going to go on to have more services.
10 I think she's just calling for more services. But
11 nobody is saying -- at least I don't think anybody
12 is saying that we shouldn't have naloxone
13 available.

14 If anybody else can --

15 DR. LURIE: Okay. Scott?

16 MR. BURRIS: I feel a little bad for having
17 asked that question to start with. I think we all
18 agree that it's great for the USDA to keep our beef
19 from having salmonella even though they don't make
20 us all into vegetarians.

21 (Laughter.)

22 MR. BURRIS: I think another thing that we

1 can actually all agree on now is how well proven,
2 from a public health and scientific point of view,
3 and from an epidemiological point of view, harm
4 reduction has been. We don't really have to talk
5 about harm reduction or treatment.

6 Harm reduction has always incorporated a
7 real desire to get people into treatment, helped to
8 get people treatment when they're ready for it,
9 when they want it, when it's the right thing for
10 them. There's no conflict here. And harm
11 reduction has worked.

12 We have good evidence from the observational
13 studies of needle exchange that they are entry
14 ports into treatment for some people. We have no
15 other population of people at risk for HIV where
16 the rate has gone down like it has with drug users.
17 Everybody else has pretty much stayed where they
18 are in our long fight against HIV. And now the
19 same thing is really true here with naloxone.
20 We've got a lot of miles behind us showing that
21 this is a feasible and effective intervention.

22 So I think we should be proceeding upon this

1 together, as I think we all agree we're going to be
2 doing. And really the only question is now the
3 urgency with which we kind of work all these thorny
4 details.

5 DR. LURIE: Okay. Let's take a question
6 from the audience.

7 MS. PETERSON: I just wanted to -- my name
8 is Joanne Peterson from Learn to Cope, and I just
9 wanted to clarify a few things and make a few
10 things very clear.

11 In the trainings that we do with our
12 families at all our chapters, they're very
13 organized, and they're very professionally done.
14 In fact, some of the people that are trained are
15 parents of young sons and daughters, who some of
16 them actually were prescribed Oxycontin or the new
17 Perc 30, which is really oxycodone and became
18 addicted and then turned to heroin. And then these
19 poor parents are left with how do I -- what do I
20 do, how do I find treatment.

21 And then they come to our meeting. We give
22 them resources. We always encourage treatment. We

1 always encourage 911, which is not many parents
2 that would not call 911. So that's always the
3 first thing that we encourage them to do. The
4 training that we learn through our department of
5 public health, we give them that training. Then we
6 give them resources on top of it.

7 And I can give you a scenario. In December,
8 one of those moms who went home that night after
9 receiving her Narcan, she heard a thump at about
10 2:00 in the morning. And her daughter fell out of
11 bed, overdosed. She gave her Narcan. She was
12 med-flighted to Mass General. Her life was saved,
13 and she's been clean ever since. She went to
14 treatment. And the same thing with the man's son.

15 I just want to clarify also that my husband
16 is a diabetic, and when he came down with his
17 type 1 diabetes, our entire family was brought into
18 the medical office. And we were taught what are
19 the signs and symptoms of hypoglycemia versus
20 hyperglycemia, how do I give him insulin, how do I
21 know when to give him insulin, how do I know
22 whether to give him orange juice or candy.

1 This is really not much different for
2 anybody to be able to learn how to save another
3 person's life. I don't see what could be wrong
4 with that as long as they're properly trained to
5 train that other person and, of course, offer them
6 the resources to go to treatment.

7 And I wish I could put every person in this
8 room today that is now in recovery that has been
9 "Narcan-ed," and it saved their lives. And like my
10 son today, he's clean and sober. I didn't have to
11 use Narcan. Back in the days when he was suffering
12 from his addiction, I didn't have that option. And
13 I didn't even -- no one really knew to teach me
14 what the signs of an overdose was. And I actually
15 saw him turning gray and blue. I heard him making
16 that snoring sound, and I am just so lucky that he
17 didn't die. And I didn't have that information. I
18 didn't have Narcan.

19 Now we have it. People are literally saving
20 other people's lives. These people are going on to
21 treatment, not all of them. But there's also
22 diabetics out there that are going to eat brownies

1 and drink beer and soda and hamburgers and not use
2 their insulin. Should we, well, if their life is
3 saved, that's it? Is that what we should say?

4 So let's just look at the nitty-gritty of it
5 all. It's to save a life. And if we're going to
6 have this many opiates out in the public, out in
7 the market, we're going to need a lot of Narcan.
8 And it should be very available, and you should be
9 able to walk into any pharmacy and just get it.

10 Thank you.

11 (Applause.)

12 DR. LURIE: Thank you.

13 DR. BARTOSZEK: I just want to respond real
14 fast about the education piece. I think that we
15 found that this very key, and I think there needs
16 to be a little bit of distinction made between the
17 naloxone in the chronic pain clinic prescribed by a
18 pain doctor, co-prescribed with their Oxycontin or
19 Percocet, and the use in the community at IV drug
20 clinics.

21 I think that there is a definite role for
22 naloxone in our pain community, which what we see

1 at Fort Bragg and other pain clinics, what
2 Dr. Dombrowski said from the ASA earlier. I think
3 there's a role for that that is not really
4 discussed, and I think that that needs to be
5 brought up a little bit more because the problem is
6 IV drug use, but it's also prescription medication
7 misuse. I just want to make that distinction.

8 DR. LURIE: Yes. That's very helpful.
9 Thank you.

10 Pam.

11 MS. LYNCH: Hi. My name is Pam Lynch, and I
12 am an advocate in Michigan working in a drug
13 treatment facility right now, and just a couple of
14 points.

15 I went to residential treatment when I was
16 24 years old. Because of sexual abuse that went on
17 in that facility, I was not successful after that
18 experience and had other outpatient experiences
19 after that in drug treatment.

20 There's good drug treatment, and there is
21 bad drug treatment. So getting people to drug
22 treatment isn't necessarily the answer to all of

1 it. I can say that drug treatment was a part of my
2 toolkit that I use to be who I am today. I can say
3 that harm reduction interventions have also been a
4 part of my toolkit that allows me to be here today
5 and to do the work that I do.

6 But I also want to point out that this is an
7 occasion that I hope that the FDA and the federal
8 government are recognizing it for what it is. It's
9 very confusing to people.

10 Three years ago we did a film festival where
11 we just -- we had a local behavioral health program
12 who had a film that they made about a woman who was
13 doctor shopping, and their movie and some of the
14 other movies for overdose prevention were on the
15 screen that night, Project Lazarus. And we had 272
16 people from the community walk through the doors of
17 that theater that day, not because they knew who I
18 was, not because they knew who this woman in
19 Munson's film was, not because they knew who
20 Project Lazarus from North Carolina was, but
21 because they want answers. And they're confused.

22 It's confusing to people why Pam Lynch,

1 who's got no recognition in the community, is the
2 one going to the jail to say, hey, you need to have
3 one of these here. It's confusing to them why they
4 can't go to the trusted, established public health
5 and substance abuse coordinating agencies who are
6 the recognized experts in this and get answers on
7 how to help their children.

8 It's confusing, and people don't understand
9 how come they've never heard of this. How come
10 it's the small programs who have brought this to
11 the table and not -- like Scott refers back to the
12 times where it was established government entities
13 who played this role.

14 And so I'm asking you to please recognize
15 this opportunity for what it is. Things need to
16 get -- something needs to happen here.

17 Thank you.

18 DR. LURIE: Please make sure to identify
19 yourself for the transcriber.

20 MS. WHEELER: So with all due respect,
21 Dr. Madras --

22 DR. LURIE: Wait. Name?

1 MS. WHEELER: Oh, hi. I'm Eliza Wheeler.
2 And I just feel like possibly you feel like your
3 statements have been misunderstood or
4 misrepresented, but to us, you've come out publicly
5 multiple times over many years in opposition in
6 various forms to naloxone distribution. And maybe
7 not explicitly so, but bringing up issues like
8 encouraging drug use or being a barrier to drug
9 treatment in some respect. And those concerns have
10 been echoed here again.

11 And I understand that you are possibly the
12 one dissenting voice here, and that might be
13 uncomfortable. But at the same time, I feel like
14 it's -- number one, it's insulting to the work we
15 do to imply that we don't offer drug treatment when
16 someone wants it. It's also insulting to folks who
17 are using drugs in their process to say that the
18 overdose or the potential death has to be the
19 catalyst for them to get treatment. That often is
20 not the case for people. They have multiple scary
21 overdoses through their drug-using life, and those
22 are not the things that necessarily push them

1 towards treatment.

2 And also, just in terms of sort of a little
3 nit-picky thing about the data that you asked for
4 several years ago, our programs are not funded. We
5 have these small programs that run on shoestring
6 budgets. Just in the last few years, there have
7 been some state departments of health that have put
8 money towards this.

9 We don't have standardized data collection
10 tools. We have one staff member slinging Narcan
11 out on the street to the people who need it. And
12 it's regrettable that we didn't have all the data
13 points available about how many folks that were
14 reversed were then into treatment, but we don't
15 have it.

16 DR. MADRAS: May I respond?

17 MS. WHEELER: Yes. We would love to answer
18 those questions.

19 DR. MADRAS: Thank you.

20 First of all, I'd like to respond with a few
21 things. Number one are the issues about whether or
22 not this would encourage drug use, whether or not

1 it would lead to higher doses was a statement that
2 was not my opinion. But it was a manuscript that
3 was published from the San Francisco survey, the
4 only one in existence at the time, that said a
5 number of people claimed that if they had Narcan,
6 they would probably use higher doses of heroin.
7 Now, what the press did in that one interview was
8 leave out the fact that I was quoting a manuscript
9 and said it was my opinion.

10 So you have to realize that the press at
11 times will misinterpret in order to make headlines,
12 and in this case, they did.

13 SEAL reported the study, and that concerned
14 me because when one engages in public
15 policy -- which is this. This is a forum for
16 public policy, a forum for change with regard to
17 availability of Narcan for this purpose. It's
18 going to be based on science, but policy is based
19 on more than science.

20 When you discuss public policy, you discuss
21 unintended consequences. And the only thing I had
22 at that time was the SEAL article with regard to

1 unintended consequences. And I said, "In order for
2 us to change public policy," and by that I meant
3 instead of calling an EMT, having people with
4 take-home Narcan. I said, "I am concerned that
5 this report was published that stated these
6 unintended consequences of increased use, increased
7 doses, walking away from rescues." And that was
8 not my view or my opinion or my feelings. That was
9 a scientific survey done of -- but that was the
10 only one that was available at the time. So that
11 was number one.

12 Number two, with regard to bringing people
13 into an emergency department as opposed to doing an
14 at-home Narcan, what I found was another paper at
15 the time -- I wasn't looking for negatives. I was
16 simply looking for the literature. And there was a
17 report on how many people who were brought in could
18 be released after two hours of observation and how
19 many others had to stay for four hours or 24 hours
20 and longer because they needed extraordinary
21 measures beyond the Narcan rescue.

22 And that paper, which was done with a large

1 population of Narcan rescue in the emergency
2 department showed that, in fact, there were
3 approximate -- and I don't know the -- I don't
4 recall the numbers now, but there was a percentage
5 of people who required overnight stays.

6 And my overall principle was to save lives,
7 but that did not get through in the press because
8 the press wanted to take a different interpretation
9 of it. And I said, "If people are safer in an
10 emergency department because 72 out of 400 are
11 going to need observation, then those 72 lives will
12 be better served."

13 That was the only data that was available at
14 the time. Since then, there has been a lot more
15 data published. It is still not perfect, but there
16 are many people who engage in this research. These
17 are not community-based studies. These are based
18 in hospitals. They're conducted by physicians.

19 And I understand your vantage, but what you
20 have to realize is that I was quoting the only
21 literature that was available at the time. And in
22 order to make policy -- my concern was to try my

1 very best to have an opinion that was in the best
2 interests of a person who could die. And I did not
3 want them to die.

4 DR. LURIE: Okay. I think that's very
5 helpful, clarifying. Thanks.

6 I think, Dr. Boyer, you had a response.

7 DR. BOYER: Yes, and I'll be honest. I
8 don't know who said what or when or about what or
9 anything. But what I will tell you is that it is
10 possible to do research on a shoestring budget, and
11 it is possible to get the sort of data that I think
12 would persuade a lot of naysayers. And there a
13 bunch of folks who don't necessarily think that
14 this is a viable thing to do. It's possible to get
15 that data easily and cheaply with a staff of one.
16 I've done ethnographic studies with a staff of one,
17 which was me, and it was unfunded and it got
18 published.

19 As far as like data, like standardized data
20 collection forms, that's just a sheet of paper with
21 questions asked the same way in identifying things.
22 So a little bit of forethought and a little bit of

1 attention to study design can lead to good,
2 compelling results.

3 And candidly, there's a lot of
4 responsibility being pointed at the policymaking
5 authorities here, but for the rest of us here, I
6 think there's a lot of responsibility on all of us
7 to get good data to support a decision that we'd
8 like somebody to undertake.

9 MR. BURRIS: And I think we all agree. If
10 anybody says there's more data that's needed,
11 nobody in this room is going to disagree. But if
12 people are not doing it now, probably they could
13 use some help. Although they might do it with a
14 shoestring budget, they might do a better job and a
15 more compelling job with a bigger budget. And they
16 might do it much better with the expertise and
17 leadership of agencies that specialize in doing
18 this kind of research.

19 So no one's going to disagree with that.
20 Let's get the data. I think the only thing people
21 are saying here is innovate and evaluate. Let's do
22 things to evaluate and not just wait until we have

1 some mythical, perfect picture of the data.

2 DR. LURIE: Okay. Doug?

3 DR. THROCKMORTON: Scott, and I want to
4 follow up on what the comment you just made, and
5 the comment -- I believe -- if I understood your
6 original comments, you were suggesting that one
7 area of additional research that was needed was the
8 non-addict population and the efficacy of naloxone
9 distribution in that setting.

10 If I understand what you were suggesting, it
11 was the data were very good as far as the addict
12 population, that expanding access and availability
13 for naloxone in that setting had a positive impact,
14 but that you were less convinced by the available
15 data with regard to opioid analgesics --

16 DR. BOYER: Opioid analgesics.

17 DR. THROCKMORTON: -- opioid prescription
18 drugs.

19 DR. BOYER: Yes. Some of the opioid
20 analgesics, if it's an immediate release
21 formulation, then naloxone should be good enough.
22 But let's face it, there are a lot of non-immediate

1 release formulations that have -- I think there are
2 long-acting opioid analgesic formulations out
3 there, which people commonly abuse and often die
4 from. And if you just get back to -- like in
5 absence of data, if you just back to what we know,
6 what's the pharmacology, what are the
7 pharmacodynamics of the drugs, what's the
8 pharmacology, what's the pharmacodynamics of the
9 antidote, it's not compelling that a single dose
10 would be enough, which gets back to the question of
11 who calls 911 and who doesn't.

12 DR. THROCKMORTON: So you're saying it's not
13 compelling based on pharmacology.

14 DR. BOYER: Correct.

15 DR. THROCKMORTON: Not based on Project
16 Lazarus data that we've heard about earlier in the
17 day?

18 DR. BOYER: Well --

19 DR. THROCKMORTON: I mean, are you
20 characterizing those other data as --

21 DR. BOYER: I just --

22 DR. THROCKMORTON: -- two or --

1 DR. BOYER: -- you know -- you know, I've
2 had so many people who come in who say I took X and
3 actually took Y, and the only reason I know this is
4 because my fellows have just started sending off
5 comprehensive toxicology screens at UMass. And we
6 can analyze for just about anything that we truly
7 want to. And the validity of self-report is -- for
8 someone who's overdosed, engaged in a stigmatizing
9 behavior, and has sufficient incentive to distort
10 or outright lie, the validity of self-report is
11 just not that great.

12 DR. LURIE: Okay.

13 DR. DASGUPTA: Nab Dasgupta from the
14 University of North Carolina.

15 The question that you're raising, Dr. Boyer,
16 about -- you're talking about comparing the
17 molecular pharmacology to the molecular
18 pharmacology of that agonist and that antagonist,
19 right? But there's also the behavior pharmacology
20 that needs to be considered in there as well.

21 We know that in rats there's a strong place
22 dependent conditioning effect for opioids and for

1 pain relief, right? I mean, Siegel's work has been
2 doing this for decades.

3 We also know from the empirical evidence
4 that folks are more likely to overdose -- to go
5 into respiratory depression from an overdose in
6 environments that they're not familiar with, like
7 hotel rooms, SROs, right?

8 DR. BOYER: Yes. And I'm pretty comfortable
9 with the condition tolerance literature --

10 DR. DASGUPTA: Just a second, please.

11 So maybe drug -- so when we talk about the
12 data in EDs and how long people have to be left in
13 the ED, maybe it's because we don't usually spend
14 time in EDs. People who overdose don't spend time
15 in EDs, are not familiar with that environment, and
16 it -- it actually accentuates that overdose.

17 So possibly -- and I think this is a valid
18 hypothesis -- that maybe drug overdoses are better
19 treated in the community, not all of them but a
20 good portion of them probably will require less
21 medical intervention --

22 DR. BOYER: And that's a testable hypothesis

1 that, candidly, I think is reasonable to be tested.
2 But to say that it's a hypothesis, ergo, it's true,
3 I think is scientifically irresponsible.

4 I mean, I just -- I love living in my own
5 ignorance, which is a pretty vast place to be
6 sometimes. But what is the extent to which
7 conditioned tolerance in a clinical trial, in a
8 fairly well controlled set of circumstances, how
9 well does that translate to the real world? I
10 mean, I think we're saying the same thing. It's a
11 hypothesis. It's a testable hypothesis.

12 DR. DASGUPTA: And with the drug --

13 DR. LURIE: If you don't mind, let's take
14 the next question because we're getting late in the
15 day.

16 MS. BELL: Dr. Boyer, I was a little
17 confused by what you're saying about Narcan,
18 naloxone, not being demonstrated to be effective
19 for opioids. I ask this because we do a lot of
20 education about prescription opioid use,
21 particularly in the jail where we have the
22 opportunity to do longer trainings and talking

1 about different types of opioids and the importance
2 of knowing what you're talking and how long it
3 acts, and that some things are long-acting and some
4 things are short-acting, and getting people to
5 think about that information, and that
6 not -- whether it's somebody who's taking somebody
7 else's pain medication for pain, which people often
8 do -- we know that people often say my back is
9 acting up, and I'm going to take my husband's
10 Percocet from his surgery last month; it's
11 something people know they shouldn't do but often
12 happens -- or whether they're taking something to
13 get high, that people often don't know what they're
14 taking and that it's important to think about that
15 and that's a risk of overdose, that's something
16 that we do a lot of education on.

17 So is the issue that if it's something
18 long-acting, and someone is given naloxone for it,
19 that they might go back into an overdose? It's
20 effective immediately? But that if they're -- if
21 they don't take into consideration --

22 DR. BOYER: If I have somebody who winds

1 up -- and I understand about condition tolerance
2 and everything. But if they've overdosed on
3 methadone and wind up in my emergency
4 department -- and it doesn't have to be just
5 methadone; it can be long-acting oxycodone
6 formulations; it can be somebody who eats a
7 fentanyl patch; it can be the person who applies
8 multiple fentanyl patches -- we'll give them a dose
9 of naloxone or the paramedics will. They'll be
10 awake for a while, and then their respiratory rate
11 begins to drop off, so we give them more naloxone.
12 And they're awake for a while, and then they get
13 respiratory depression. And then they get more
14 naloxone. And that's the point at which we say
15 let's just make it easy on everybody. Let's just
16 start a naloxone drip.

17 I don't see how a single dose of intranasal
18 naloxone, in the field, without getting that person
19 to care, is going to save that person's life if
20 they have died multiple times in front of me that
21 I've just managed -- and I've reversed it because
22 we've given more naloxone.

1 MS. BELL: In our program, that's not what
2 we promote. I mean, we talk about methadone being
3 very long-acting and that if you give someone
4 naloxone, you still need to get them to the
5 emergency room. You need to stay with them. You
6 might need to give them another dose. You need to
7 get them to the emergency room.

8 So we're not -- I don't think any of the
9 programs are just promoting give them a single dose
10 of naloxone --

11 DR. BOYER: No, and I'm not suggesting that
12 you're not. What I'd like to know is how many of
13 those folks wind up in the emergency department
14 after they've overdosed on, say, methadone.

15 DR. LURIE: Okay. There are three more
16 people in line after you, and those will be the
17 last three in the interest of finishing more or
18 less on time. Try and keep it a focused question,
19 if you don't mind.

20 MS. KIRSCHNER: My name is Jen Kirschner.
21 My question will be for Professor Burris.

22 First, I do have a comment that we talk a

1 lot about opiate addiction is a brain disease
2 within the individual. But I'd like to quote
3 Dr. David Edelstein from NIDA at a talk he gave at
4 Johns Hopkins the other week, "That addiction is
5 also a social pathology and that treatment can only
6 get us so far without changing the socioeconomic
7 landscape."

8 Anyway, my question for Mr. Burris is, I
9 feel like today we've heard about physicians and
10 other qualified people like nurse practitioners who
11 can prescribe naloxone to former or current drug
12 users, or on the other hand, making it over-the-
13 counter.

14 What would it look like if we want to do
15 something like have these prescribers give it to
16 third parties?

17 MR. BURRIS: Well, that's the rub. There's
18 no question that any licensed prescriber can
19 prescribe naloxone to a person for whom it is
20 personally indicated. When you start giving drugs
21 to someone to give to someone else, you're going
22 very quickly into a fuzzy or even across-the-line

1 kind of zone because essentially what you're doing
2 is deputizing them to be a medical provider.

3 Now, we don't care about that, as has been
4 mentioned a couple of times. We talk about
5 parents. We just actually sort of pretend that
6 line isn't there. We don't apply it to parents.
7 Parents can give to their kids, or I can give it to
8 my aged mother or something like that. And, in
9 fact, a lot of programs are operating in that kind
10 of fuzzy zone now, and it may be that that'll work
11 fine.

12 What this big fight here is really about is
13 how we go from having -- well, I don't want to say
14 pathetically -- a bravely small band of people who
15 are taking this issue on to have a comprehensive
16 solution, or at least a comprehensive intervention,
17 that will reach most of the people who need it most
18 of the time they need it. And I think for that, we
19 won't be able to deal with the fuzzy lines. We're
20 going to have to have clear rules.

21 One kind of clear rule is it's an over-the-
22 counter drug. So you don't have to worry about

1 prescribing. Another kind of clear rule is where a
2 state authorizes a broader range of people to
3 prescribe to a broader range of other people, which
4 states can do under their law.

5 You know, we're now 25 years into needle
6 exchange, and we still have very poor coverage on
7 the state level. We don't want to be in this same
8 situation 25 years from now with a condition that
9 is currently killing more people than car
10 accidents. So we're going to need some big change
11 fast.

12 DR. LURIE: Okay. Dr. Coffin?

13 DR. COFFIN: Phillip Coffin. I think
14 we -- well, an epinephrine pen often times gives
15 you a window of opportunity in anaphylaxis to get
16 somebody to medical care. So the nice thing about
17 naloxone is that it gives that window, whether it's
18 medical care or a hypothetical intervention after
19 an overdose, which I have never seen or heard about
20 at this point, that might increase treatment
21 uptake; although there are data that 20 percent of
22 people -- at least in Baltimore from

1 Dr. Robin Pollini, that 20 percent of people who
2 overdosed enrolled in treatment within 30 days,
3 which is a pretty impressive number.

4 As an investigator, I've heard a lot of talk
5 about sort of our failure to provide adequate data,
6 and I would like to propose and ask -- I understand
7 there's been a great increase in funding for
8 overdose research in the last 10 to 15 years.

9 That increase is from, honestly, close to
10 zero to a handful, a small handful of studies. And
11 with 15 to 20,000 opioid overdose deaths a year, I
12 think this demands a greater national response.
13 And I wonder, especially with the reorganizations
14 at NIH and, of course, all of the horrible budget
15 shortfalls everywhere, how we can prioritize
16 overdose investigations and help the investigators
17 find some of the data that's being requested.

18 DR. COMPTON: I'd like to respond just a
19 little bit to that. First off, that wasn't really
20 a question. That was more of an encouragement to
21 people like me and the others from NIH to consider
22 this a high priority area.

1 You can certainly take our presence at this
2 meeting and our sponsorship of this meeting as an
3 indication that we think this is a very serious
4 issue, and we look forward to applications from you
5 and many other colleagues to help expand the
6 research database.

7 I would also -- this is a little bit of
8 comment and a little bit of question for the panel
9 in terms of I certainly heard a major theme of the
10 need for medical education and looking at how do we
11 move from a grassroots-built set of initiatives
12 around the country to something that's more
13 integrated within the broadly defined medical
14 system, whether that's the substance abuse
15 treatment system, the methadone programs, general
16 medicine, emergency departments that interact with,
17 at a minimum, drug addicts.

18 But also, I'm hearing pain patients and
19 those at risk for overdose because of high dosages
20 of opiates, or opioids. And I think that I'm
21 putting on the table the need for research on this,
22 but also for practice developments in this area as

1 well.

2 DR. LURIE: Go ahead.

3 DR. BRASON: Addressing that in the medical
4 community in North Carolina, we have done some
5 research -- and obviously with what we've done just
6 on our Wilkes County as Project Lazarus -- we are
7 reaching the entire medical community now in North
8 Carolina. We have created a toolkit for
9 prescribers on prescribing opioids, patient
10 education for addiction, how to manage the chronic
11 pain patient.

12 We've created a toolkit for emergency
13 departments so that they can understand the proper
14 prescribing for that individual, how to monitor,
15 how to use the PMP, all of those aspects. And the
16 North Carolina Hospital Association, North Carolina
17 College of Emergency Physicians, division of public
18 health, medical society, medical board are all on
19 board.

20 So we are doing a comprehensive medical
21 education to all prescribers, whether it's MD, PA,
22 nurse practitioner, and reaching every hospital,

1 every emergency department, and essentially, every
2 practice in North Carolina over the next 18 months
3 to just do what you were talking about so they have
4 that education so there can be that intervention
5 and prevention on the prescribing and on the
6 dangers of overdose.

7 While at the same time, if in fact an
8 overdose does occur, here's the naloxone so that
9 you are aware that you've just been discharged from
10 the hospital. You've had a brain injury from that
11 car accident, and here's your pain medication.
12 Don't take more medication just because you have
13 more pain. Call me and let's find out what else is
14 going on because we've essentially lost individuals
15 in our community just because of that.

16 So that's sort of how we're addressing the
17 medical community, not really going at it from a
18 research perspective at this point. Just saying
19 this is the epidemic that we're at today. We have
20 to intervene now and not later.

21 DR. BARTOSZEK: And we're doing the exact
22 thing at Fort Bragg, and we have -- to train all of

1 our hundreds of primary care providers. And we
2 actually have a grant written and a protocol
3 written to study it, to look at the outcomes of the
4 education piece plus the naloxone, and all the
5 other primary preventative measures that we do to
6 decrease opioid risk.

7 DR. LURIE: Okay. Then the final question
8 from the audience.

9 MS. SOTHERAN: Yes, Jo Sotheran from
10 National Alliance of Methadone Advocates. This is
11 a question primarily for Dr. Burris and Dr. Brason.

12 Anybody who comes out of the world from
13 methadone treatment knows two things. One is about
14 regulation, because we have it up to the eyebrows.
15 The other is about methadone is the most researched
16 medication in the world, and we still have
17 problems.

18 The other thing was somebody pointed to the
19 role of big government. And I'd like to ask about
20 how you would maybe envision that because
21 eventually methadone treatment did change, and
22 we've seen the effects. It actually used to be

1 regulated by the FDA, in fact. Now it's regulated
2 by another agency. And this happened in spite of
3 very complex differences in state regulation.

4 So I'd like to kind of ask for some ideas
5 about how the feds, particularly the FDA because
6 they now control it, might develop a constructive
7 relationship with the states going forward in this.

8 Thanks.

9 DR. BRASON: I can speak to it from
10 methadone in specific opiate treatment programs
11 that are under SAMHSA CSAT. And we heard from Nick
12 Reuter this morning when he gave us the table of
13 contents on the toolkit that SAMHSA will be -- we
14 were hoping this afternoon. I guess that didn't
15 happen, so sometime soon, the prescriber's toolkit
16 for the opiate treatment programs.

17 In that table of contents was from SAMHSA
18 the naloxone component with overdose education as
19 part of that. So that's one answer that the
20 government is providing regarding methadone. And,
21 as I mentioned, the OTPs in North Carolina now have
22 decided each one is going to now co-prescribe

1 naloxone to every new enrollee because,
2 unfortunately, last year, we did lose 20
3 individuals who were new enrollees into methadone
4 programs, and that needs to stop.

5 So we have the state division of health and
6 human services supporting that and encouraging that
7 as well as SAMHSA and the federal government
8 working directly to do that, as he said, the first
9 agency to perhaps do that.

10 MR. BURRIS: That was such a wonderful
11 softball. I know I'm going to lie awake tonight
12 thinking of all the things I missed to say. But
13 let's start with the surgeon general's summit on
14 drug overdose and what we should do about it.
15 Let's find somebody in the federal government who's
16 going to be the overdose czar who's going to take
17 responsibility for coordinating all the different
18 pieces of CDC and NIDA, HHS, SAMHSA, FDA, that have
19 to work together to figure out what we're going to
20 do with this problem. And we've got to figure out
21 from FDA if it's not an orphan drug -- so we can't
22 subsidize its development that way -- how are we

1 going to deal with the economic realities that Dr.
2 Wermeling was talking about?

3 We could get Congress involved. Congress
4 could pass a rider to the appropriations bill
5 requiring that states who want to receive federal
6 substance abuse funding have got to assure Congress
7 within one year that they have developed legal
8 mechanisms that assure that overdose reversal with
9 naloxone is available to anybody in that state.

10 Medical education and training. The REMS
11 is, I suppose, one model. As was pointed out
12 today, we haven't even -- as Dr. Dasgupta pointed
13 out, we haven't begun to think about incorporating
14 the reversal element naloxone in training that way.

15 What about pain care? We're talking about
16 the fact there are people using these drugs and
17 maybe misusing them not because they want to have a
18 really good time but because they are having a
19 really bad time already and need pain care. What
20 are we doing to make sure that we have more
21 qualified pain care referrals to make when people
22 need them? That seems to be a shortage profession,

1 and I think it's going to become a worse one. We
2 face some risks.

3 As the state attorney generals and the DEA
4 start to be confronted with this problem, they're
5 going to use the tools they have. They're going to
6 crack down on people, and we're going to be back to
7 the days when we had fear among physicians of
8 prescribing too many opioids. We have to worry
9 again that we're going to go back to the days when
10 cancer patients or people who just had broken legs,
11 have been in a car crash, will come home with
12 insufficient pain care.

13 So there are all those questions, which I
14 think people are very aware of. I mean,
15 Dr. Volkow's article, for example, was quite good
16 on that.

17 But you can see the range of things. So in
18 some sense, this meeting is about the need to pull
19 those strings together and the need for leadership
20 and -- just exactly what you were saying,
21 Dr. Compton, sort of a more complex view. Research
22 will be part of that, but action today will be part

1 of that.

2 And we really can't just have a piece. What
3 we've got today is a world of pieces. And that is
4 not going to stop this epidemic.

5 DR. LURIE: Let that be the last word.

6 (Applause.)

7 DR. LURIE: For our closing remarks, I'd
8 like to introduce Sarah Wattenberg. She is the
9 senior advisor for substance abuse policy in the
10 Office of the Assistant Secretary for Health.
11 She's also responsible for keeping Doug and Wilson
12 and I in line and the behavioral health
13 coordinating committee. And in that, I can assure
14 you she's a failure.

15 Here she is.

16 **Closing Remarks - Sarah Wattenberg**

17 MS. WATTENBERG: Good afternoon, everyone.

18 I thought this was a great meeting today.

19 And at times, it was hard. It was emotionally
20 hard, I think, but I think it was good. And what
21 I'm going to do is give that dry, boring and short
22 closing to help bring down the heat, bring down the

1 heart rates, and really just review a little bit
2 about what we've talked about today, and to just
3 give my own personal impression, which is that we
4 are all here today because we care deeply about
5 this problem.

6 I think that that needs to be said. We all
7 have different perspectives, but we're here because
8 we want to figure out how to bring the perspectives
9 together so that we can do something productive to
10 address what we are seeing.

11 So I'm going to start by again reiterating
12 thanks to FDA, NIDA, CDC and SAMHSA for joining
13 together to make this meeting happen today. In
14 particular, I want to thank Peter Lurie and Doug
15 Throckmorton for their leadership, Mary Gross, Jan,
16 Matt, wherever you all are, for coordinating
17 logistics, making sure we had food, getting the
18 PowerPoint presentations in and herding the cats.
19 It's not easy to do that, and I think you did a
20 great job.

21 One of the reasons why I want to sort of
22 give yet thanks again to my federal partners is

1 because I want to underscore that this is not, in
2 fact, an isolated event. For the past two years,
3 through the Behavioral Health Coordinating
4 Committee and the Prescription Drug Abuse
5 Pharmaceutical Abuse Committee, these agencies
6 actually have been coming together very regularly
7 to talk about this problem, to see what we can do,
8 do we have the right data, what we can do better,
9 how can we improve. And this meeting today is
10 partly a result of that.

11 So I want you to understand that you have
12 our attention, all of you. And I also hear that
13 you want us to do more, which is also okay.

14 So I want to thank all of our speakers,
15 moderators, panelists and especially the public and
16 the advocates in the advocacy organizations for
17 coming today.

18 To the advocates, thank you for sharing your
19 stories and your passion. I do feel that we have
20 heard your sense of urgency today. And I don't
21 think anyone will leave here today going untouched
22 by your pain.

1 To the speakers, thank you for your
2 excellent presentations and your reflections. You
3 were articulate and thoughtful and at times brave
4 in sharing your opinions. And I also heard you say
5 that we needed to do more.

6 So to summarize today, we initiated a public
7 discussion about whether to make naloxone more
8 widely available outside the medical setting to
9 reduce fatal overdoses. To appropriately
10 contemplate that issue, we invited people to share
11 all of the relevant scientific, regulatory, social,
12 legal, ethical, and it seems like everything else
13 information.

14 We heard about the use of naloxone in a
15 variety of settings with different high-risk
16 populations, different models of interventions,
17 along with some of the potential risks and benefits
18 associated with the interventions.

19 The FDA then provided some clear regulatory
20 pathways, though perhaps burdensome, for expanding
21 the use of naloxone should that be pursued.

22 Information was presented about new

1 formulation development, the over-the-counter
2 process, the ethical issues related to studying
3 naloxone in patients who cannot provide informed
4 consent, issues related to the business case, and
5 some of the cost and reimbursement issues.

6 Once the regulatory roadmap became clearer
7 for how the broader use of naloxone could happen,
8 our last panel opined on whether or not it should
9 happen.

10 I am not going to recount the discussion for
11 all the obvious reasons, but also because they just
12 had it. But I will remark that it stimulated a
13 range of opinions and passion about this topic.
14 And I personally believe that the back and forth
15 and the exchange was one that needed to be had.
16 It's why we are here today. This is what we
17 wanted. This is what we need to think about as we
18 move forward.

19 So I am going to close the meeting today by
20 just reminding everybody that the goal was not to
21 answer the questions but rather to raise the
22 issues, explore the risks and benefits, and better

1 understand potential pathways for moving forward.

2 And I think we did that.

3 Thank you for coming today.

4 (Applause.)

5 (Whereupon, at 5:30 p.m., the meeting was
6 concluded.)

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