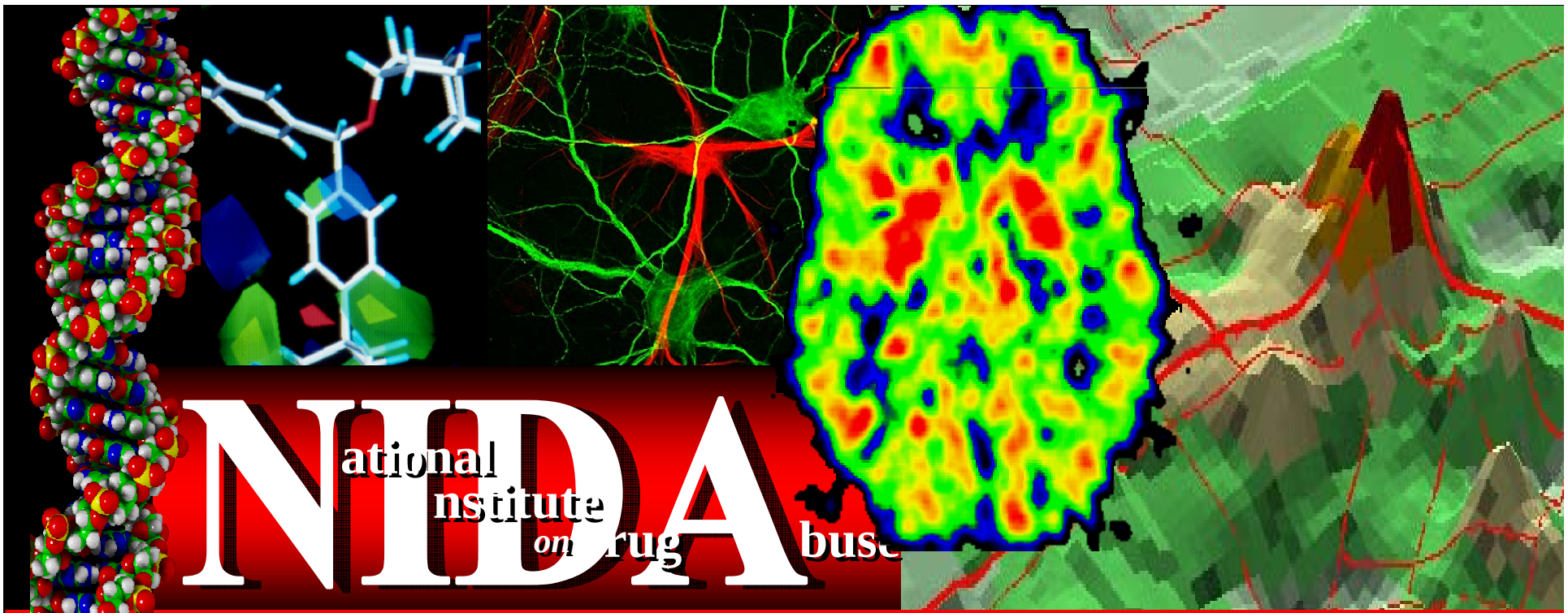




NIDA
National Institute on Drug Abuse

Outcomes in Drug Use, Abuse & Addiction Research

Wilson M. Compton, M.D., M.P.E.

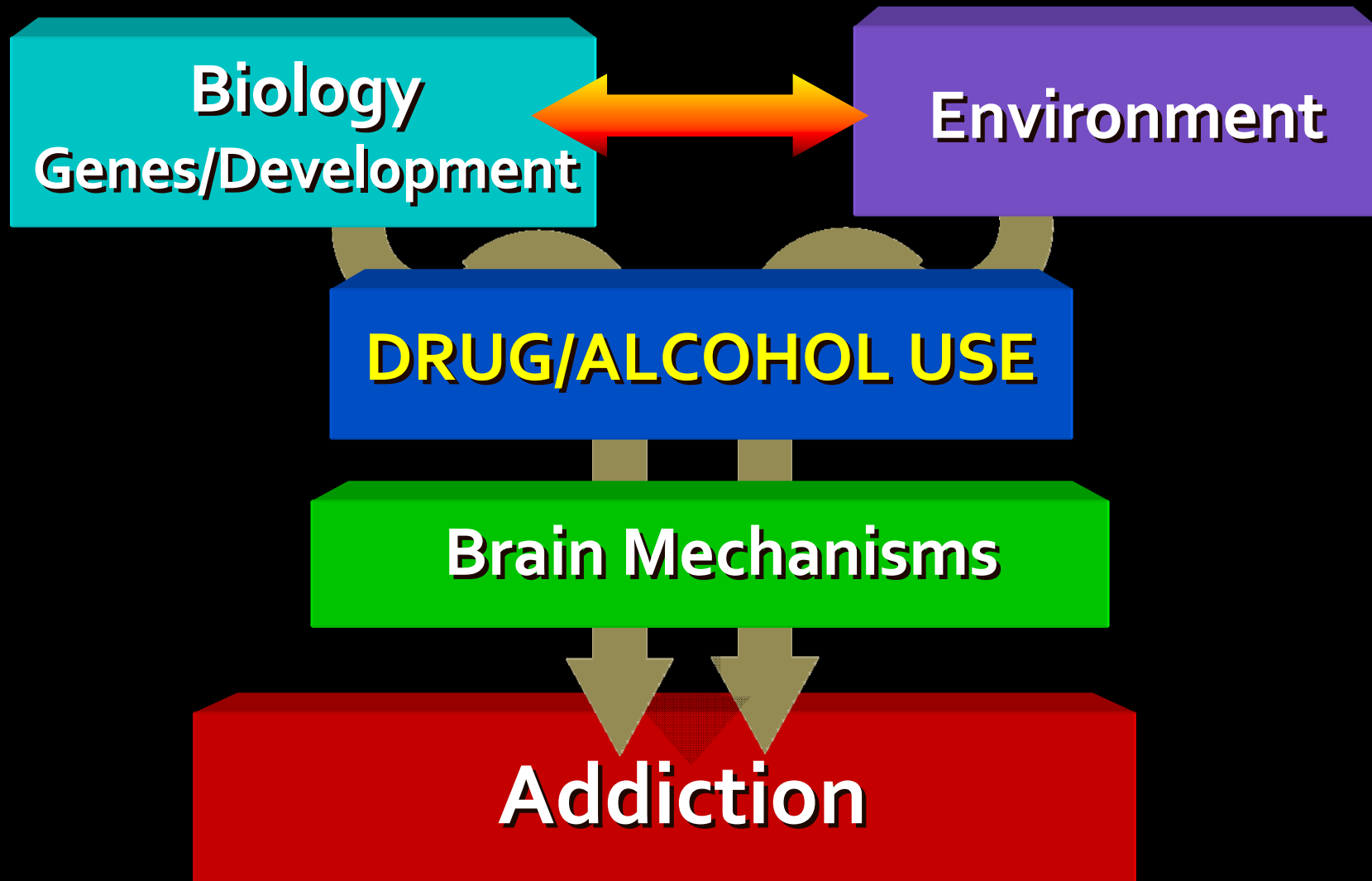
Director, Division of Epidemiology, Services and Prevention Research

National Institute on Drug Abuse

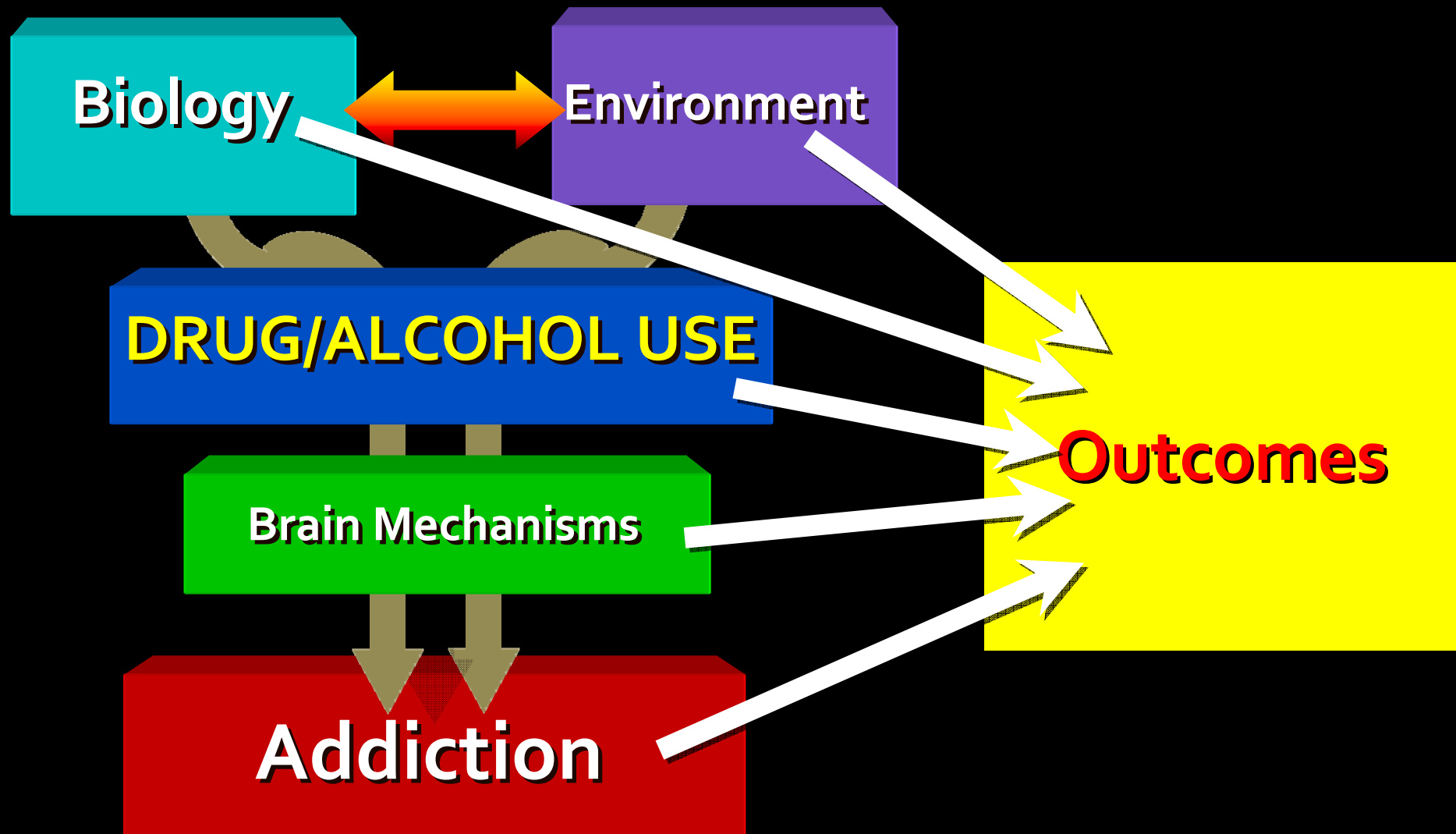


Substance Abuse & Addiction

Involve *Multiple Factors*



Outcomes of Substance Abuse & Addiction also Involve *Multiple Factors*



Outcomes for U.S. Food and Drug Administration (FDA) Stimulant Dependence Medication Approval

Success/failure analysis required (no group means).

“Success” must be clinically significant.

Preferably, success will be defined by a period of abstinence that lasts through the end of treatment.

With justification, a grace period may precede the period of abstinence that is required for “success.”

For approval, pivotal studies should be conducted for a minimum of 6 months.

Celia Winchell, M.D.

Medical Team Leader for Addiction Drug Products

FDA Division of Anesthesia, Analgesia, and Rheumatology Products

The Challenge of Outcomes

- *Abstinence vs. Reductions in Use*
- *Recovery*
- *Health Outcomes*
- *Using Consistent Measures*
 - *"Data Harmonization" for Research*
 - *Clinical settings (e.g. Electronic Health Records)*

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- **Drug-taking behavior (i.e. “abstinence”) is the primary outcome for drug abuse treatment clinical trials.**

(See Donovan, et al., Addiction, 2011;107:694-708)

- **So, abstinence is a typical outcome. What about reductions in use? When does a reduction become meaningful?**
- **For example, is reduction in cocaine use associated with psychosocial benefit?**

Using Data from Cocaine Dependence Pharmacotherapy Trials to Examine Clinical Correlates of Reductions in Cocaine Use

Phase II, double-blind RCTs for cocaine dependence

Study medication (n)

- Baclofen (n=160)
 - Ondansetron (n=63)
 - Selegiline (n=300)
 - Carbergoline (140)
 - Modafinil (210)
 - Reserpine (140)
 - Tiagabine (140)
- 8-week treatment (n=523)
- 12-week treatment (n=630)
- N=1,153**

Source: NIDA's Medication Trial Database, Ivan Montoya, Personal Communication, March 2012

- **Urine sample for quantitative toxicology analysis**
 - Pre-randomization
 - Thrice weekly during treatment
- **Outcome variables**
 - Brief Substance Craving Scale (BSCS)
 - Clinical Global Impression (CGI)
 - Observed (CGI-O)
 - Self-rated (CGI-S)
 - Addiction Severity Index (ASI)
 - HIV Risk Behavior Scale (HRBS)

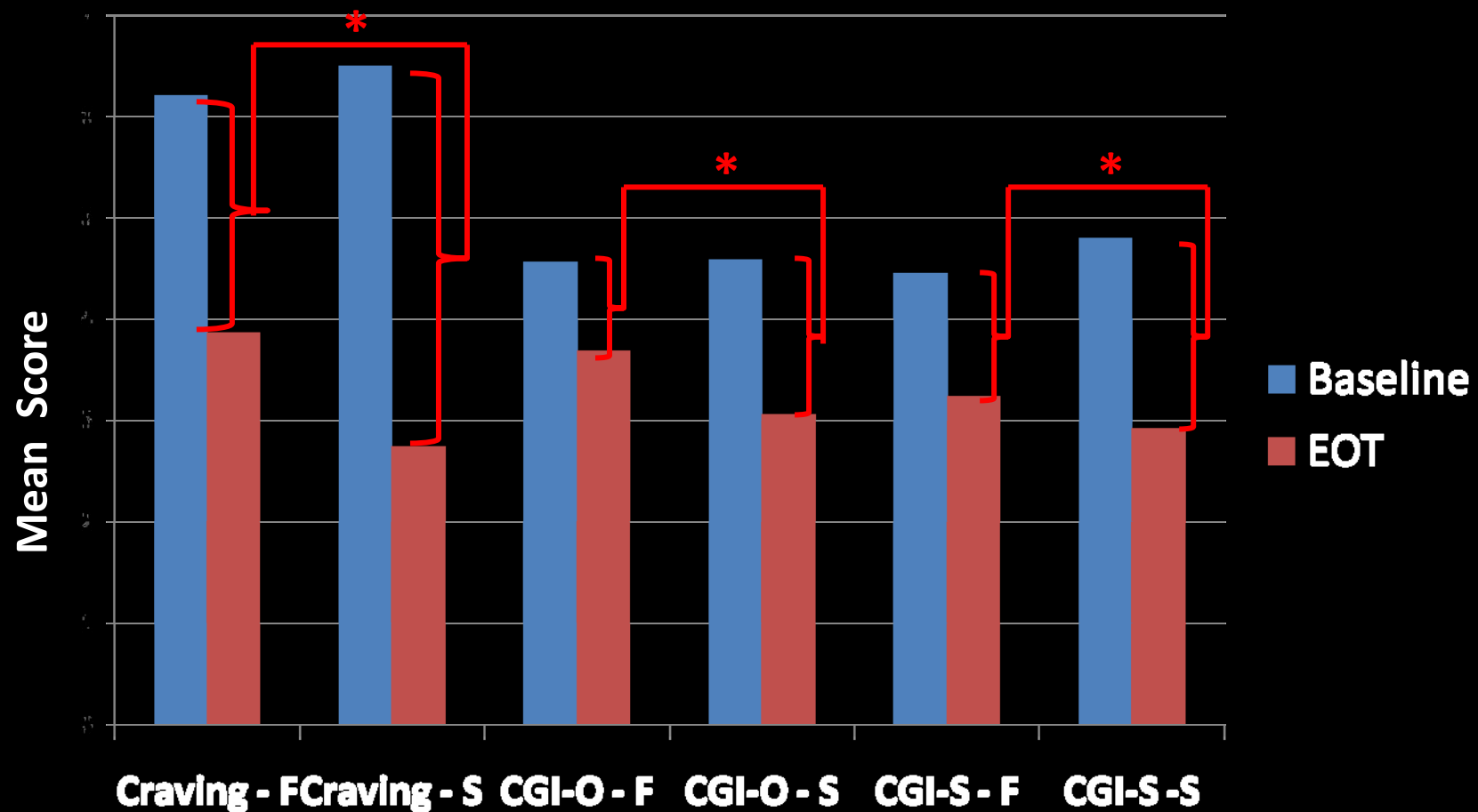
*Source: NIDA's Medication Trial Database, Ivan Montoya,
Personal Communication, March 2012*

Data Analysis

- Comparisons of Successful (reduction of 50%+ in urine benzoylecgonine between baseline and end of study) vs. Failure (reduction of less than 50%)
- End of study defined as weeks 6-8 for 8-week studies and weeks 9-12 for 12-week studies
- Comparisons for each outcome variable as difference in mean scores at baseline and end of study
- Separate analysis for 8- and 12-week studies
- Subjects with missing data excluded from analysis
- Stepdown Bonferroni correction *t*-tests applied

Difference in Mean BSCS, CGI-O and CGI-S between Treatment Failure and Success

(12-week study, n=405)

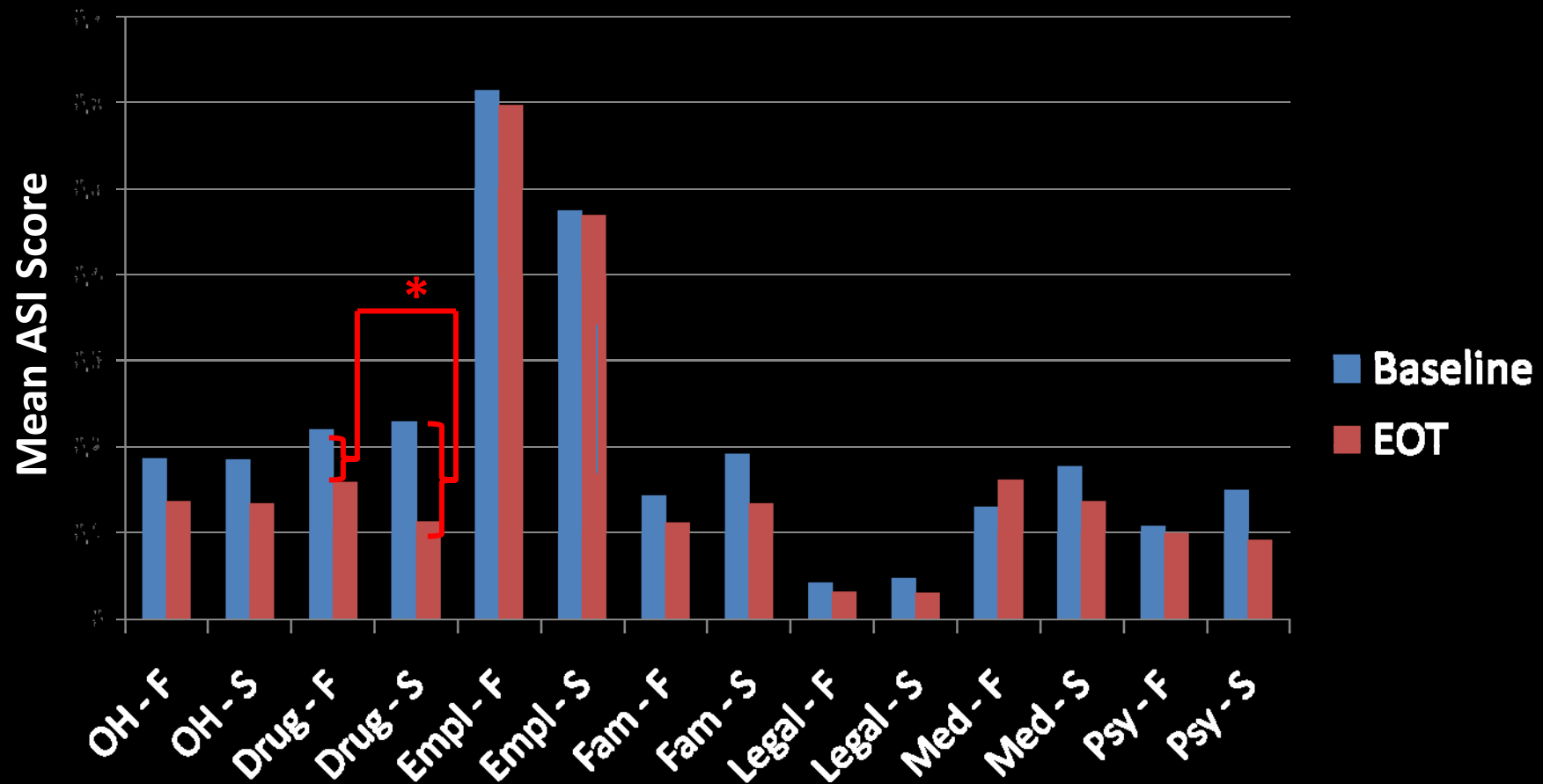


* $p < .01$

Source: NIDA's Medication Trial Database, Ivan Montoya, Personal Communication, March 2012

Difference in Mean ASI Scores between Treatment Failure and Success

(12-week study, n=314)

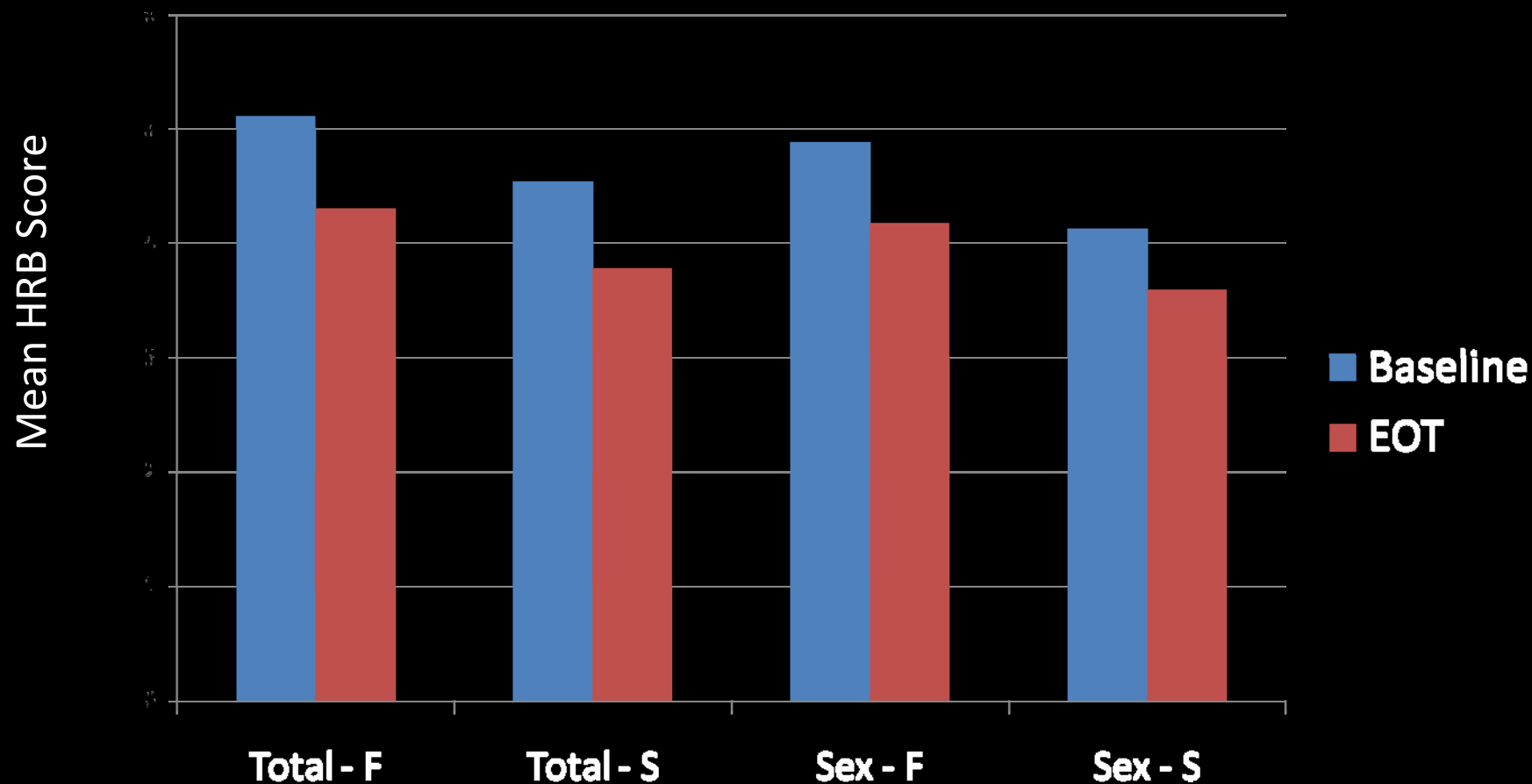


* $p < .01$

Source: NIDA's Medication Trial Database, Ivan Montoya, Personal Communication, March 2012

Difference in Mean HIV Risk Behavior Scores between Treatment Failure and Success

12-week (study, n=347)



Source: NIDA's Medication Trial Database, Ivan Montoya, Personal Communication, March 2012

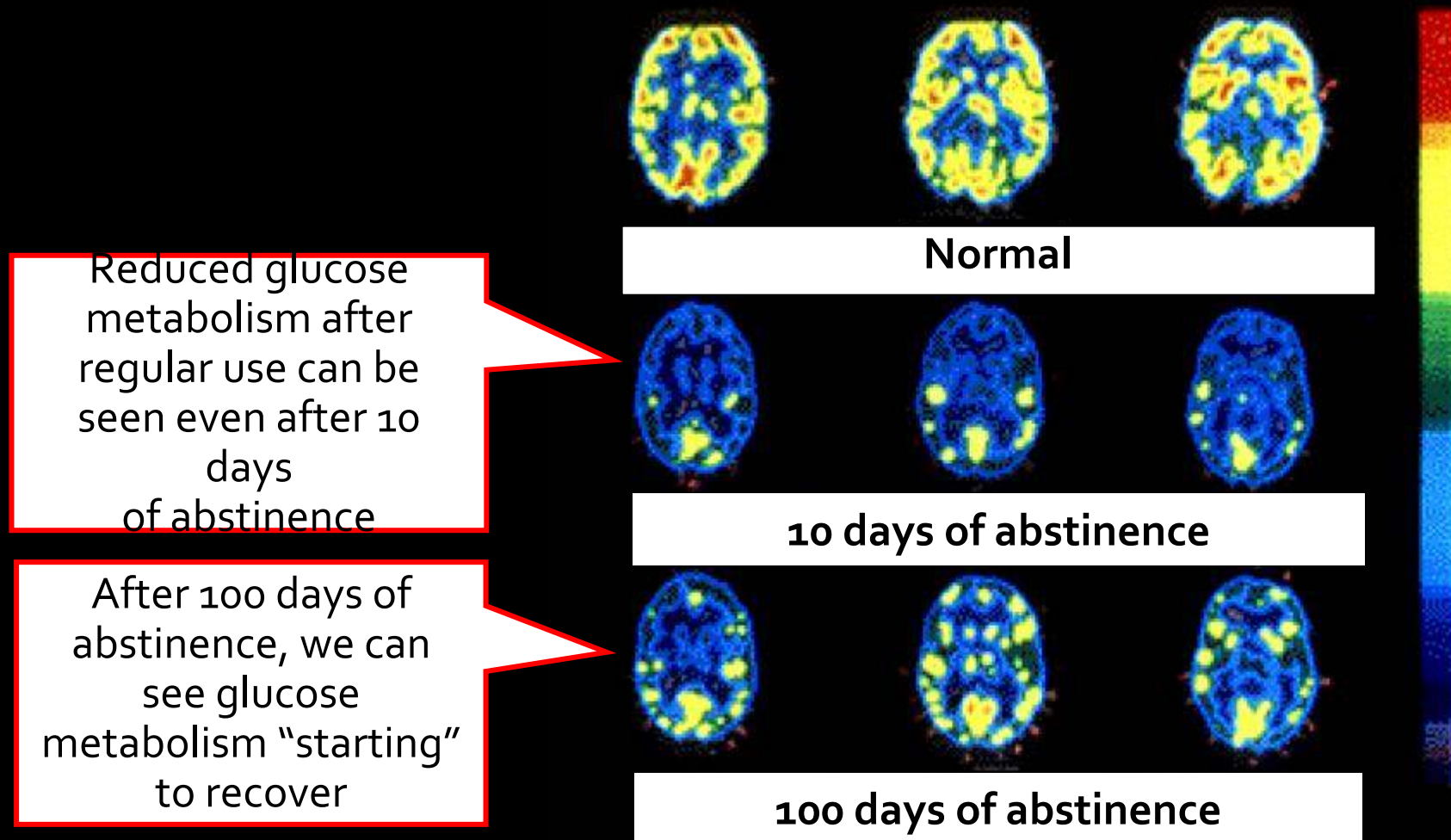
Key Questions: *Abstinence v. Reductions in Use*

- Reductions in consumption are acceptable outcomes for alcohol studies but not so clearly for tobacco and illicit drug studies. Are there clinically meaningful reductions in consumption other than abstinence for tobacco and illicit drug research?
- What outcomes should be considered in these studies?
 - Health
 - Social (employment, crimes, etc.)
 - Quality of life

The Challenge of Outcomes

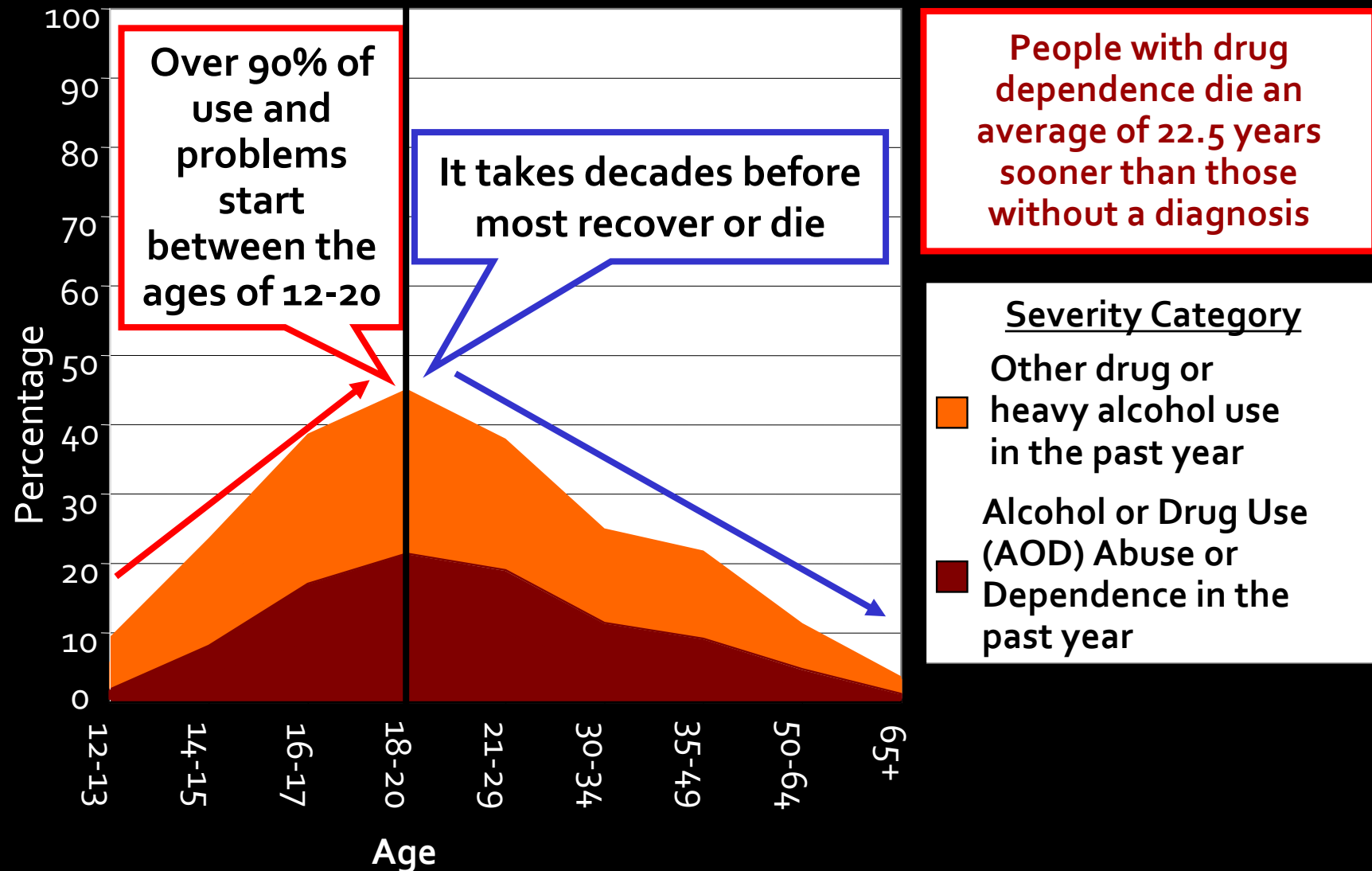
- *Abstinence vs. Reductions in Use*
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Prolonged Substance Use Injures The Brain: *Healing Takes Time*



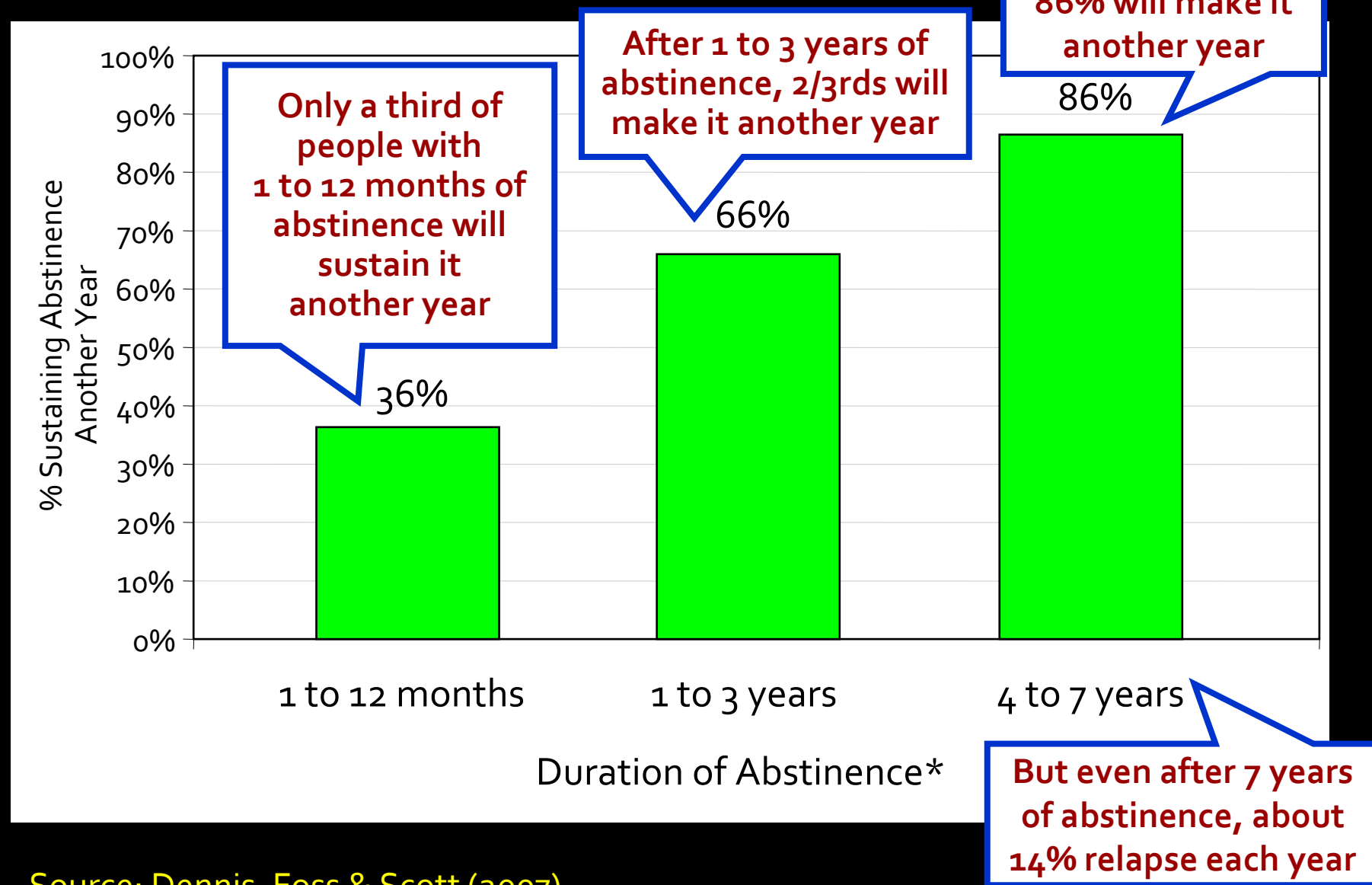
Source: Volkow ND, Hitzemann R, Wang C-I, Fowler JS, Wolf AP, Dewey SL. Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 11:184-190, 1992; Volkow ND, Fowler JS, Wang G-J, Hitzemann R, Logan J, Schlyer D, Dewey S, Wolf AP. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* 14:169-177, 1993.

Alcohol and Other Drug Abuse, Dependence and Problem Use Peaks at Age 20



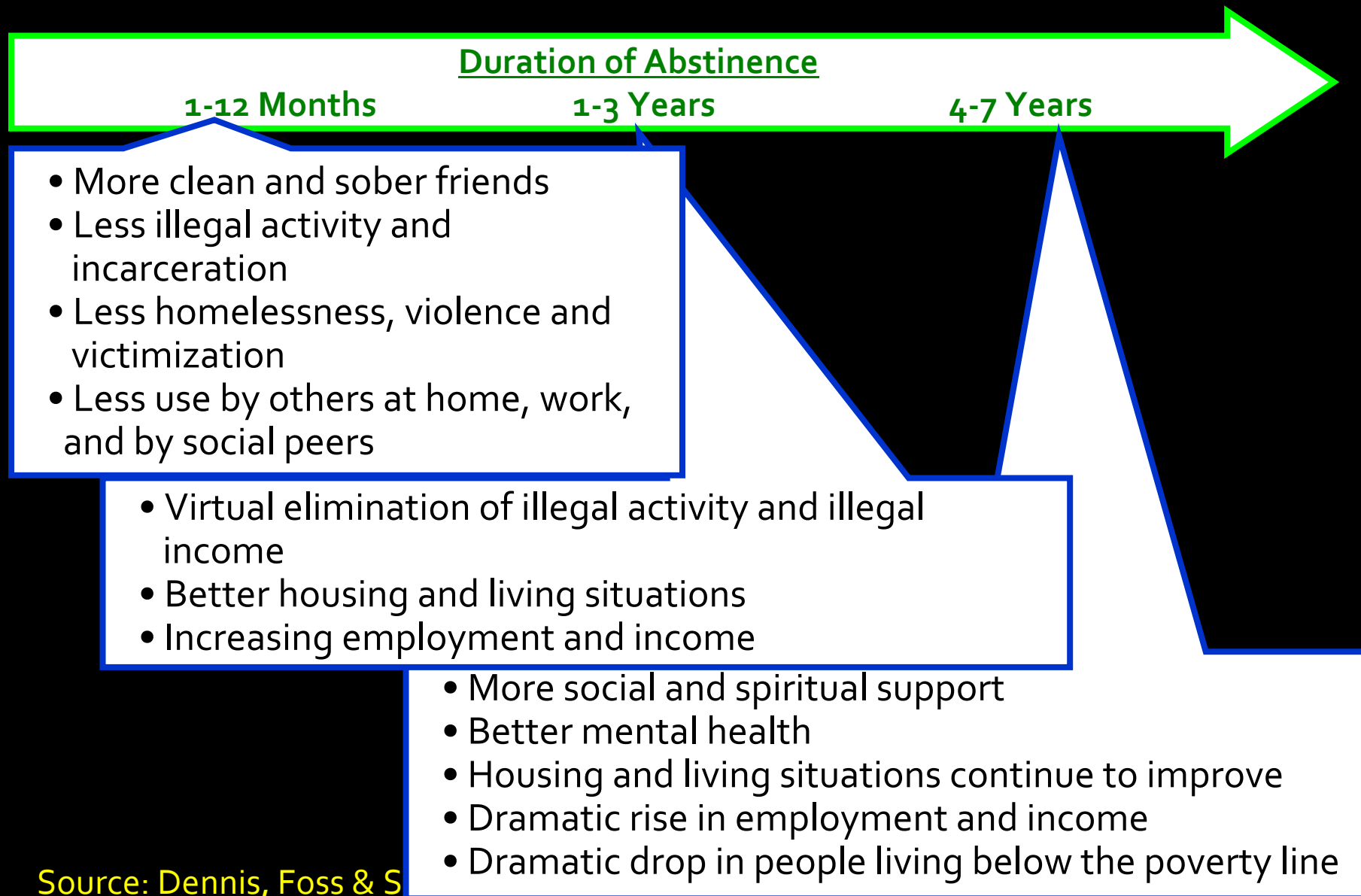
Source: 2002 NSDUH and Dennis & Scott, 2007, Neumark et al., 2000

The Likelihood of Sustaining Abstinence Another Year Grows Over Time



Source: Dennis, Foss & Scott (2007)

What does recovery look like on average?



Key Questions: *Recovery Outcomes*

- To determine “recovery status”, the definition of recovery is essential. How is recovery defined?
- What are the key factors involved in a stable abstinence and recovery?
- Is *Recovery* the same as *Remission* (or *Abstinence*)?
- Does the age at which abstinence starts influence outcomes?

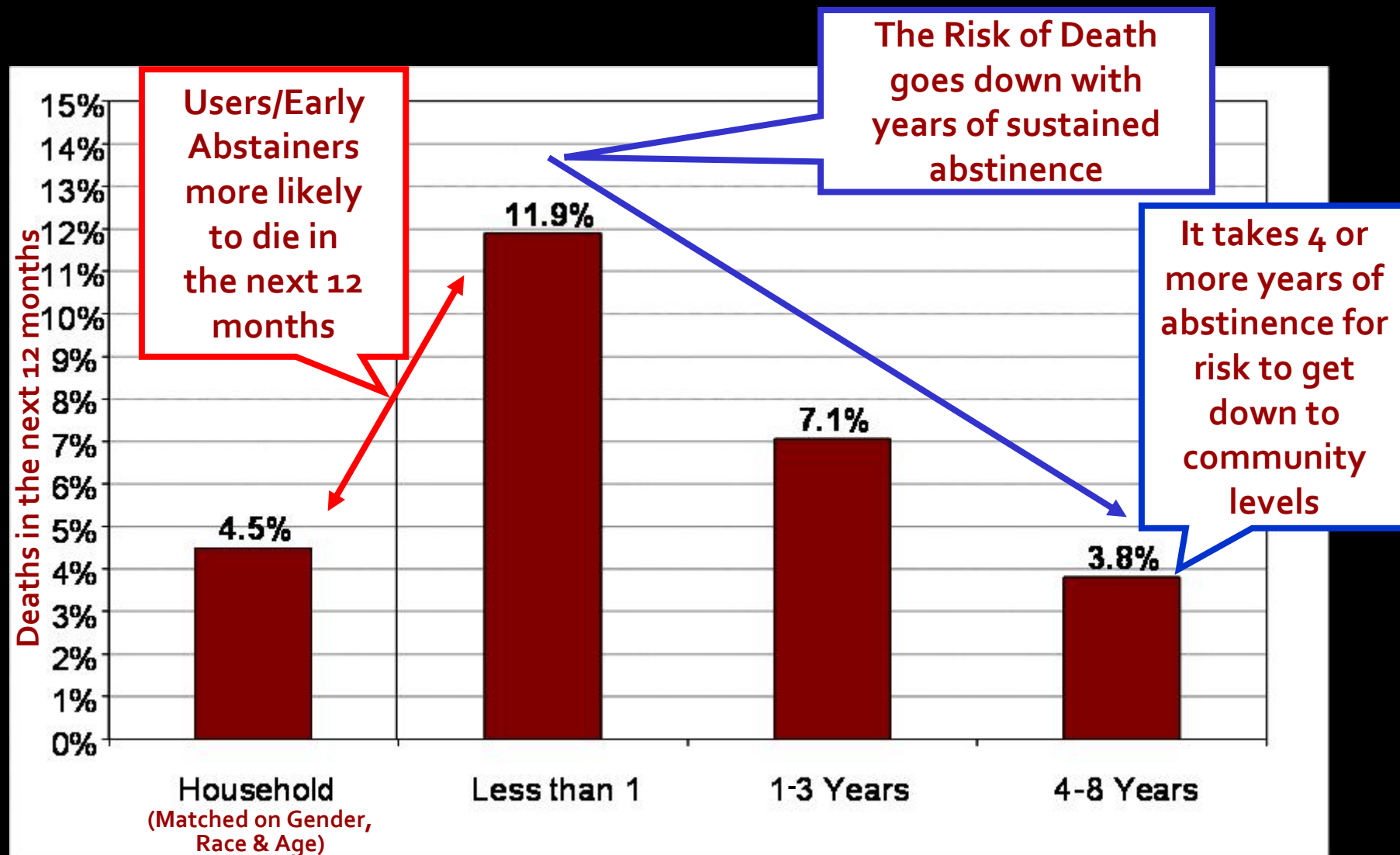
The Challenge of Outcomes

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Mortality in 33 Year Follow Up of Heroin Addicts: *Lost 18.3 Years of Potential Life Before Age 65*

- 29.4% Violent death (homicide, suicide, accidents)
- 26.2% Fatal overdose
- 14.0% Liver diseases/hepatitis
- 11.8% Cardiovascular diseases
- 20.0% Miscellaneous (under 6% each)

Sustained Abstinence Reduces Risk of Death*



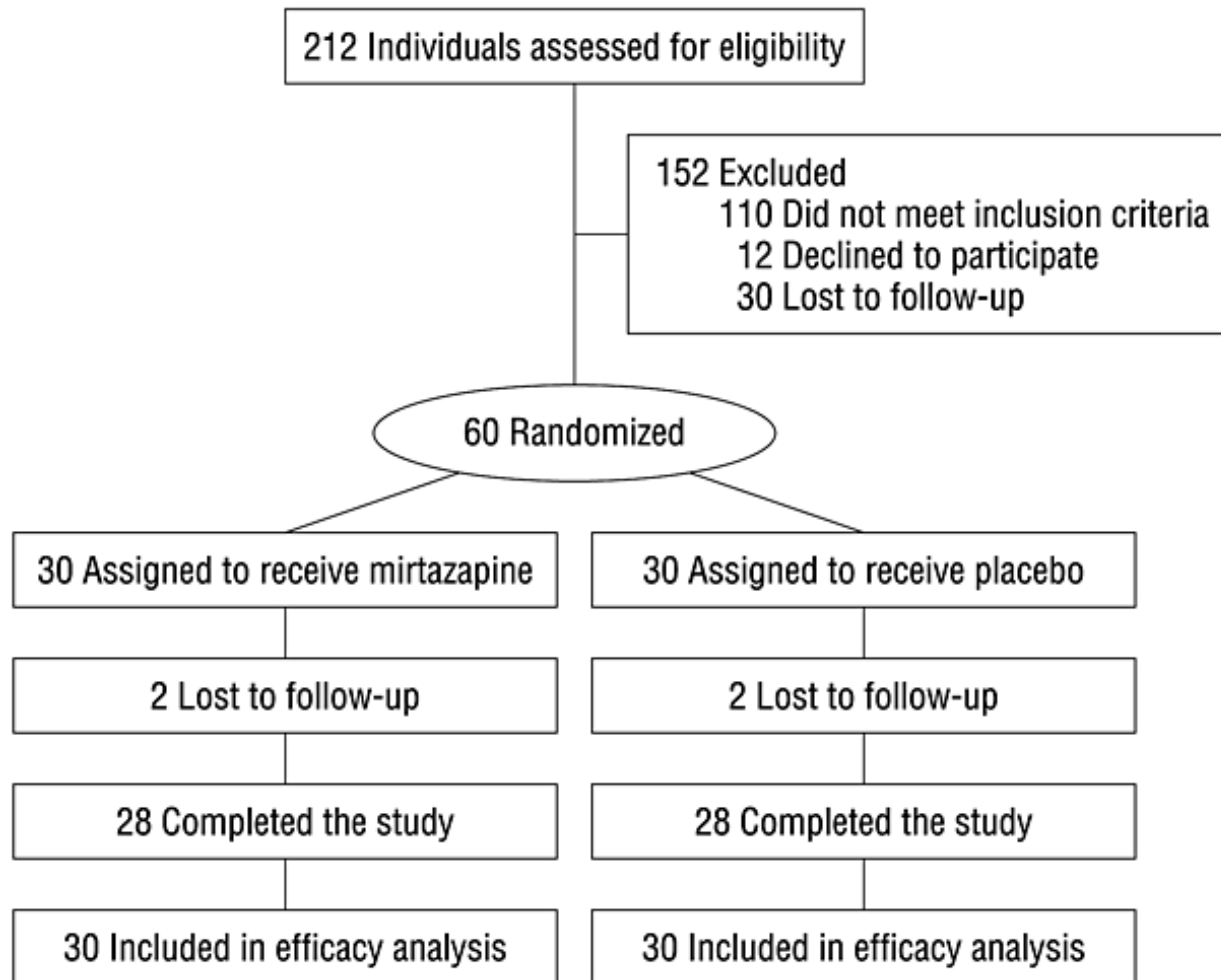
Source: Scott, Dennis, Laudet, Funk & Simeone AJPH 2011

* $p < .05$

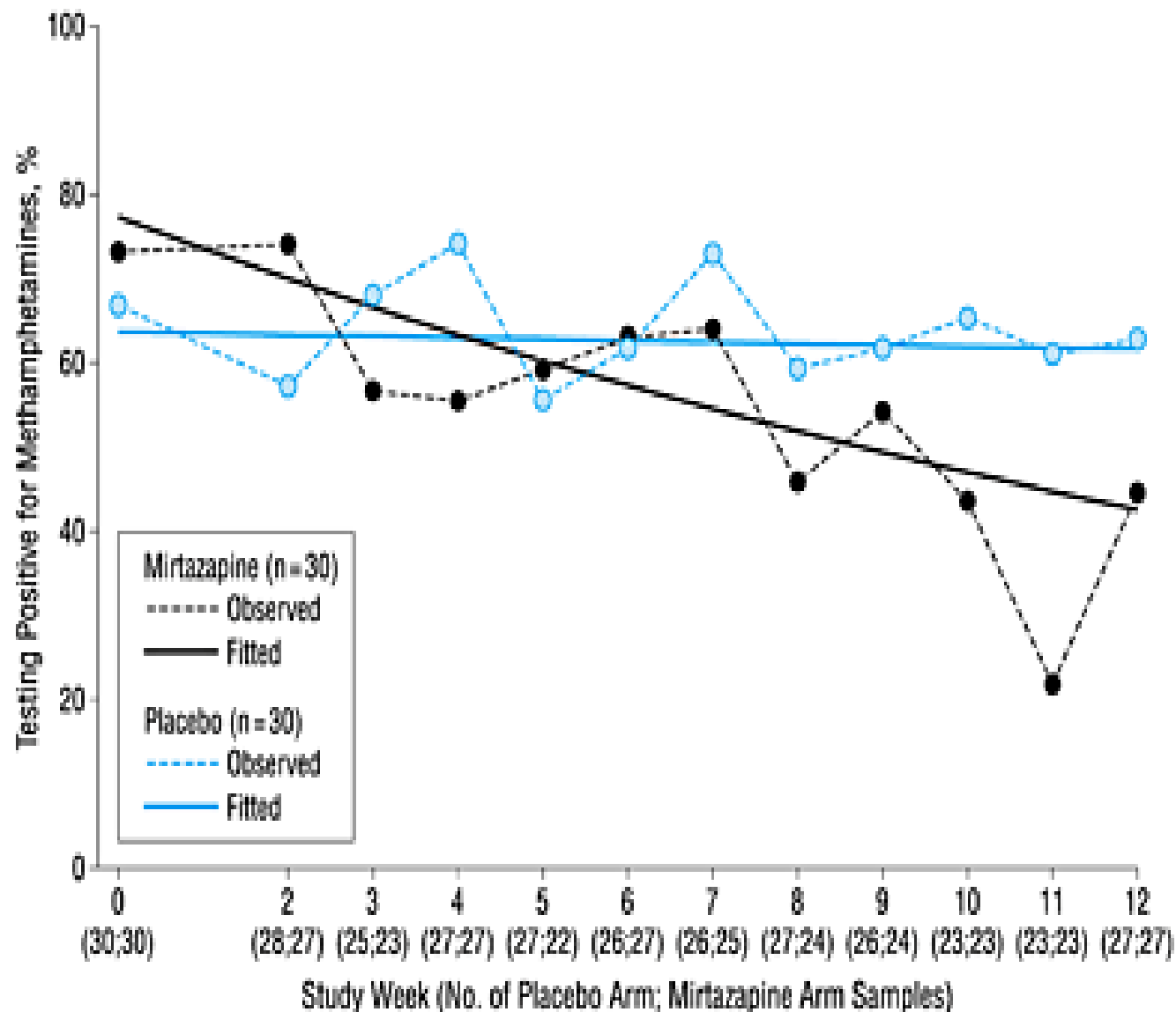
Key Questions: *Health Outcomes*

- In addition to mortality reductions, what are the key health improvements in drug abuse treatment?
 - Cancer?
 - Cardiovascular health?
 - Accidents and injuries?
 - HIV?

Mirtazapine to Reduce Methamphetamine Use: A Randomized Controlled Trial



Observed and fitted weekly urinalysis results (by treatment)



Changes in Sexual Risk Behavior (by Treatment)

Behavior	Mean (SD)				Risk Ratio (95% CI) ^b	P Value
	Baseline	4-Week Visit	8-Week Visit	12-Week Visit		
No. of male partners with whom methamphetamine was used						
Placebo	6.6 (10.3)	11.3 (42.1)	3.6 (9.1)	4.8 (10.4)	0.45 (0.24-0.82)	.009
Mirtazapine	5.4 (8.9)	2.6 (6.7)	2.4 (5.5)	1.4 (3.8)		
No. of male partners						
Placebo	9.3 (12.8)	13.2 (44.9)	5.9 (12.1)	24.8 (94.4)	0.20 (0.04-0.93)	.04
Mirtazapine	11.6 (19.5)	4.0 (6.6)	3.6 (6.2)	3.1 (5.0)		
Episodes of anal sex with serodiscordant partners						
Placebo	3.6 (8.1)	9.3 (42.3)	3.4 (11.6)	4.9 (15.6)	0.31 (0.14-0.66)	.003
Mirtazapine	4.0 (8.6)	2.3 (6.6)	1.7 (5.4)	1.3 (3.8)		
Episodes of unprotected anal sex with serodiscordant partners						
Placebo	3.4 (8.1)	9.3 (42.3)	3.4 (11.6)	4.5 (15.3)	0.34 (0.17-0.70)	.003
Mirtazapine	3.7 (8.1)	2.1 (6.5)	1.7 (5.5)	1.2 (3.8)		
Episodes of insertive unprotected anal sex with serodiscordant partners						
Placebo	2.7 (7.0)	8.8 (42.2)	3.2 (11.6)	4.0 (15.1)	0.29 (0.14-0.58)	.001
Mirtazapine	2.8 (7.0)	1.5 (4.2)	1.4 (5.3)	0.7 (2.0)		
Episodes of receptive unprotected anal sex with serodiscordant partners ^c						
Placebo	0.7 (2.8)	0.9 (3.8)	0.4 (1.0)	1.0 (3.3)	0.27 (0.05-1.57)	.14
Mirtazapine	1.6 (4.5)	0.9 (3.1)	0.4 (1.1)	0.9 (3.4)		

^aSexual behaviors are defined as self-reported sexual activity within the past 4 weeks. Serodiscordant partner is defined as a human immunodeficiency virus (HIV)-positive individual with an HIV-negative or an unknown HIV-status partner or an HIV-negative individual with an HIV-positive or an unknown HIV-status partner.

^bPoint estimates were adjusted for the motivated to participate in the trial to receive counseling variable and its interaction with time to control for imbalance at baseline.

^cThis was the only behavior not evenly distributed between the 2 arms ($P = .049$).

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What is Harmonization?

(Curran et al., Developmental Psychology 44: 365-380, 2008)

- **Having commensurate measurement across independent studies**
 - **Constructs have the same theoretical meaning**
 - **Measures reflect the same construct**
 - **Variables are scored with identical values**
 - **Values are scaled commensurately, and function equivalently**

Source: Kevin Conway, NIDA

What is Harmonization?

(Curran et al., Developmental Psychology 44: 365-380, 2008)



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Source: Kevin Conway, NIDA

Degrees of Harmonization: Nicotine Dependence

Construct
Level

Nicotine Dependence

Measure
Level

Fagerstrom Test of Nicotine Dependence
(FTND)

Item
Level

i1
time to first
cigarette of
the day

i2
difficulty
refraining
from
smoking
where
forbidden

i3
which
cigarette
least likely
to give up

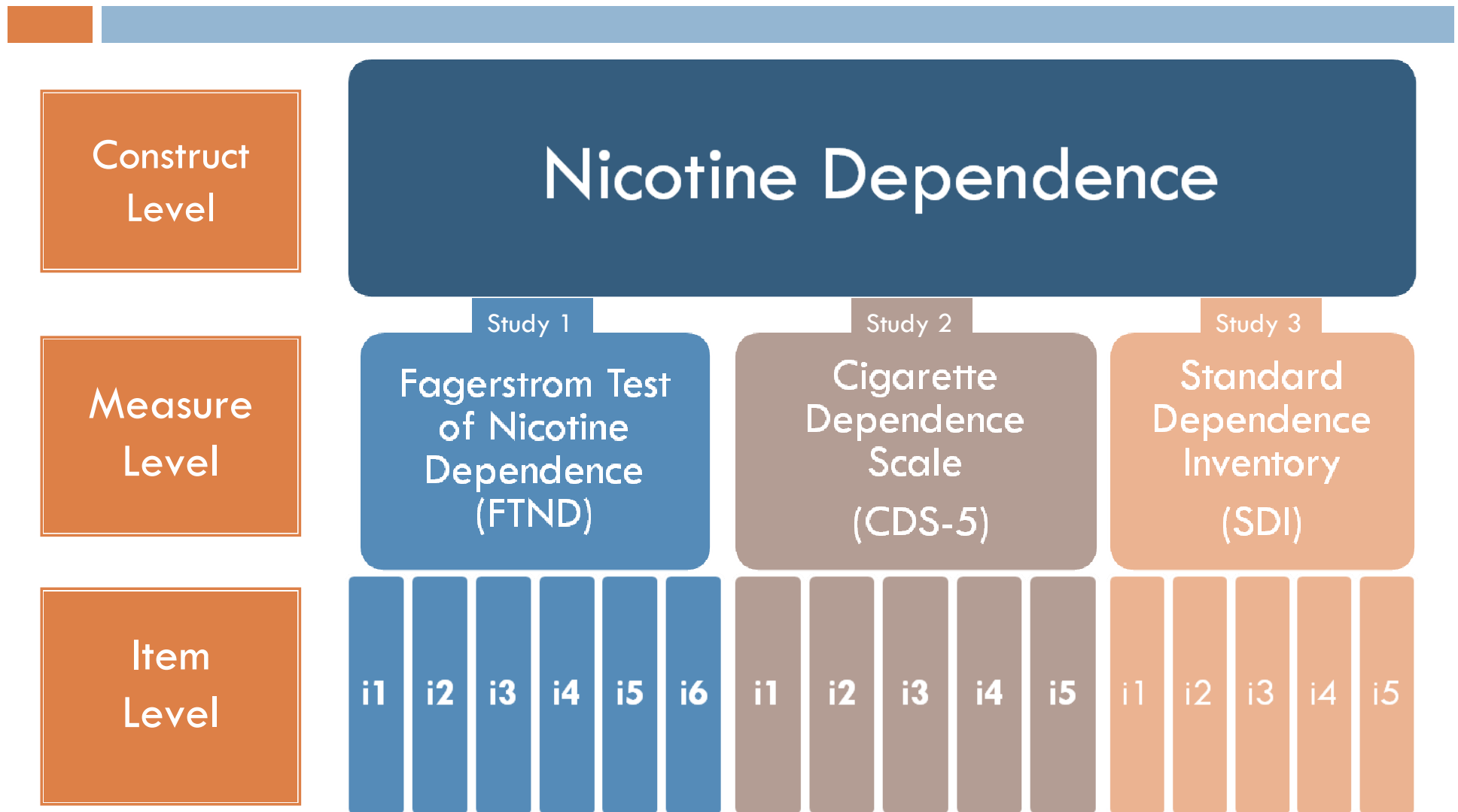
i4
number of
cigarettes
smoked per
day

i5
prefer
smoking
during early
part of the
day

i6
smoke even
when ill
and in bed
all day

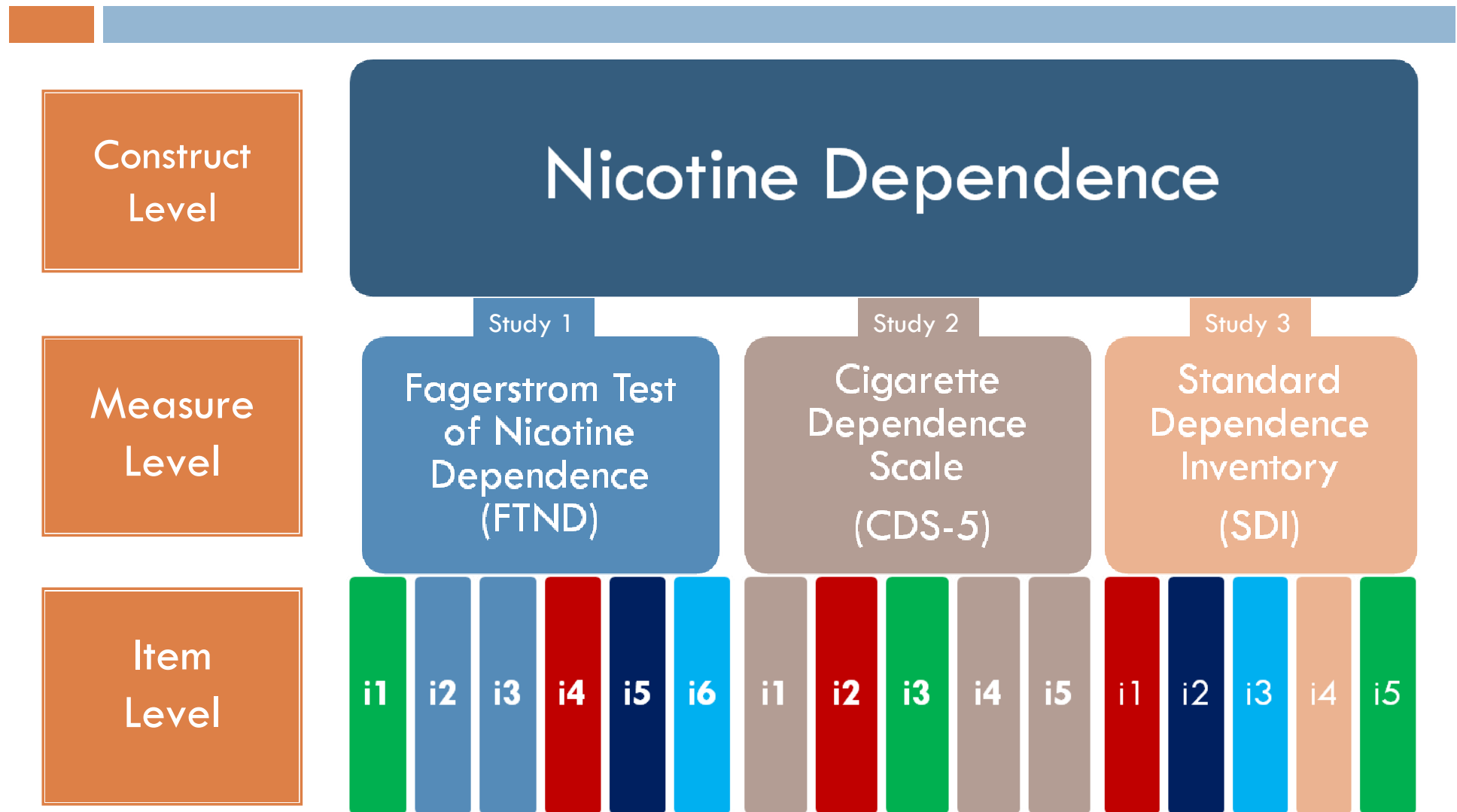
Source: Kevin Conway, NIDA

Case 2: Construct-Level Harmony



Source: Kevin Conway, NIDA

Case 2: Construct-Level Harmony



Source: Kevin Conway, NIDA

Building consensus for standard measures of phenotypes and exposures



- PhenX is a three year project led by RTI International and funded by the National Human Genome Research Institute (NHGRI) to contribute to the integration of genetics and epidemiologic research
- PhenX has prioritized 21 research domains related to complex diseases and environmental exposures
- Consensus building is being used to develop a recommended minimal set of high priority measures for use in Genome-wide Association Studies (GWAS) and other large-scale genomic research efforts
- High priority measures will maximize benefits of future research by enabling cross-study comparisons and analysis
- Selection and specification of the measures are driven by the scientific community via the PhenX Steering Committee, Working Groups and community consensus.
- The PhenX Toolkit presents the selected high priority measures to the scientific community

[More...](#)

PHENX TOOLKIT



The PhenX Toolkit makes the results of the project readily accessible via The Internet and enable researchers to implement the high priority measures.

The PhenX Toolkit is now available at: www.phenxtoolkit.org

[More...](#)

STEERING COMMITTEE



A Steering Committee of distinguished experts from the scientific community guides the selection of the measures and promote their use. Research domains include diseases and conditions; lifestyle factors and anthropometrics; and environmental exposures.

[More...](#)

WORKING GROUPS



Working Groups (WGs) are assembled for each research domain. Each WG is responsible for selecting a small set of measures and protocols for obtaining the measure. Recommended measures are vetted with the scientific community through a consensus outreach process.

[More...](#) | [How to get involved](#)

Construct Level

Measure Level

Item Level

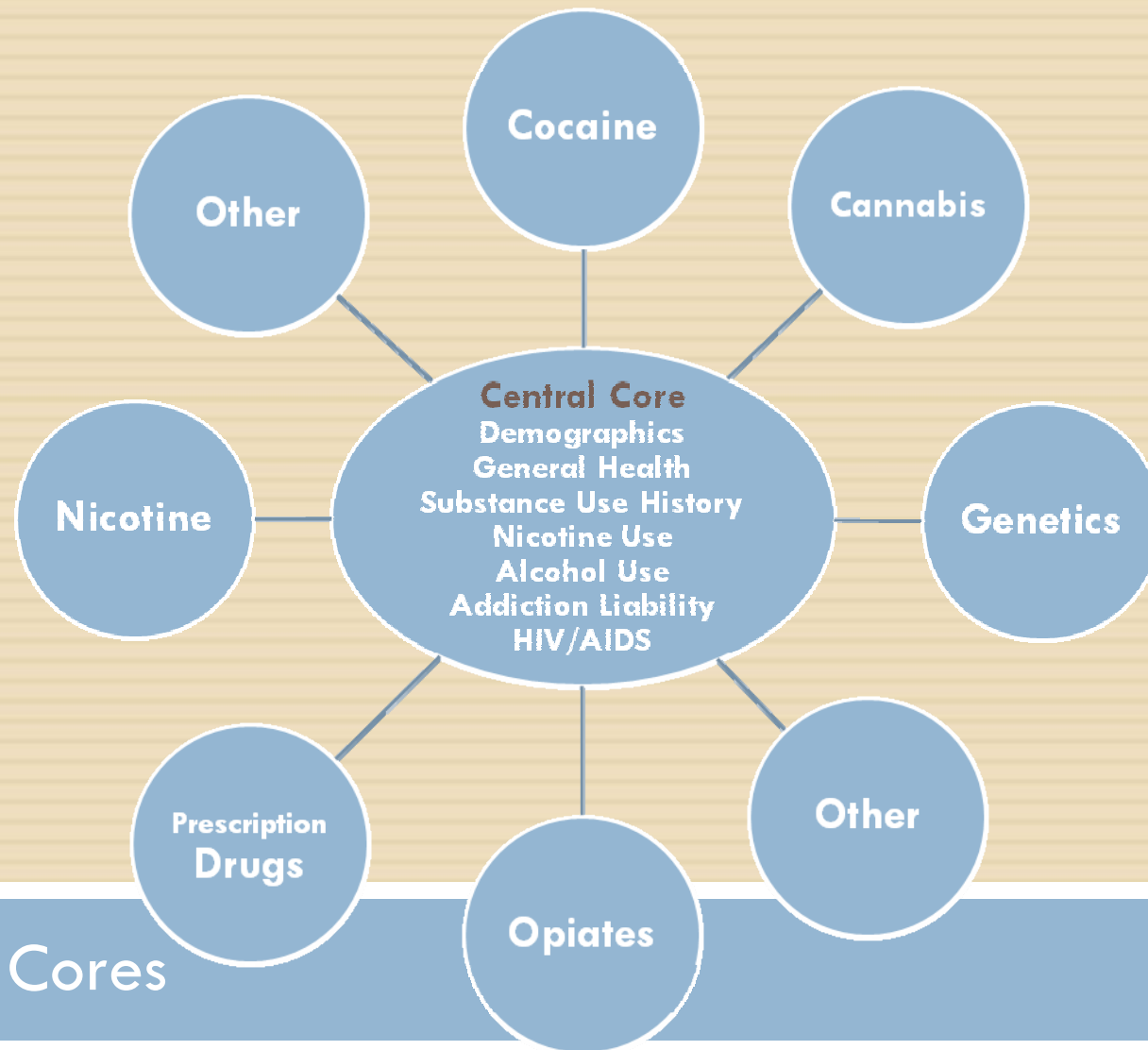
The Cores

Central core questions are asked in every study

Specialty core questions will be asked based on the specific interests of the study

Example: A genetics of nicotine study would use three cores (Central, Genetics and Nicotine)

Source: Kevin Conway, NIDA



Ongoing Harmonization Activities



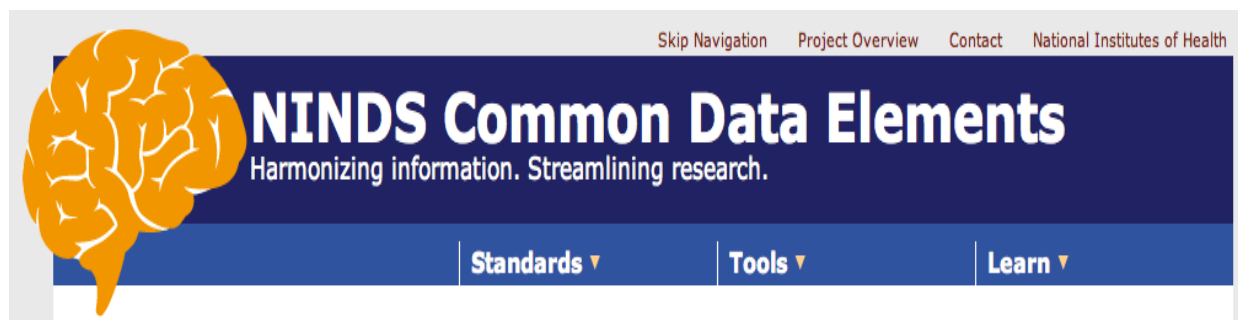
www.phenx.org



- CCTN Common Assessment Battery
- Genetics Consortium
- Seek, Test, and Treat Grantees



- Task Force on Recommended Alcohol Questions



The Challenge of Outcomes

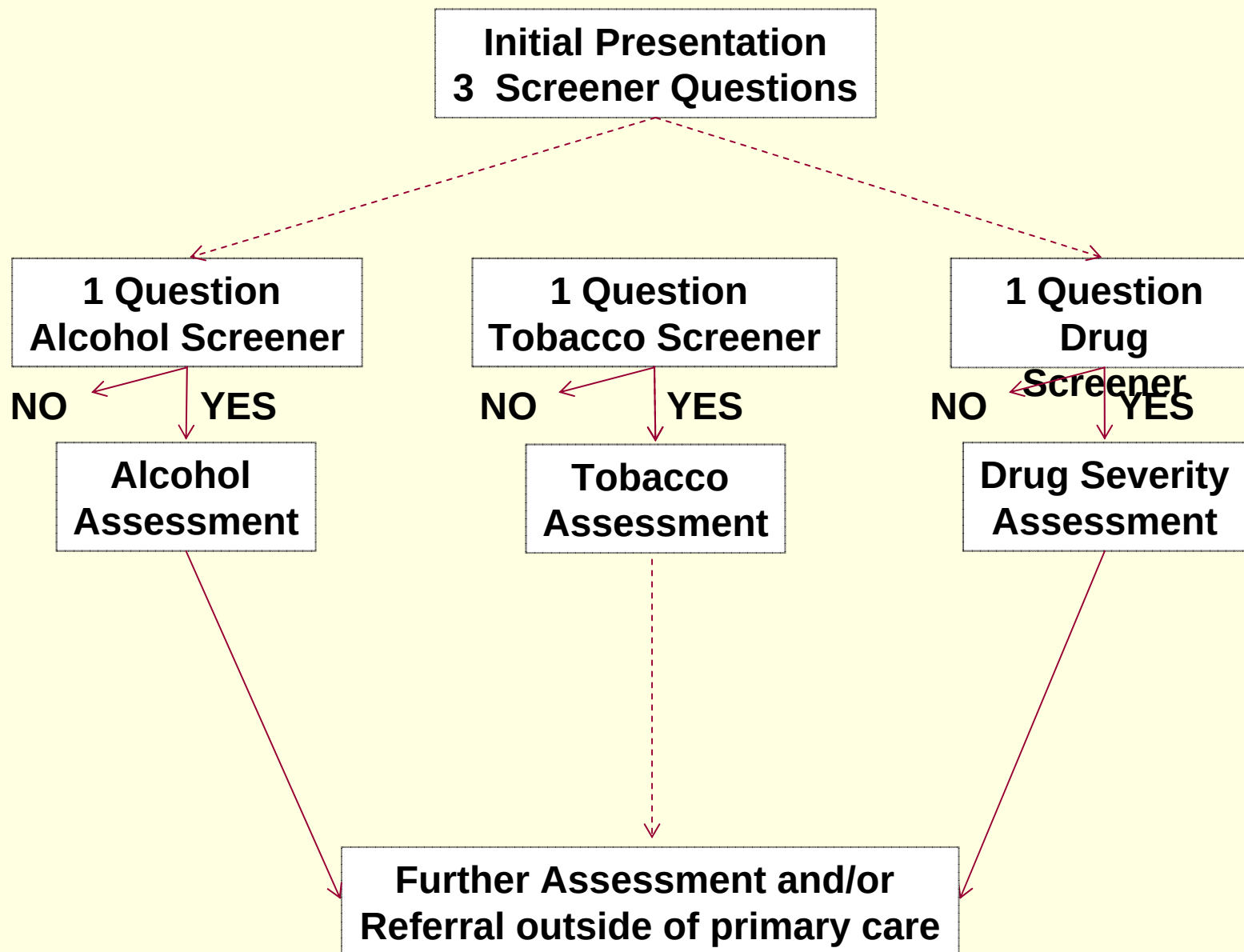
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Electronic Health Record (EHR)

- **Federal encouragement to adopt with “meaningful use”**
- **Multiple vendors developing EMR**
 - **Hospital based systems**
 - **Individual practice based systems**
 - **Interoperability (EMRs → EHR)**
- **Content**
 - **Clinical care**
 - **Research**

Electronic Health Record (EHR)

- **Federal meaningful use criteria**
 - **Incentive through reimbursement**
 - **Incorporate concepts and data elements to qualify for meaningful use**
 - **Example**
 - **Meaningful use stage 1 (2011-2012)**
 - **Screen for tobacco use in > 50% of clinic population**
 - **Meaningful use stage 2 (proposed, for 2013)**
 - **Screen for tobacco use in 80% of clinic population**
 - **Screen and brief intervention for alcohol use disorders**
 - **Screen for illicit and prescription drugs**



Key Questions: *Measurement*

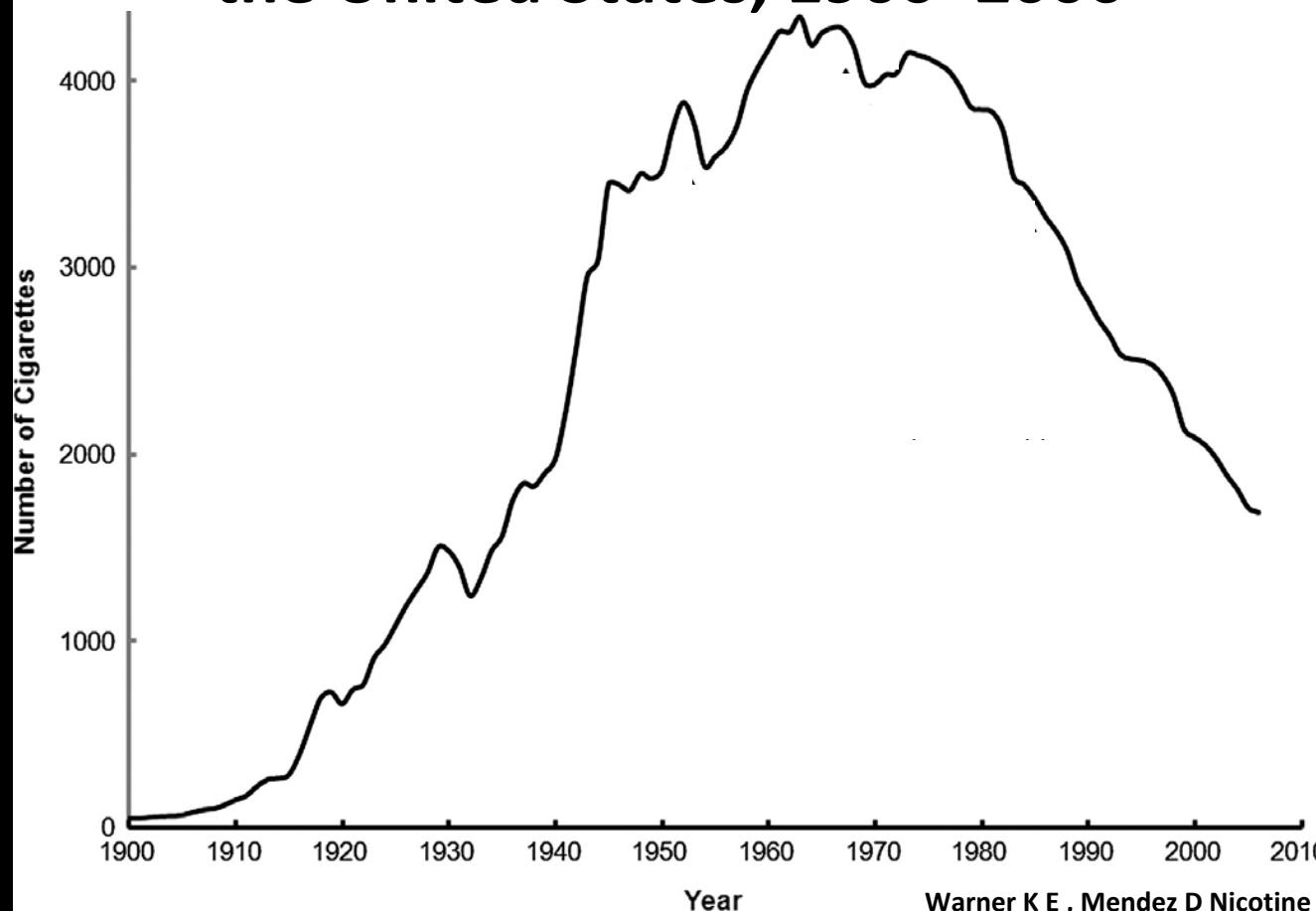
- How can consistent, robust measurement systems be implemented across clinical settings and research studies?
- What are the minimum domains and what are other domains of potential interest?

Summary: Multiple Outcome Domains for Research and Practice

- *Abstinence vs. Reductions in Use*
- *Recovery*
- *Health Outcomes*
- *Using Consistent Measures*
 - *"Data Harmonization" for Research*
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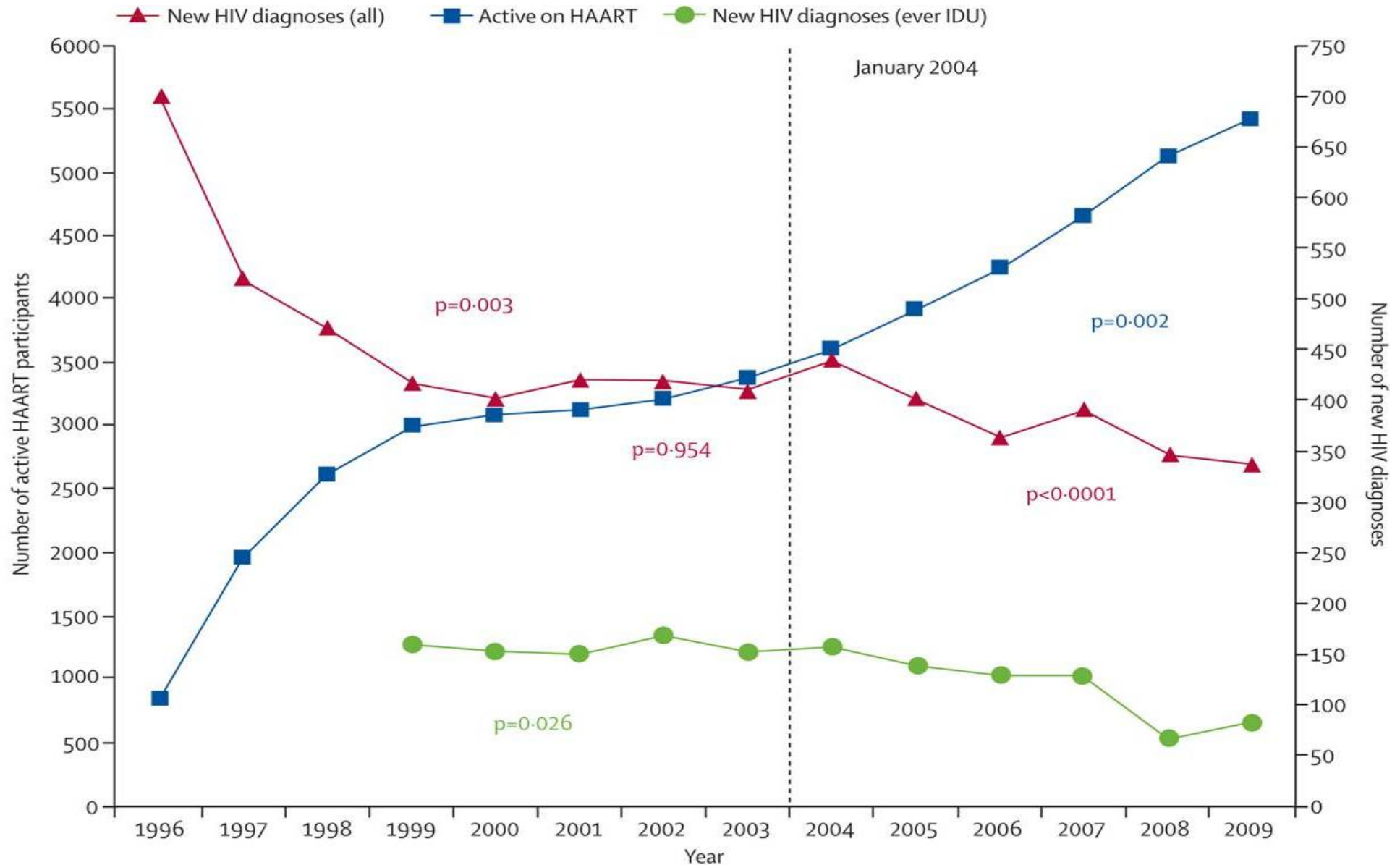
Ultimate outcomes include population impacts measured at the community, region or national level.

**Adult per capita cigarette consumption,
the United States, 1900–2006**

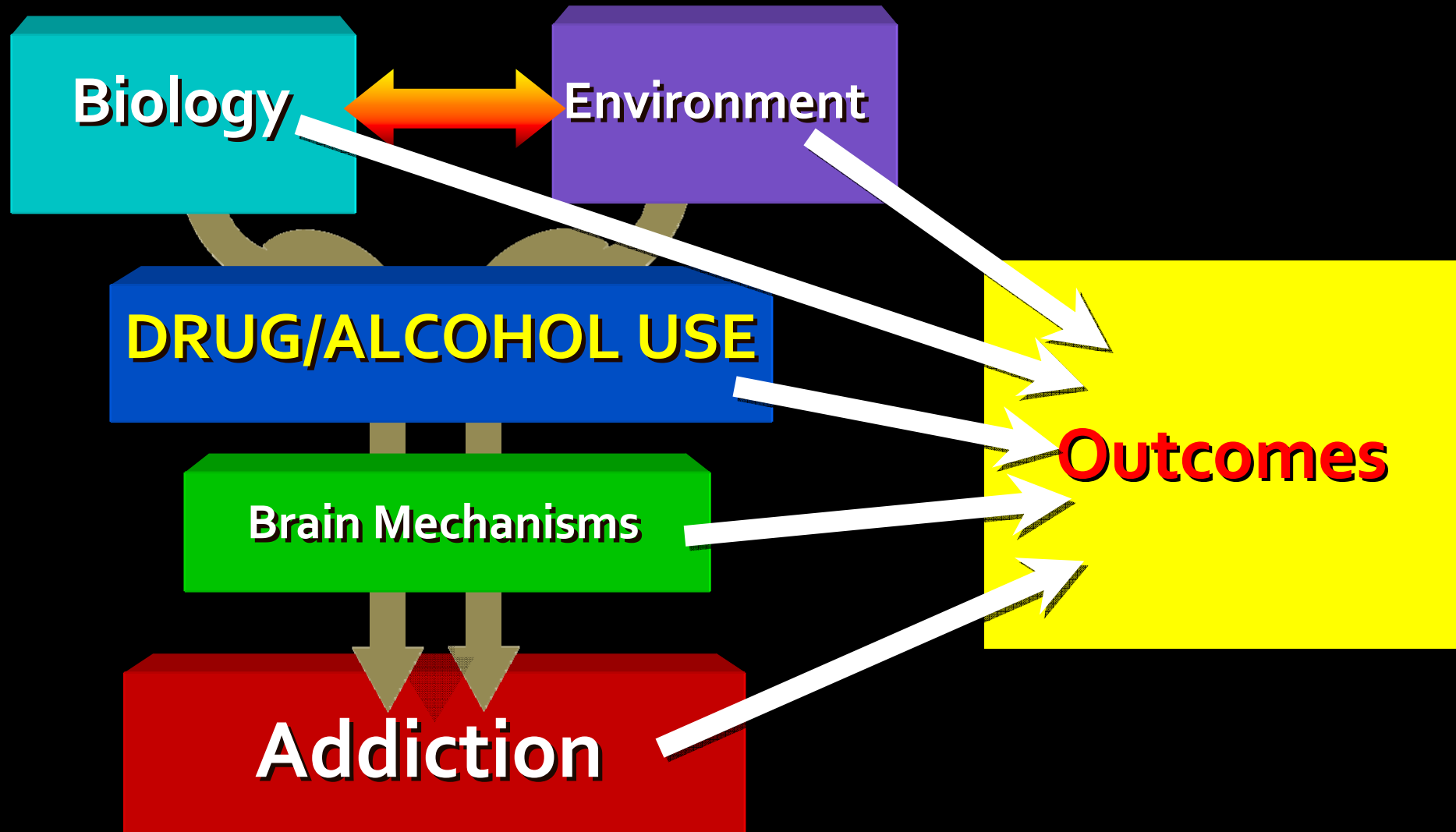


HIV Incidence Decreases as HAART Treatment Increases Among IDU in Vancouver, Canada 1996 – 2009

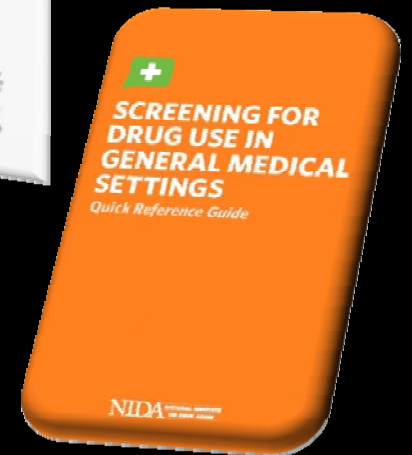
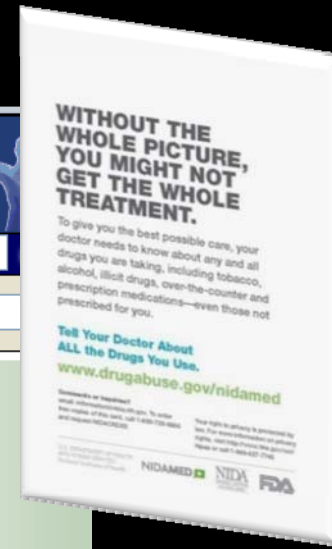
Montaner, et al., Lancet 2010



Outcomes of Substance Abuse & Addiction Involve *Multiple Factors*



Visit Our Website @



www.drugabuse.gov

Public Health Problem - (More from the NIDA Director)

Recursos y materiales educativos sobre las drogas de abuso, marihuana, extasis, nicotina, alcohol, etc.

Smoking/Nicotine

NIDAMED

Application for 2005 NIDA

smoking.drugabuse.gov

Treatment Research

http://www.nida.nih.gov/nidamed/