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Statistical Challenges of Meta-Analyses of Randomized Clinical Trials in a Regulatory Setting

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Disclaimer

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Outline

- **Motivating Example: meta-analysis of neuropsychiatric adverse events in trials for varenicline (Chantix)**
- Large trial designed to evaluate neuropsychiatric safety
- Lessons learned

Neuropsychiatric (NPS) safety signal with varenicline

- (2006) Chantix was approved as an aid to smoking cessation
- (2007) European Medicines Agency (EMA) alerted FDA to the concern about suicidality with varenicline
- (2007 to 2008) Adverse event reports supported the signal
- (2009) Boxed warning added to varenicline and bupropion and large RCT required
- **(2014) Pfizer conducted meta-analysis of Phase 2-4 trials**
- (2016) Pfizer submitted results of PMR trial A3051123

Chantix – Example Report

- F/36/varenicline
- A consumer reported experiencing a complete personality change, a violent temper going into unnecessary rage and stated that her brain felt like it had completely been scrambled, from about day 14 of treatment
- The consumer believed this was not due to smoking cessation, as she has quit smoking before and never ever felt like this.

Meta-analysis objectives

Characterize the neuropsychiatric safety of varenicline relative to placebo based upon the following treatment emergent adverse events:

1. Suicidal ideation and behavior

2. Aggressive behavior and violence

3. Overall psychiatric events excluding sleeping disorders

Endpoints

- **Suicidal ideation and behavior**:
  - C-SSRS
  - Suicide/Self Injury Standardized MedDRA Query (SMQ)
- **Aggressive behavior and violence**:
  - Hostility/Aggression SMQ
- **Overall Psychiatric Events**:
  - Psychiatric Disorders MedDRA System Organ Class
  - Custom NPS endpoint:
    - Severe: anxiety, depression, feeling abnormal, hostility
    - Moderate or severe: agitation, aggression, delusions hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, completed suicide

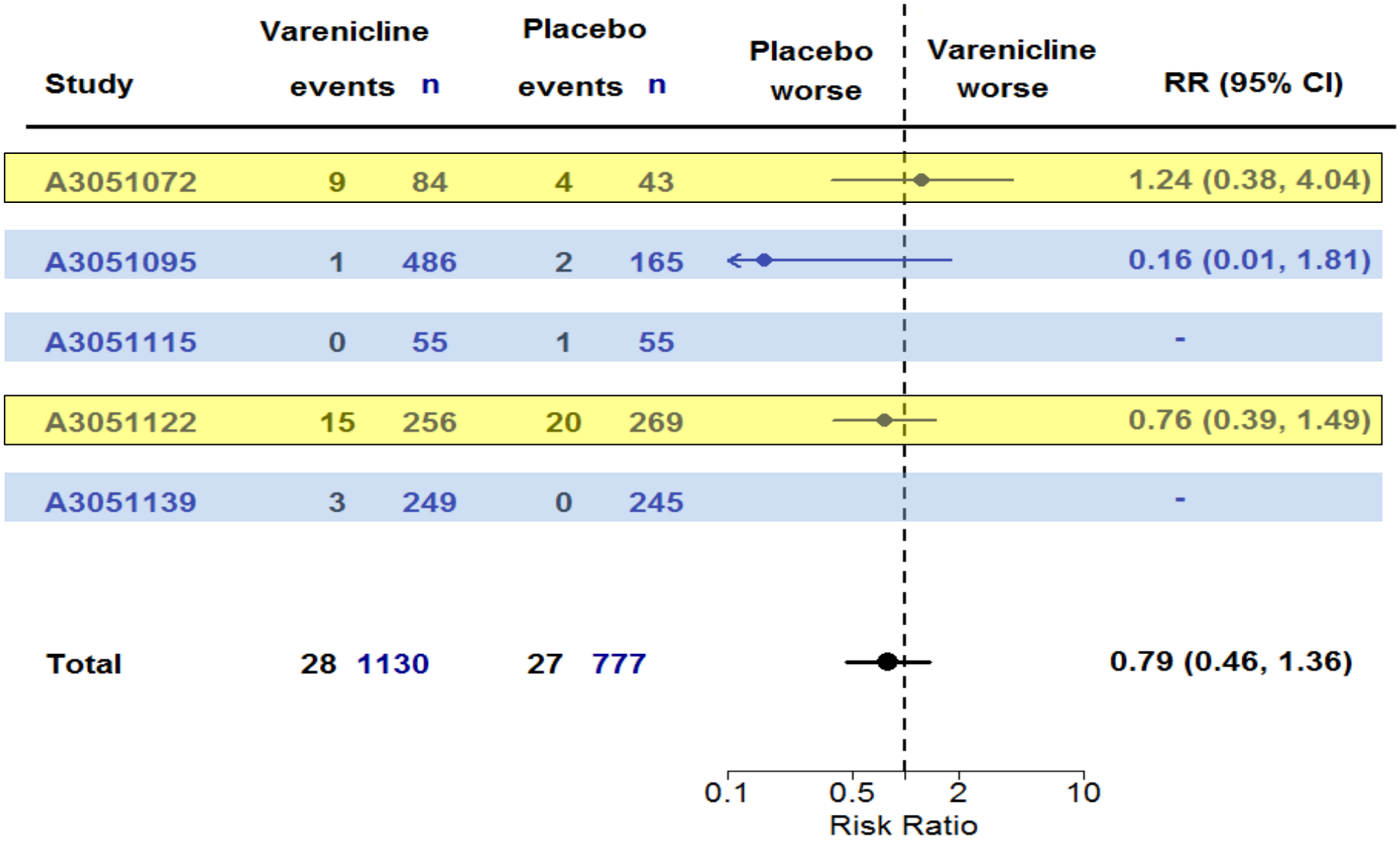
Meta-Analysis Trial Database

Study	Population / Goal	Duration		Sample Size		
		On treatment	Total follow-up	Varenicline	Placebo	Zyban
5-Study Cohort (Captured C-SSRS)						
A3051072	Schizophrenia	12 weeks	24 weeks	84	43	-
A3051095	Flexible quit date	12 weeks	24 weeks	486	165	-
A3051115	Assessment of neuropsychiatric symptoms	12 weeks	12 weeks + 30 days	55	55	-
A3051122	Depression	12 weeks	52 weeks	256	269	-
A3051139	Re-treatment	12 weeks	52 weeks	249	245	-
PHASE 2						
A3051002	Dose-ranging	6 weeks	52 weeks	377	123	126
A3051007	Titration	12 weeks	52 weeks	506	121	-
A3051016	Flexible dosing	12 weeks	52 weeks	157	155	-
A3051037	Long-term safety	52 weeks	52 weeks	251	126	-
A3051046_48	Study in Japan	12 weeks	52 weeks	464	154	-
PHASE 3						
A3051028	Zyban comparison	12 weeks	52 weeks	349	344	329
A3051036	Zyban comparison	12 weeks	52 weeks	343	340	340
A3051045	Taiwan and Korea	12 weeks	24 weeks	126	124	-
A3051049	CV disease	12 weeks	52 weeks	353	350	-
A3051054	COPD	12 weeks	52 weeks	248	251	-
A3051055	Multinational Asian sites	12 weeks	24 weeks	165	168	-
PHASE 4						
A3051080	Africa, Mid-East, S. America	12 weeks	24 weeks	390	198	-
A3051104	Smokeless tobacco	12 weeks	26 weeks	213	218	-
			TOTAL	**5072**	**3449**	**795**

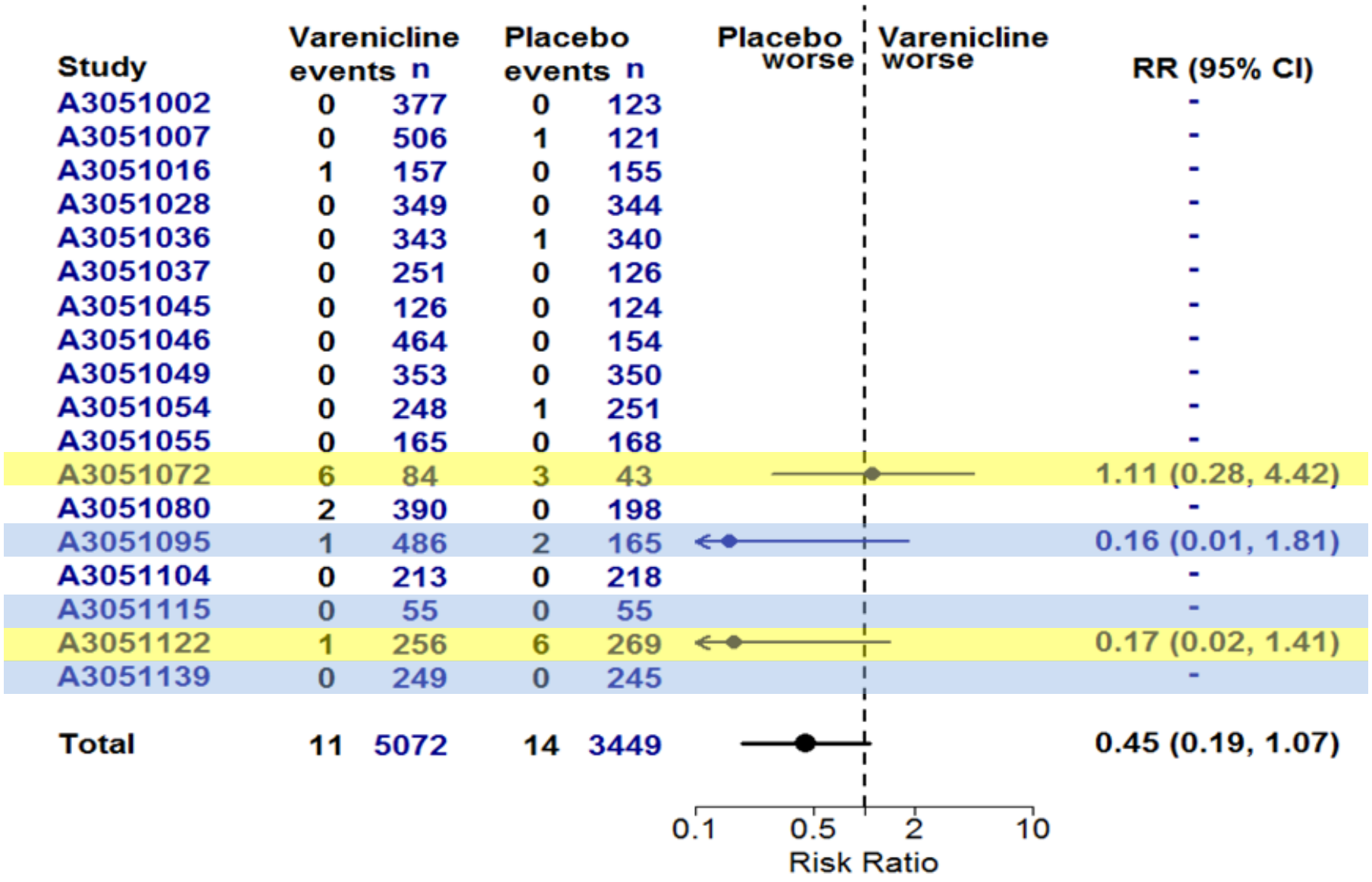
Statistical Methods

- Includes events reported during treatment phase plus 30 days
- **Suicidal ideation/behavior on C-SSRS:**
  - Poisson regression
  - Covariates: pre-dose history of suicidal ideation/behavior, study and treatment
- **SMQs, Overall Psychiatric Events and Custom NPS Endpoint:**
  - Mantel-Haenszel relative risk and risk difference
  - Stratified by trial
- Reported 95% confidence intervals are uncorrected for multiplicity

Suicidal Ideation or Behavior on C-SSRS



Suicide / Self-Injury SMQ



Comparison of C-SSRS and SMQ

Endpoint in the 5 studies that collected C-SSRS	Varenicline N = 1130 Events	Placebo N = 777 Events
Suicidal Ideation or Behavior on C-SSRS	28	27
Suicide / Self Injury SMQ	8	11

Challenges of this Meta-Analysis

- Heterogeneity
  - Populations: schizophrenia, high CV risk, depression, COPD
  - Trial goals: titration, dose-ranging, efficacy, long-term safety
- The safety signal from spontaneous reports was vaguely characterized
- Trials were not designed to evaluate NPS safety
- Reliance on routine Adverse Event reporting (lack of adjudication or uniform CRF to collect events of interest)
- Limited sample size of subjects with highest risk (schizophrenia, depression)

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Trial A3051123

- Sample size 8,000
  - 4,000 with history of psychiatric disorders
  - 4,000 without history of psychiatric disorders
- Treatment arms: placebo, NRT, Zyban (bupropion), Chantix (varenicline)
- Duration 24 weeks: (12 weeks treatment + 12 weeks follow-up)
- Endpoint captured from AE reports + active solicitation (interview)
- Composite endpoint:
  - Severe: anxiety, depression, feeling abnormal, hostility
  - Moderate or severe: agitation, aggression, delusions hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, completed suicide

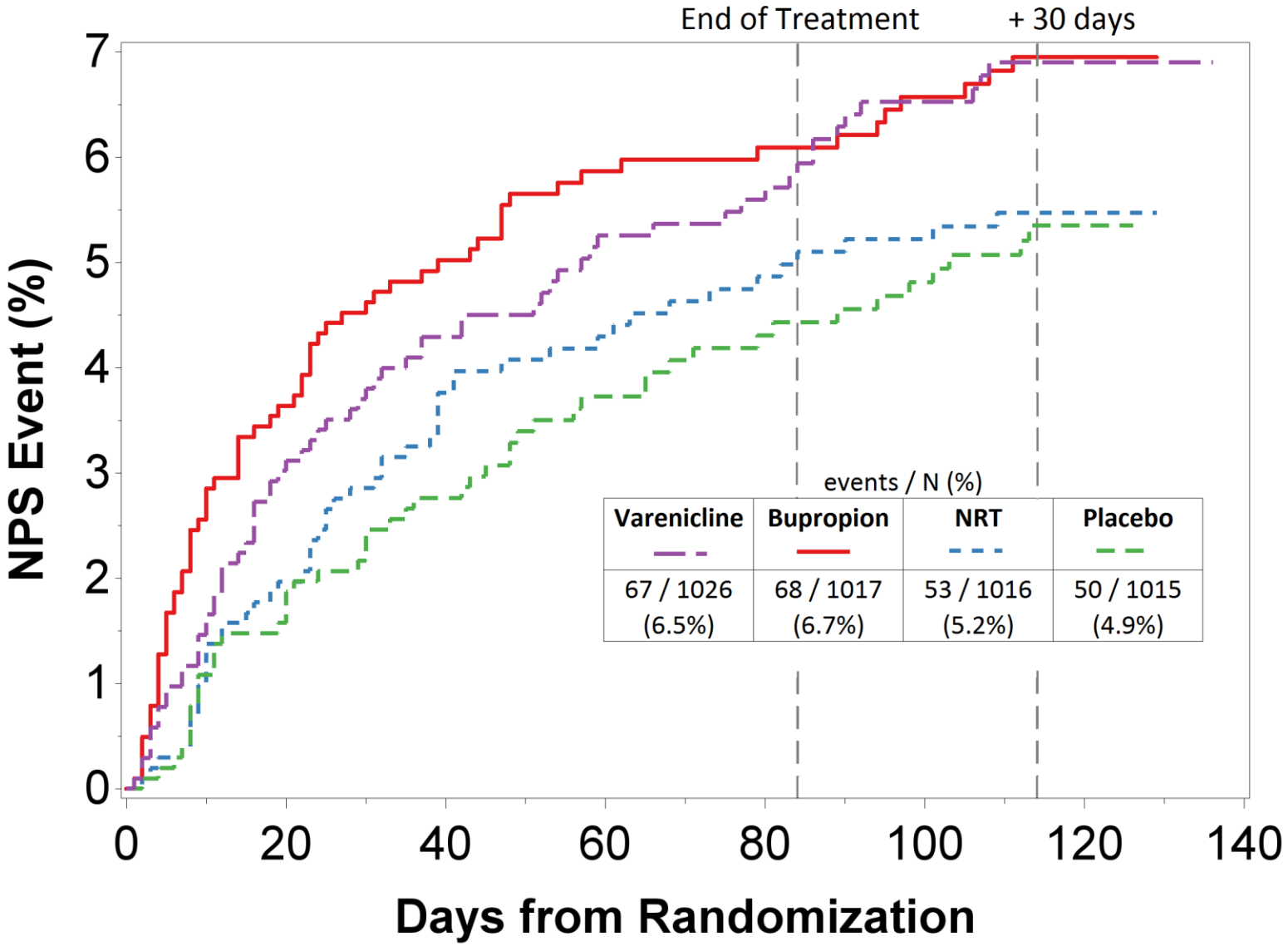
Trial Objective

- The **primary objective** of the PMR trial was to **estimate** the risk of NPS events by treatment and cohort
- No pre-specified statistical hypotheses
- No pre-specified risk margin to rule out
- No multiplicity corrections – all confidence intervals are shown at the nominal 95% confidence level

Primary Analysis Methods

- **Analysis population:** all treated subjects
- **Event ascertainment**
  - All events occurring from first dose to last dose + 30 days
- **Primary endpoint**
  - NPS composite event
- **Statistical model**
  - Estimate risk difference of NPS events (and nominal 95% CI) for every pair-wise comparison of treatments by cohort (Non-PHx and PHx) through a generalized linear model for binary data with an identity link function.

Primary Results: PHx Cohort



Severe Only NPS Events

	Varenicline events / N (%)	Bupropion events / N (%)	NRT events / N (%)	Placebo events / N (%)
Non-PHx Cohort	1 / 990 (0.1%)	4 / 989 (0.4%)	3 / 1006 (0.3%)	5 / 999 (0.5%)
PHx Cohort	14 / 1026 (1.4%)	14 / 1017 (1.4%)	14 / 1016 (1.4%)	13 / 1015 (1.3%)

Secondary Endpoints: C-SSRS

PHx Cohort

	Varenicline N = 1026	Bupropion N = 1017	NRT N = 1016	Placebo N = 1015
Suicidal Behavior	0	1 (0.1%)	0	2 (0.2%)
Suicidal Ideation	27 (2.6%)	15 (1.5%)	20 (2.0%)	25 (2.5%)
Self-Injurious Behavior	2 (0.2%)	1 (0.1%)	0	1 (0.1%)

Trial Results (2016 AC Meeting)

- Summary of Safety:
  - In the PHx Cohort, a higher incidence of NPS events was observed on varenicline and bupropion relative to placebo
  - However, incidence of severe NPS events and of suicidal ideation and behavior was similar in all treatment arms

- Boxed warning was removed in December 2016

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Some lessons learned:

- General ranking of data quality:
  1. Large dedicated safety trial
  2. Prospective meta-analysis
  3. Retrospective meta-analysis

- If possible, plan research questions and Statistical Analysis Plan before collecting data

- For retrospective meta-analyses:
  - Consider heterogeneity of trials, endpoints, populations
  - Assumptions may be needed to harmonize covariates and endpoints
  - Allocate enough resources for data cleaning and harmonization
  - Have a plan to address missing data

Some lessons learned (continued):

- Test your assumptions - sensitivity analyses
- Standardization is important in clinical trials

- The interpretability and impact of a meta-analysis depend on:
  - Pre-specified plan for data collection, inclusion criteria, event definition and analysis
  - Quality of the data
  - Plausibility of your assumptions and generalizability of your results
  - Quality of your analysis
  - Clear and effective communication of your results


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Risk Difference: PHx Cohort