



# **Validating a computable phenotype: Should results change a trial's primary outcome?**

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Supported by NIMH Cooperative Agreements UH3 MH007755 and U19 MH092201

# Outline

- Suicide Prevention Outreach Trial design
- What we knew
- What we said
- What we've learned
- What should we do?

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# Suicide Prevention Outreach Trial design

- Pragmatic trial of two outreach programs (vs usual care) to prevent suicide attempt
- Participants automatically identified from routinely administered depression questionnaires
- Randomly assigned to usual care (no contact) or to offer of one of two outreach programs:
  - Care management intervention to prompt/maintain engagement in treatment
  - Online DBT skills training intervention supported by online coach
- Suicide attempts over 12-18 months ascertained using EHR and insurance claims data

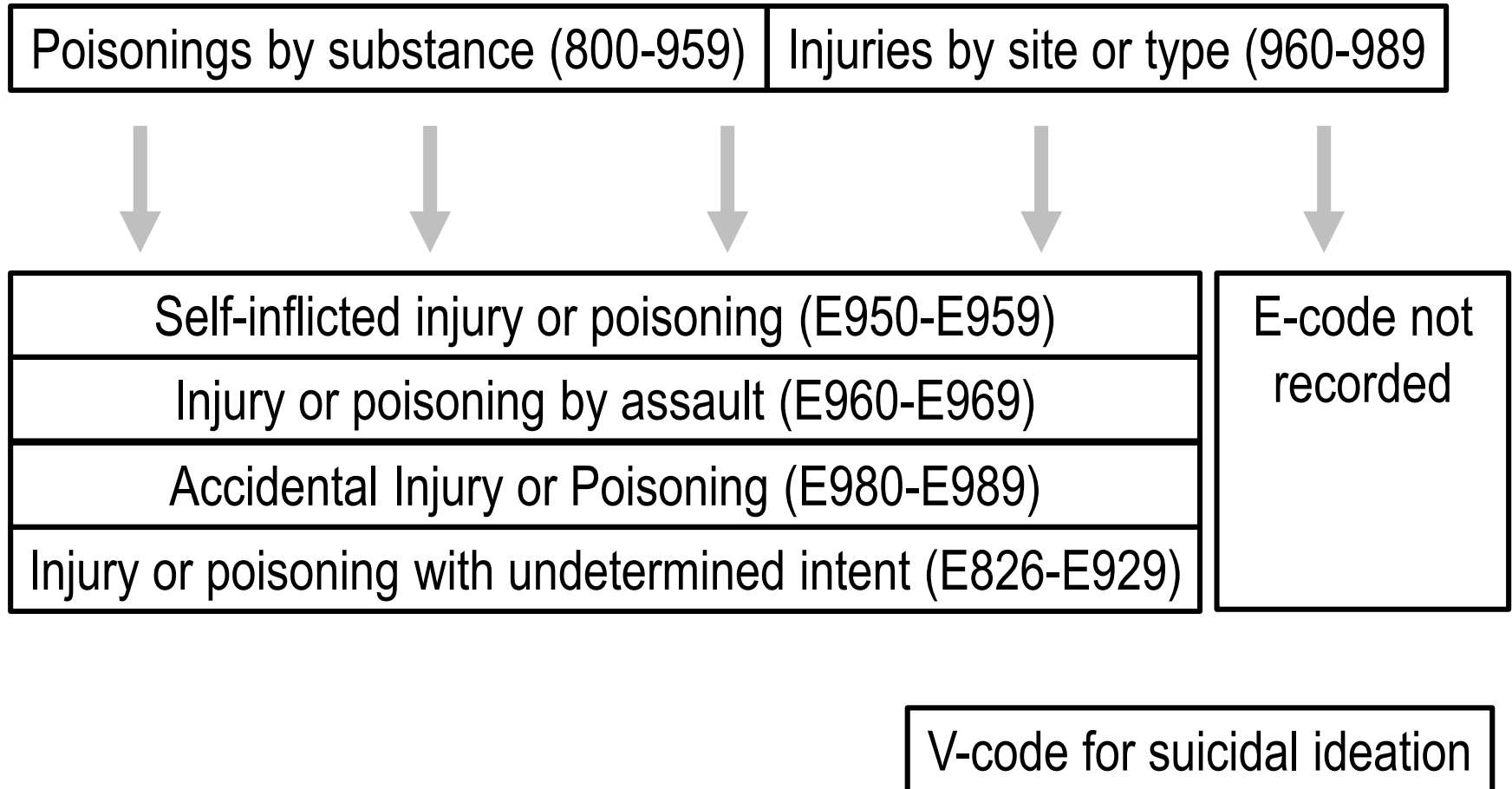
# Assessing suicide attempt outcomes: Why rely on EHR and claims data (vs. interview)

- Efficiency – Necessary to assess outcomes for 19,000 participants over 12-18 mos.
- Relevance – Self-harm leading to ED or inpatient care is likely more serious – and therefore more relevant to patients and health systems.
- Bias – Ascertainment via interviews would be subject to bias due to intervention effects on participation or recall.

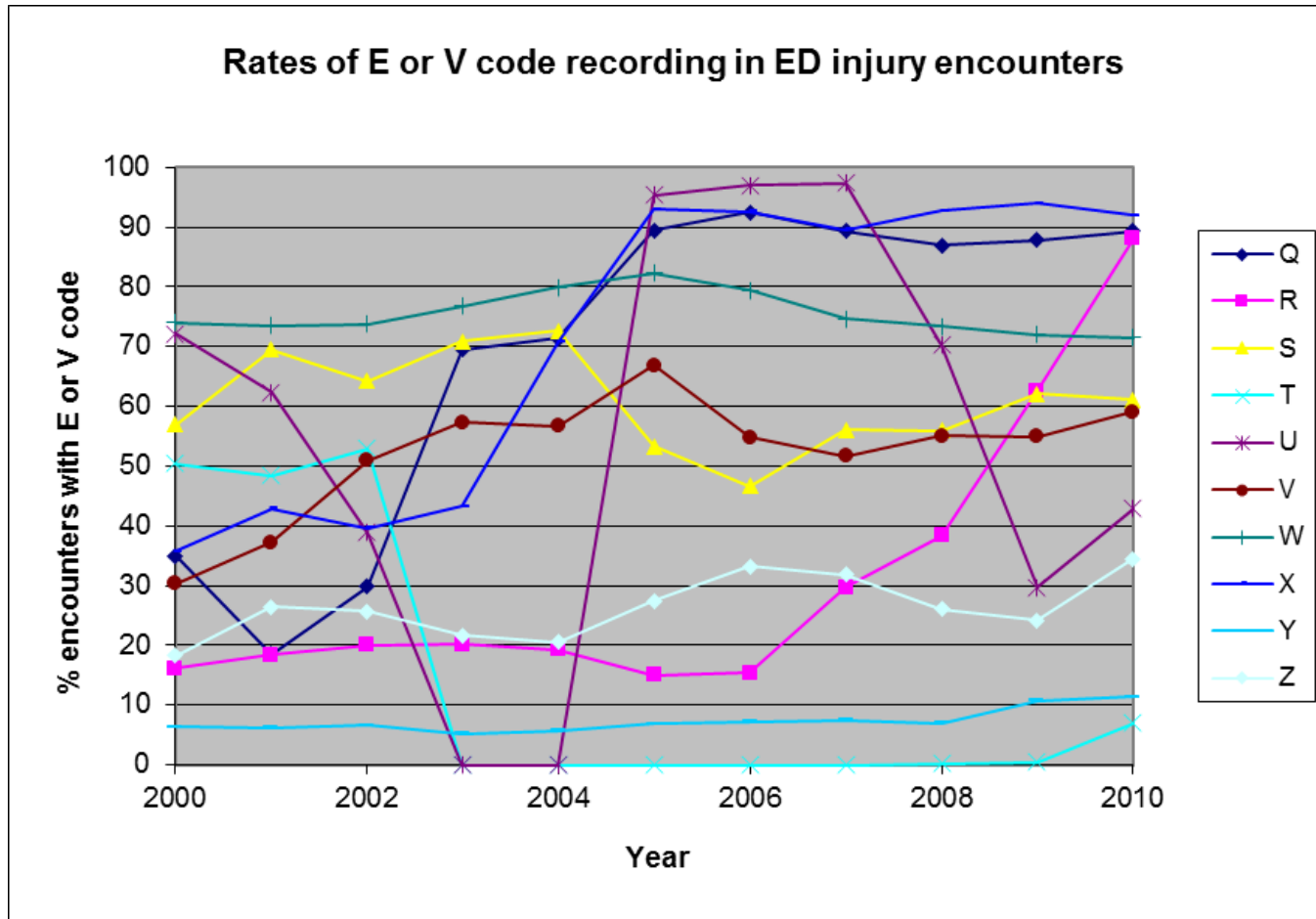
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# ICD-9 classification of injuries and poisonings



# Variability of E-code recording



Lu CY et al. *Pharmacoepidemiol Drug Saf.* 2014; 23:218



# E-code recording in study sites in 2010

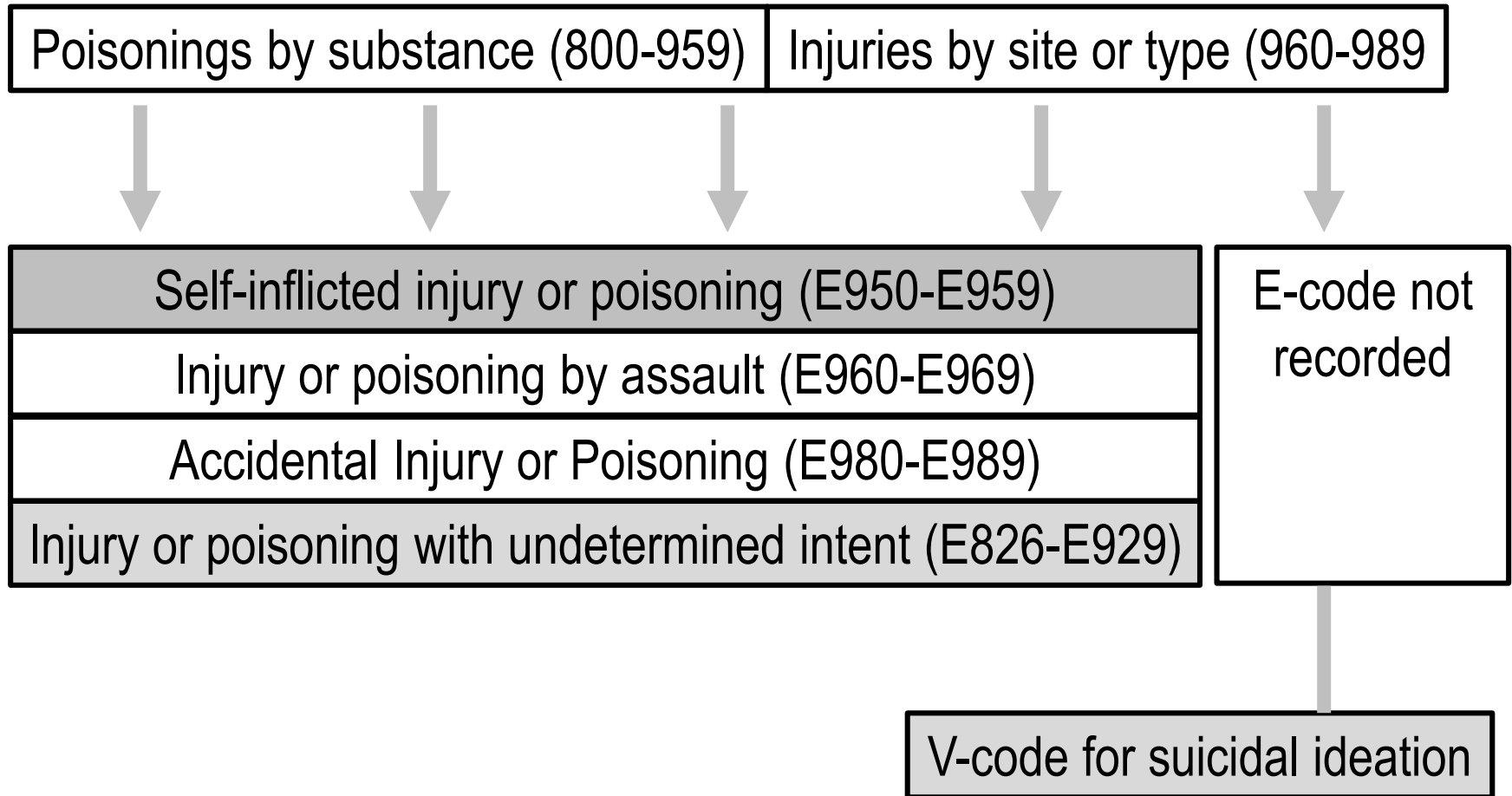
	KP Washington	KP Northwest	KP Colorado	Health Partners
Inpatient	81%	75%	63%	80%
ED	76%	67%	66%	87%

# Confirmation of self-harm by review of ED and inpatient notes at 3 initial sites

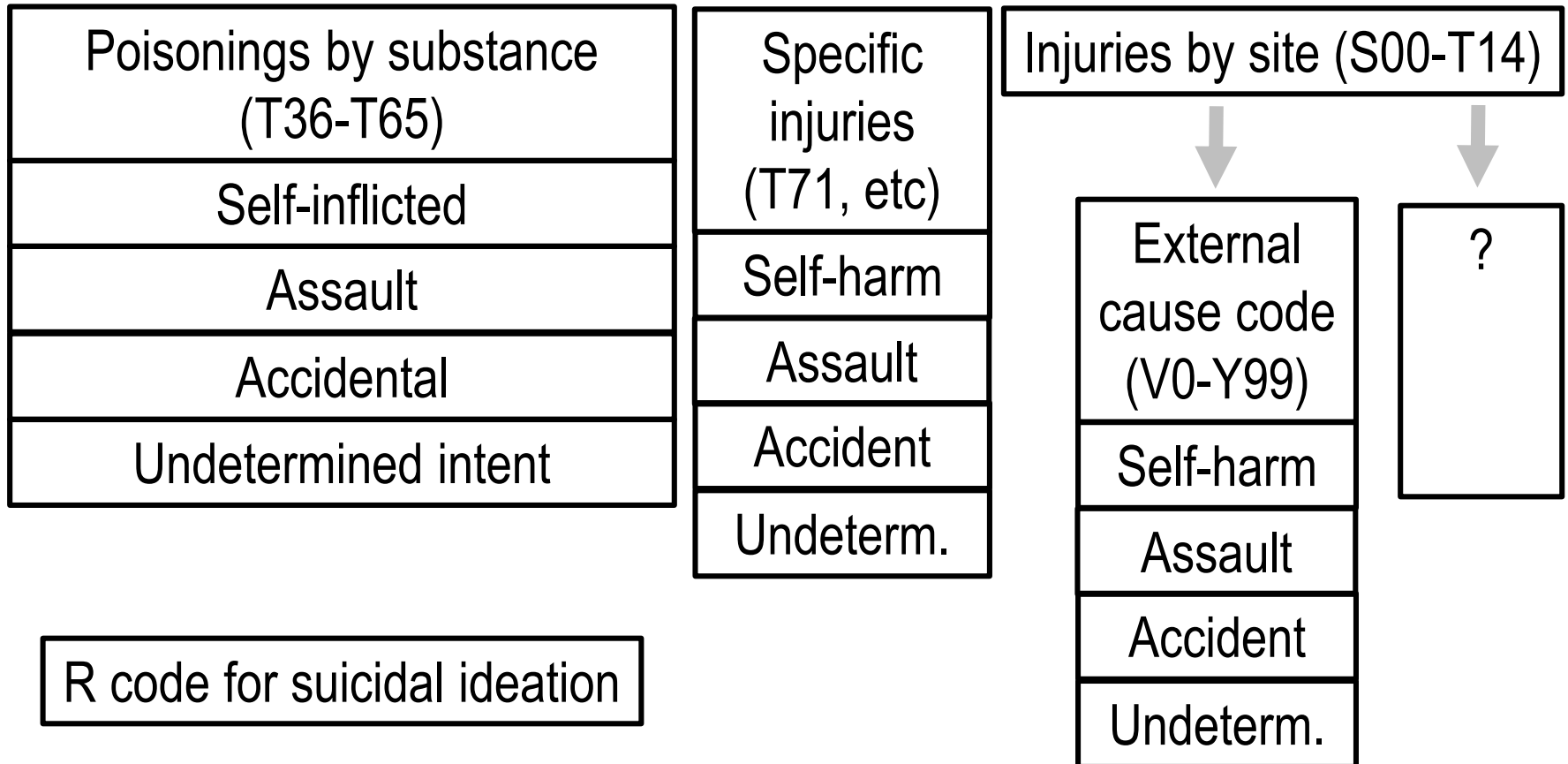
E-Code Diagnosis	Total			With Recent Mental Health Diagnosis or Treatment		
	Number Reviewed	Number Confirmed	Rate (95% CI)	Number Reviewed	Number Confirmed	Rate (95% CI)
Self-inflicted	300	238	79% (74% to 83%)	229	208	91% (86% to 94%)
Undetermined	150	106	71% (63% to 77%)	123	98	80% (71% to 86%)

“Undetermined intent” category often incorrectly used to reflect uncertainty about intent to die rather than uncertainty about intentional vs. unintentional

# ICD-9 classification of injuries and poisonings



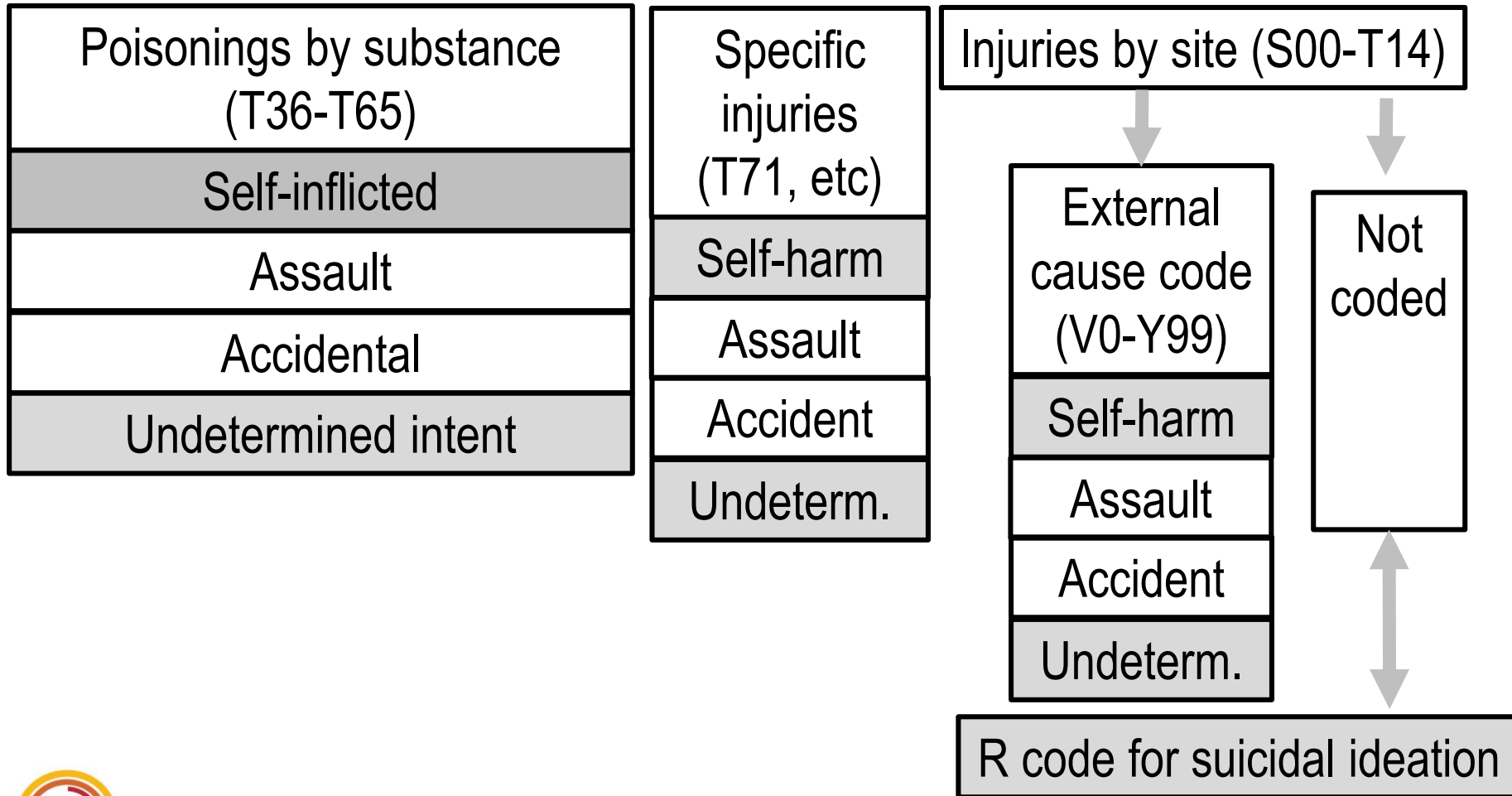
# ICD-10 classification of injuries and poisonings (arriving some October)



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# ICD-10 classification of injuries and poisonings



# From clinicaltrials.gov registration

## Outcome Measures

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### Primary Outcome Measures ⓘ:

1. Suicide Attempts [ Time Frame: 18 Months after randomization ]

EHR will be searched for any suicide attempts during the 18 months after randomization.

## From protocol paper:

Nonfatal suicide attempts will be identified from EHRs (for care delivered by participating health systems) and insurance claim data (for care received outside of participating health systems) using three criteria:

- Any outpatient or inpatient diagnosis of definite self-inflicted injury or poisoning
- Any outpatient or inpatient diagnosis of possible self-inflicted injury or poisoning
- Any outpatient or inpatient diagnosis of other injury or poisoning associated with a diagnosis of suicidal ideation during the same encounter

Simon et al. *Trials*. 2016; 17:452



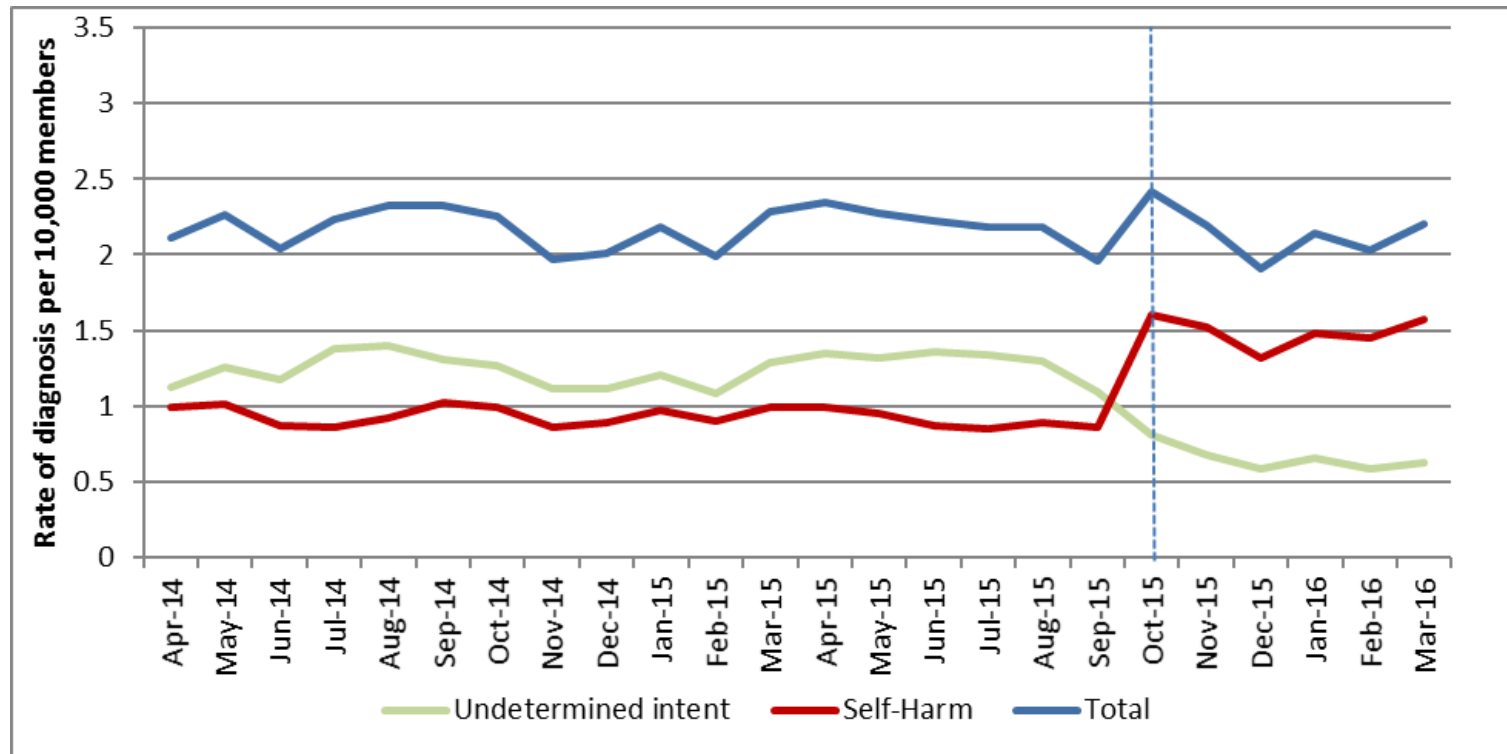
# Our original outcome specification did not:

- Propose to review self-inflicted or “undetermined intent” diagnoses to detect false positives
- Propose to look for “false negatives” among injuries and poisonings classified as accidental
- Attempt to distinguish between suicidal intent (intent to die) and self-inflicted injury or poisoning
- Distinguish between injury or poisoning categories that might have higher or lower probability of representing self-harm

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# Changes in coding of injuries and poisonings with transition to ICD-10



Stewart et al. Psychiatr Serv. 2017; 68:215

# Shift from “undetermined” to “self-inflicted categories

- Good news: Total event rate is stable
- Good news: Higher confidence for events now definitely classified
- Not-so-good-news: Should that “undetermined” group still be included?

# High false positive rate in “unexpected” attempts

51 cases of ICD10 self-inflicted injury or poisoning within 30 days of completing PHQ9 questionnaire and responding “not at all” regarding thoughts of death or self-harm.

- 6% - No records available
- 20% - No injury or poisoning
- 35% - Implausible self-harm (e.g. bee sting)
- 39% - Definite or possible self-harm

Ludman et al. *J Clin Psychiatry* 2018; 79:17

# First look at actual codes in KPWA study sample

- All injury/poisoning diagnoses for initial encounters
- Count # of occurrences and # of people with any occurrence
- Examine most frequent codes for:
  - Any injury/poisoning
  - Injury/poisoning coded as self-harm
  - Injury/poisoning coded as having “undetermined” intent

# Top 10 codes at KPWA – Any injury/poisoning

Code	#Events	#People	Description
S39.012A	453	146	Strain of muscle, fascia and tendon of lower back, initial encounter
S16.1XXA	394	117	Strain of muscle, fascia and tendon at neck level, initial encounter
S09.90XA	265	132	Unspecified injury of head, initial encounter
S33.5XXA	135	30	Sprain of ligaments of lumbar spine, initial encounter
S46.911A	128	31	Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, right arm, initial encounter
S06.0X0A	123	39	Concussion without loss of consciousness, initial encounter
S29.012A	117	41	Strain of muscle and tendon of back wall of thorax, initial encounter
T45.1X5A	116	30	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
S13.4XXA	95	34	Sprain of ligaments of cervical spine, initial encounter
T14.8XXA	90	65	Other injury of unspecified body region, initial encounter

# Top 10 codes at KPWA

## Self-harm injury/poisoning

Code	#Events	#People	Description
T42.4X2A	49	13	Poisoning by benzodiazepines, intentional self-harm, initial encounter
T50.902A	48	21	Poisoning by unspecified drugs, medicaments and biological substances, intentional self-harm, initial encounter
X78.8XXA	34	13	Intentional self-harm by other sharp object, initial encounter
T14.91XA	25	13	Suicide attempt, initial encounter
T42.6X2A	21	8	Poisoning by other antiepileptic and sedative-hypnotic drugs, intentional self-harm, initial encounter
T43.592A	16	7	Poisoning by other antipsychotics and neuroleptics, intentional self-harm, initial encounter
X83.8XXA	16	10	Intentional self-harm by other specified means, initial encounter
T40.2X2A	14	5	Poisoning by other opioids, intentional self-harm, initial encounter
T39.1X2A	11	6	Poisoning by 4-Aminophenol derivatives, intentional self-harm, initial encounter
T50.902D	11	8	Poisoning by unspecified drugs, medicaments and biological substances, intentional self-harm, subsequent encounter



# Top 10 codes at KPWA

## Undetermined intent injury/poisoning

Code	#Events	#People	Description
T51.0X4A	16	3	Toxic effect of ethanol, undetermined, initial encounter
T46.2X4D	5	1	Poisoning by other antidysrhythmic drugs, undetermined, subsequent encounter
T42.6X4A	4	1	Poisoning by other antiepileptic and sedative-hypnotic drugs, undetermined, initial encounter
T50.904A	4	1	Poisoning by unspecified drugs, medicaments and biological substances, undetermined, initial encounter
T56.894A	3	3	Toxic effect of other metals, undetermined, initial encounter
T63.484A	3	1	Toxic effect of venom of other arthropod, undetermined, initial encounter
T39.1X4A	2	1	Poisoning by 4-Aminophenol derivatives, undetermined, initial encounter
T42.4X4A	2	1	Poisoning by benzodiazepines, undetermined, initial encounter
T63.304A	2	2	Toxic effect of unspecified spider venom, undetermined, initial encounter
T40.2X4A	1	1	Poisoning by other opioids, undetermined, initial encounter

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# NEVER...

Re-evaluate or change the outcome definition after we've made any between-group comparisons

# We are concerned about both...

- False positives: injuries or poisonings mis-coded as self-inflicted or having undetermined intent
- False negatives
  - Self-inflicted injuries or poisonings inaccurately coded as accidental or (less likely) due to assault
  - Self-inflicted injuries coded by site of injury only, with no coding for mechanism or intent

# Caveats about reviewing clinical notes:

- Reviewers could be unblinded by mention of intervention exposure
  - Possible, but cumbersome, to scrub data prior to review
- Records will not be available for some encounters with external facilities
  - Especially concerning if missingness is related to intervention

# Our options

- Regarding false positives:
  - Do nothing, and stick with original outcome specification
  - Review a random sample of candidate events and (we hope) confirm original outcome specification
  - Review all candidate events and only keep those that are confirmed

(might have different answers for self-harm and undetermined)
- Regarding false negatives:
  - Do nothing, and stick with original outcome specification
  - Review all undetermined (and maybe accidental) events
  - Review undetermined (and maybe accidental) events in selected “high probability” injury and poisoning categories