Validating a computable phenotype: Should results change a trial’s primary outcome?

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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

<table>
<thead>
<tr>
<th>Poisonings by substance (800-959)</th>
<th>Injuries by site or type (960-989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-inflicted injury or poisoning (E950-E959)</td>
<td>E-code not recorded</td>
</tr>
<tr>
<td>Injury or poisoning by assault (E960-E969)</td>
<td></td>
</tr>
<tr>
<td>Accidental Injury or Poisoning (E980-E989)</td>
<td></td>
</tr>
<tr>
<td>Injury or poisoning with undetermined intent (E826-E929)</td>
<td></td>
</tr>
</tbody>
</table>

V-code for suicidal ideation
Variability of E-code recording

Lu CY et al. *Pharmacoepidemiol Drug Saf.* 2014; 23:218
## E-code recording in study sites in 2010

<table>
<thead>
<tr>
<th></th>
<th>KP Washington</th>
<th>KP Northwest</th>
<th>KP Colorado</th>
<th>Health Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>81%</td>
<td>75%</td>
<td>63%</td>
<td>80%</td>
</tr>
<tr>
<td>ED</td>
<td>76%</td>
<td>67%</td>
<td>66%</td>
<td>87%</td>
</tr>
</tbody>
</table>
Confirmation of self-harm by review of ED and inpatient notes at 3 initial sites

<table>
<thead>
<tr>
<th>E-Code Diagnosis</th>
<th>Total</th>
<th>With Recent Mental Health Diagnosis or Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number Reviewed</td>
<td>Number Confirmed</td>
</tr>
<tr>
<td>Self-inflicted</td>
<td>300</td>
<td>238</td>
</tr>
<tr>
<td>Undetermined</td>
<td>150</td>
<td>106</td>
</tr>
</tbody>
</table>

“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

Poisonings by substance (800-959) | Injuries by site or type (960-989)

- Self-inflicted injury or poisoning (E950-E959)
- Injury or poisoning by assault (E960-E969)
- Accidental Injury or Poisoning (E980-E989)
- Injury or poisoning with undetermined intent (E826-E929)

V-code for suicidal ideation

E-code not recorded
ICD-10 classification of injuries and poisonings (arriving some October)

Poisonings by substance (T36-T65)
- Self-inflicted
- Assault
- Accidental
- Undetermined intent

Specific injuries (T71, etc)
- Self-harm
- Assault
- Accident
- Undetermined

Injuries by site (S00-T14)
- External cause code (V0-Y99)
- Self-harm
- Assault
- Accident
- Undetermined

R code for suicidal ideation
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# ICD-10 classification of injuries and poisonings

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<th>Poisonings by substance (T36-T65)</th>
<th>Specific injuries (T71, etc)</th>
<th>Injuries by site (S00-T14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-inflicted</td>
<td>Self-harm</td>
<td>External cause code (V0-Y99)</td>
</tr>
<tr>
<td>Assault</td>
<td>Assault</td>
<td>Self-harm</td>
</tr>
<tr>
<td>Accidental</td>
<td>Accident</td>
<td>Assault</td>
</tr>
<tr>
<td>Undetermined intent</td>
<td>Undetermin.</td>
<td>Accident</td>
</tr>
</tbody>
</table>

**R code for suicidal ideation**

**Not coded**
Outcomes Measures

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

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

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

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

<table>
<thead>
<tr>
<th>Code</th>
<th>#Events</th>
<th>#People</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S39.012A</td>
<td>453</td>
<td>146</td>
<td>Strain of muscle, fascia and tendon of lower back, initial encounter</td>
</tr>
<tr>
<td>S16.1XXA</td>
<td>394</td>
<td>117</td>
<td>Strain of muscle, fascia and tendon at neck level, initial encounter</td>
</tr>
<tr>
<td>S09.90XA</td>
<td>265</td>
<td>132</td>
<td>Unspecified injury of head, initial encounter</td>
</tr>
<tr>
<td>S33.5XXA</td>
<td>135</td>
<td>30</td>
<td>Sprain of ligaments of lumbar spine, initial encounter</td>
</tr>
<tr>
<td>S46.911A</td>
<td>128</td>
<td>31</td>
<td>Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, right arm, initial encounter</td>
</tr>
<tr>
<td>S06.0X0A</td>
<td>123</td>
<td>39</td>
<td>Concussion without loss of consciousness, initial encounter</td>
</tr>
<tr>
<td>S29.012A</td>
<td>117</td>
<td>41</td>
<td>Strain of muscle and tendon of back wall of thorax, initial encounter</td>
</tr>
<tr>
<td>T45.1X5A</td>
<td>116</td>
<td>30</td>
<td>Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter</td>
</tr>
<tr>
<td>S13.4XXA</td>
<td>95</td>
<td>34</td>
<td>Sprain of ligaments of cervical spine, initial encounter</td>
</tr>
<tr>
<td>T14.8XXA</td>
<td>90</td>
<td>65</td>
<td>Other injury of unspecified body region, initial encounter</td>
</tr>
</tbody>
</table>
Top 10 codes at KPWA
Self-harm injury/poisoning

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

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