Analytic Challenges from the STOP CRC Trial: Pragmatic Solutions for Pragmatic Problems

William M Vollmer, PhD

April 24, 2015
Overview

- A number of issues related to implementation of the STOP CRC study have raised questions about the appropriateness of our originally proposed analysis plan

- We would like to review those issues and get your feedback on some proposed analytic solutions
Strategies and Opportunities to STOP Colorectal Cancer in Priority Populations: the STOP CRC Study

Gloria Coronado, KPCHR, Portland, OR
Beverly Green, GHRI, Seattle, WA
STOP CRC Primary Objective

Test the effectiveness of automated EMR-driven strategies to raise CRC screening rates in safety-net clinics
STOP CRC Design

- Cluster randomized trial
STOP CRC Design

- Cluster randomized trial
  - Intervention delivered at clinic level
STOP CRC Design

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- 26 federally qualified health clinics that are part of OCHIN network
STOP CRC Design

- Cluster randomized trial
  - Intervention delivered at clinic level
- 26 federally qualified health clinics that are part of OCHIN network
- EMR used to drive system-level intervention
STOP CRC Intervention - 1

- OCHIN uses EMR to:
  - Identify individuals eligible for screening per USPSTF guidelines
  - Confirm still an active clinic patient (visit w/i past 12 months)
  - Update list on an ongoing basis over time
  - Make real-time reports available to clinics via a customized report in Reporting Workbench
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- Identify comparable population for usual care clinics
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  - **Confirm still an active clinic patient (visit w/i past 12 months)**
  - Update list on an ongoing basis over time
  - Make real-time reports available to clinics via a customized report in Reporting Workbench
- Identify comparable population for usual care clinics
- Recruitment continues for 1 yr for main analysis
Clinics “work” their lists in whatever manner best fits with their internal workflows.
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Actual “intervention” consists of prescribed sequence of proactive outreach efforts, including mailed FIT kits
STOP CRC Outcome
STOP CRC Outcome

**Individual level**

- Completion of FIT kit within 12 months of becoming screen eligible
STOP CRC Outcome

Individual level
- Completion of FIT kit within 12 months of becoming screen eligible

Clinic level
- % targeted patients who complete a FIT kit
### Accrual of Intervention Clinic Patients

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<thead>
<tr>
<th>Patient</th>
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**year 1 Accrual period**

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Overview of Analytic Issues
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- Overlap of year 1 measurement window and year 2 intervention rollout for control clinics
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Overview of Analytic Issues

- Overlap of year 1 measurement window and year 2 intervention rollout for control clinics
- Use of real-time EMR tools that may be discordant with our static randomization tables
- Implementation delays and ACA rollout
- Conceptualization of year 2 analysis sample
Control clinics will receive intervention in year 2, yet year 1 measurement window extends into year 2 for many individuals.
Accrual of Intervention Clinic Patients

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### Year 1 Accrual Period

- Patient 1: Accrual (AS) in January, Follow-up (F) in February
- Patient 2: Accrual (A) in March, Send Kit (S) in April
- Patient 3: Accrual (AS) in February, Follow-up (F) in March
Accrual of Intervention Clinic Patients

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Analytic Issue #1: Year 2 Intv Rollout

- Control clinics will receive intervention in year 2, yet year 1 measurement window extends into year 2 for many individuals.

- I had envisioned we wouldn’t “turn on” intervention for these individuals until their year 1 measurement window had elapsed, however that turns out to not be possible given the nature of the intervention tool.
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- I had envisioned we wouldn’t “turn on” intervention for these individuals until their year 1 measurement window had elapsed, however that turns out to not be possible given the nature of the intervention tool.

Impact:

- Year 2 intervention rollout window overlaps year 1 measurement window for some control subjects.
# Year 2 Rollout for Control Clinic Patients

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### Year 1 Accrual Period

### Year 2 Accrual Period
### Year 2 Rollout for Control Clinic Patients

#### Patient Study Timeline

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#### Accrual Periods

- **Year 1 Accrual Period**: Months 1 to 12
- **Year 2 Accrual Period**: Months 13 to 24

**Legend**

- **A** = accrued into study (first time patient deemed screen eligible)
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Analytic Issue #2: Implementation Delays

- Intervention has taken much longer to roll out than we initially anticipated (6+ month lags common)
# Illustration of Startup Lag

## Intervention Clinic Patients

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Illustration of Startup Lag
Intervention Clinic Patients

year 1 Accrual period

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Analytic Issue #2: Implementation Delays

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- Influx of new patients generated by ACA and leadership turnover at some sites has led to delays in scheduling visits that cause some patients to no longer meet criteria for “active clinic patient” once rollout does begin
  - Reporting workbench only shows individuals who still meet the 12-month visit window requirement
  - Impact of this has been exacerbated by implementation delays
Illustration of Loss of Clinic Visit Eligibility
Illustration of Loss of Clinic Visit Eligibility
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Impact:

- Msmt window out of sync with “true” start of intervention
- Some participants never receive intervention, though still in analysis sample
Going through the exercise of laying out these scenarios highlighted one further issue.

- Always planned to look at the year 2 data as part of secondary analyses
- Some study questions are clearly longitudinal in nature e.g., how many intervention subjects complete a FIT in both years 1 & 2?
- But the question of what does the year 2 rollout in control clinics look like is more of a cross-sectional question.
Analytic Issue #3: Longitudinal vs Cross-sectional Framework for Year 2

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    e.g., how many intervention subjects complete a FIT in both years 1 & 2?
  - But the question of what does the year 2 rollout in control clinics look like is more of a cross-sectional question.

Impact:
- Raises ambiguity about how we should define our analysis sample for year 2.
### Longitudinal vs Cross-sectional Perspective

**Intervention clinics**

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Longitudinal vs Cross-sectional Perspective

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Choice seem obvious:
- year 2 abuts year 1 for already accrued pts
### Longitudinal vs Cross-sectional Perspective

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### Choice seem obvious:
- year 2 abuts year 1 for already accrued pts
- continue to accrue new patients as they become eligible

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### Longitudinal vs Cross-sectional Perspective

#### Control clinics

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Note that this is distinct from the overlap issue, which doesn’t even come into play in this example.
Longitudinal vs Cross-sectional Perspective

- If we want to ask what is lag from mailing of a FIT kit to its actual return, that implies yet a totally different way of measuring windows
  - Limit analysis to those who were ever mailed a FIT kit
  - Measure time from date FIT kit was mailed
Recap

- Inability to selectively turn on intervention for control clinics in year 2 creates overlap of msmt windows
Recap

- Inability to selectively turn on intervention for control clinics in year 2 creates overlap of msmt windows
- Delayed rollout in year 1, coupled with external factors and our use of real-time intervention tool, means current analysis plan will underestimate the true impact of the intervention
Recap

- Inability to selectively turn on intervention for control clinics in year 2 creates overlap of msmt windows
- Delayed rollout in year 1, coupled with external factors and our use of real-time intervention tool, means current analysis plan will underestimate the true impact of the intervention
- Ambiguity over how to frame analysis of year 2 data
Proposed Solutions

- We have considered numerous alternative analyses, all of which have limitations
Proposed Solutions

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- My proposal is to stick with originally planned primary analysis, but present a series of alternative analyses and acknowledge in Discussion strengths and weaknesses of each and argue there for what we feel is “best” analysis.
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- We have considered numerous alternative analyses, all of which have limitations.
- My proposal is to stick with originally planned primary analysis, but present a series of alternative analyses and acknowledge in Discussion strengths and weaknesses of each and argue there for what we feel is “best” analysis.
- Nonetheless, still have to deal with overlap issue even for primary analysis.
Addressing Overlap
Addressing Overlap

- Control clinics have agreed to delay start of intervention for six months.
Addressing Overlap

- Control clinics have agreed to delay start of intervention for six months.
- Redefine accrual window plus msmt window to be no greater than 18 months
Addressing Overlap

- Control clinics have agreed to delay start of intervention for six months.
- Redefine accrual window plus msmt window to be no greater than 18 months
  - Do in same way for intv and control clinics to avoid bias
Addressing Overlap

- Control clinics have agreed to delay start of intervention for six months.
- Redefine accrual window plus msmt window to be no greater than 18 months
  - Do in same way for intv and control clinics to avoid bias
  - Use of longer msmt window and shorter accrual window will still give us time to see an intervention effect even despite delayed startup in year 1
# Dealing With Overlap: Impact in Control Clinics

## Control Clinics

<table>
<thead>
<tr>
<th>patient</th>
<th>Study Year 01</th>
<th>Study Year 02</th>
<th>Study Year 03</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>AS F</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Year 1 Accrual Period

- **A** = accrued into study (first time patient deemed screen eligible)
- **S** = FIT kit sent to patient
- **F** = FIT kit returned

### Year 2 Accrual Period

- 6 month accrual period and 12 months msmt window

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Dealing With Overlap: Impact in Control Clinics

Control clinics

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<tr>
<td>2</td>
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<td>AS, F</td>
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Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
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<tbody>
<tr>
<td>year 1 Accrual period</td>
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<td></td>
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<td></td>
<td>year 2 intv rollout</td>
</tr>
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A = accrued into study (first time patient deemed screen eligible)
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6 month accrual period and 12 months msmt window
Dealing With Overlap: Impact in Control Clinics

Control clinics

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<tr>
<td>2</td>
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<td>AS F</td>
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</tbody>
</table>

Month 1 2 3 4 5 6 7 8 9 10 11 12

year 1 Accrual period
year 2 Accrual period

A = accrued into study (first time patient deemed screen eligible)
S = FIT kit sent to patient
F = FIT kit returned

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Dealing With Overlap: Impact in Control Clinics

Control clinics

Patient Study Year 01 Study Year 02 Study Year 03

1 A

2 A S F A S F

Month 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12

year 1 Accrual period year 2 intv rollout year 2 Accrual period

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Dealing With Overlap:
Impact in Control Clinics

Control clinics

Patient | Study Year 01 | Study Year 02 | Study Year 03
--- | --- | --- | ---
1 | A | | 
2 | A | AS | F 

Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12
year 1 Accrual period | | | | | | | | | | | | | | | | | | | | | | | | | | year 2 Accrual period 
A = accrued into study (first time patient deemed screen eligible)
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• For patients accrued through month 6, overlap is avoided
Dealing With Overlap: Impact in Control Clinics

Control clinics

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</table>

Month: 1 2 3 4 5 6 7 8 9 10 11 12

A = accrued into study (first time patient deemed screen eligible)
S = FIT kit sent to patient
F = FIT kit returned

- For patients accrued through month 6, overlap is avoided
- Patients accrued after month 6, for whom overlap would be an issue, are excluded from analysis sample
Dealing With Overlap:
Impact in Intervention Clinics

**Intervention clinics**

<table>
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<tr>
<th>patient</th>
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<th>Study Year 02</th>
<th>Study Year 03</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>S</td>
<td>F</td>
</tr>
</tbody>
</table>

Month: 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12

**year 1 Accrual period**

A = accrued into study (first time patient deemed screen eligible)

S = FIT kit sent to patient

F = FIT kit returned

**year 2 Accrual period**

Even with the delayed startup we still capture this intervention person’s returned fit kit.
Dealing With Overlap: Impact in Intervention Clinics

Intervention clinics

A = accrued into study (first time patient deemed screen eligible)
S = FIT kit sent to patient
F = FIT kit returned

Even with the delayed startup we still capture this intervention person’s returned fit kit.
Addressing Overlap:
A further variant
Addressing Overlap: A further variant

- Previous example assumed same accrual window (6 months) and msmt window (12 months) for everyone.
Addressing Overlap: A further variant

- Previous example assumed same accrual window (6 months) and msmt window (12 months) for everyone.
- Alternative is accrue through 12 months, but adjust msmt window to minimum of 12 months or time to start of intervention rollout in year 2
Addressing Overlap: A further variant

Control clinics

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<tbody>
<tr>
<td>1</td>
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Month

- year 1 Accrual period
- year 2 Accrual period

- A = accrued into study (first time patient deemed screen eligible)
- S = FIT kit sent to patient
- F = FIT kit returned

- Under earlier rule we dropped this person from year 1 analysis sample
### Addressing Overlap: A further variant

**Control clinics**

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<tr>
<td>1</td>
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- **Month 1**
  - A = accrued into study (first time patient deemed screen eligible)
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- **Year 1 Accrual period**
- **Year 2 Accrual period**

- **Year 2 intv rollout**

- Now include, but with a shortened msmt window
Addressing Overlap: A further variant

Control clinics

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Month 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12

year 1 Accrual period
year 2 Accrual period

year 2 intv rollout

A = accrued into study (first time patient deemed screen eligible)
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- Those accrued even later have even shorter msmt windows
Addressing Overlap: A further variant

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<td>A</td>
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Month 1-12

Year 1 Accrual period

Year 2 Accrual period

- Early accruals still followed for no more than 12 months

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Addressing Overlap: A further variant

### Control clinics

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</table>

**Bottom Line:**
- Accrue through full 12 months
- Msmt window varies, but ≤ 12 months
- No overlap with year 2 rollout

A = accrued into study (first time patient deemed screen eligible)
S = FIT kit sent to patient
F = FIT kit returned
Pros:

- Doesn’t waste any subjects
- Uses maximum available window while still avoiding overlap
- Can still be done in comparable manner for intv and control clinics
- Unlikely to introduce any systematic bias into analysis
Addressing Overlap: A further variant

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Addressing Overlap: A further variant

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- Perhaps okay since lag makes meaning of a 12-month probability somewhat meaningless anyway
Addressing Overlap: A further variant

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- Meaning of our probability varies from person to person in some sense (e.g., prob of returning FIT in xx months)
- Perhaps okay since lag makes meaning of a 12-month probability somewhat meaningless anyway
- We also know from previous work that most FIT kits will be returned within 3 months of mailing anyway
Secondary Analysis 1

Ignore first 6 months of data and don’t start accruing subjects until August 2014
Secondary Analysis 1

Ignore first 6 months of data and don’t start accruing subjects until August 2014

Pros:

- Gets us much closer to actual rollout of intervention
- Could be done in comparable manner for intv and control clinics
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- Could be done in comparable manner for intv and control clinics

Cons:
- Would require us to redefine analysis sample
  - i.e., not simply looking at those who become elig after Aug under current rules
- Potential for bias since some intervention activity did happen in those first 6 months and this could affect subsequent “eligibility”
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- Potential for bias since some intervention activity did happen in those first 6 months and this could affect subsequent “eligibility”

Only accrue for 6 months and either use 6-month fixed msmt window or varying windows from 6-12 months as described previously
Secondary Analysis 2

Redefine eligibility criteria to require clinic visit in past 1 or 2 months rather than past 12 months
Secondary Analysis 2

Redefine eligibility criteria to require clinic visit in past 1 or 2 months rather than past 12 months

Pros:
- Would greatly minimize the problem of patients who are no longer visit eligible once clinics actually started to implement the intv
  - i.e., likely to meet 12-month operational definition of active clinic member despite rollout delays
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Same overlap issues as for primary analysis plan
Secondary Analysis 2

Redefine eligibility criteria to require clinic visit in past 1 or 2 months rather than past 12 months
Secondary Analysis 2

Redefine eligibility criteria to require clinic visit in past 1 or 2 months rather than past 12 months

- Probably won’t use since
  - Likely won’t buy us much compared to previous approach, which should largely address this problem too
  - Limited staff resources
Secondary Analysis 3

Our analytic problems essentially arise because:

1) We are trying to estimate a steady state process during what is really a startup year

2) Our msmt and accrual windows are out of sync, which causes conceptual problems when we get to year 2
Secondary Analysis 3

Our analytic problems essentially arise because:

1) We are trying to estimate a steady state process during what is really a startup year

2) Our msmt and accrual windows are out of sync, which causes conceptual problems when we get to year 2

Might a fundamentally different approach overcome these issues?
Step Wedge Design Framework

- We can think of our design as a type of step wedge design in which we wish to estimate separate startup and steady state effects.
Step Wedge Design Framework

- We can think of our design as a type of step wedge design in which we wish to estimate separate startup and steady state effects.
- Use as our outcome a HEDIS-like measure that is assessed on a fixed calendar basis for everyone.
### Step Wedge Design Framework

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Care (UC)</td>
<td>UC</td>
<td>Startup</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
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One observation per clinic (“HEDIS” score), though in theory could calculate for subgroups similar to current analysis plan.
Step Wedge Design Framework

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Pros:

• Should in theory be able to estimate separate Startup and Steady State effects versus UC, though latter will be estimated less precisely
• No overlap issues to worry about
• Gets at a more policy relevant metric
Step Wedge Design Framework

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Pros:
- Should in theory be able to estimate separate Startup and Steady State effects versus UC, though latter will be estimated less precisely
- No overlap issues to worry about
- Gets at a more policy relevant metric

Cons:
- Doesn’t address direct impact of intervention
  - Denominator includes patients with existing coverage from prior colonoscopy or sigmoidoscopy and hence aren’t candidates for intervention
Step Wedge Design Framework

- What to do about delayed rollout in year 2?
  - Do we start “year 2” in month 19 and ignore months 13-18, or do we start in month 13?
Step Wedge Design Framework

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  - Do we start “year 2” in month 19 and ignore months 13-18, or do we start in month 13?

- If goal is to have year 2 “startup” effect mimic that for year 1, then measuring from month 13 makes sense
  - Year 1 startup effect includes all of the delay due to training, etc
Step Wedge Design Framework

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- If goal is to have year 2 “startup” effect mimic that for year 1, then measuring from month 13 makes sense
  - Year 1 startup effect includes all of the delay due to training, etc
  - That is still happening in months 13-18, we have just delayed turning on of the intervention report for the clinics
  - However for practical purposes clinics didn’t start using this report for at least six months anyway in year 1, so we are just formalizing in year 2 what happened anyway in year 1.
Framing year 2 analyses

- Key realization is that we aren’t comparing intervention versus control clinics in year 2 so much as we are asking a series of implementation questions
Framing year 2 analyses

- Key realization is that we aren’t comparing intervention versus control clinics in year 2 so much as we are asking a series of implementation questions.
- Different questions may require us to build totally different data files that not only include different subsets of the total sample, but that also have fundamentally different data structures.
Framing year 2 analyses

- Key realization is that we aren’t comparing intervention versus control clinics in year 2 so much as we are asking a series of implementation questions.
- Different questions may require us to build totally different data files that not only include different subsets of the total sample, but that also have fundamentally different data structures.
- Emphasizes the need to be very explicit about the questions we want to ask and what sort of data files will be required to answer them.
Summary

- The challenge of implementing pragmatic trials that are embedded within large, complex health systems are likely to lead to a variety of issues that may threaten the validity (or at least utility) of the primary analysis plan.
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- A number of alternative, secondary analyses may need to be considered to facilitate a more robust interpretation of the intervention impact.
Summary

- The challenge of implementing pragmatic trials that are embedded within large, complex health systems are likely to lead to a variety of issues that may threaten the validity (or at least utility) of the primary analysis plan.
- A number of alternative, secondary analyses may need to be considered to facilitate a more robust interpretation of the intervention impact.
- The specifics of our problems may not generalize to other studies, though I suspect they may more broadly typify the types of issues others will face.
Summary

Welcome comments on

- Our proposed solutions
- Whether you agree with me that the conduct of pragmatic trials is more likely to raise such issues
- How we might better design trials to minimize the impact of such issues