Sequential and SequentialDesign: Tools For Prospective Sequential Medical Product Safety Surveillance

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▪ The views expressed are the authors’ and not necessarily those of the Food and Drug Administration, or the Department of Health and Human Services
Agenda

- Overview of Sequential Surveillance Theory
- Vaccine Safety Surveillance
- Drug Safety Surveillance
- Interactive Demonstration of Sequential Software
- Q&A
Overview of Sequential Surveillance Theory

Bruce Fireman
Sequential v. Non-Sequential Surveillance

Cumulative Outcome Events

Time of Statistical Signal (alpha<0.05);
Week 28, RR: 1.81;
Compare to an End-of-Study Analysis
Why Sequential Surveillance?

- Opportunities to detect elevated risk sooner
- However, one has to monitor for longer periods of time (i.e., accrue more events) to achieve the same statistical power at end-of-study.

Traditional Epidemiological Study Design:

Sequential Surveillance Study Design:
# Sequential Statistical Analysis Born in Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Clinical Trials</th>
<th>Observational Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data Characteristics</strong></td>
<td>Primary use data collected for research</td>
<td>Secondary use data collected for healthcare</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>Add 1 Patient at a Time</td>
<td>Add 1 Database at a Time</td>
</tr>
<tr>
<td><strong>Optimal Performance</strong></td>
<td>Minimize interim hypothesis tests to minimize time to reach end-of-study with desired power</td>
<td>Maximize ability to detect a signal (i.e., test often) and continue monitoring to achieve same power</td>
</tr>
</tbody>
</table>
MaxSPRT builds off Wald’s Sequential Probability Ratio Test (SPRT) but creates a composite alternative hypothesis.

- Uses exact statistics instead of asymptotic theory or normal approximations.
- Supports Poisson type data or Binomial data.
Early Sequential Surveillance in the Vaccine Safety Datalink

Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

Tracy A. Lieu, MD, MPH,*† Martin Kulldorff, PhD,* Robert L. Davis, MD, MPH,** Edwin M. Lewis, MPH,§ Eric Weintraub, MPH,‡ Katherine Yih, PhD, MPH,* Ruihua Yin, MS,* Jeffrey S. Brown, PhD,* and Richard Platt, MD, MSc,* for the Vaccine Safety Datalink Rapid Cycle Analysis Team
Early Sequential Surveillance in the Vaccine Safety Datalink

Real-Time Vaccine Safety Surveillance for the Early Detection of Safety Events

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Edwin M. Lewis, MPH,§ Eric Wein
Jeffrey S. Brown, PhD,* and Richard

Active Surveillance for Adverse Events: The Experience of the Vaccine Safety Datalink Project

W. Katherine Yih, Martin Kulldorff, Bruce H. Fireman, Irene M. Shui, Edwin M.
Lewis, Nicola P. Klein, James Baggs, Eric S. Weintraub, Edward A. Belongia, Allison
Naleway, Julianne Gee, Richard Platt and Tracy A. Lieu

Pediatrics published online Apr 18, 2011;
DOI: 10.1542/peds.2010-17221
Methodological Improvements I

- Expansion from strictly continuous to hybrid continuous/group sequential hypothesis testing approaches
  - Eliminated “alpha wasting” (and consequent losses in power) when unspent but allocated alpha accrued

- Creation of minimum threshold for hypothesis testing to prevent early signaling
There is always a continuous design with shorter expected time-to-signal than the best group sequential design.

**Recommendation:** Perform hypothesis tests on data as they arrive in whatever batches they arrive in.
Methodological Improvements II

- Optimal alpha spending to minimize expected time-to-signal
  - Assumes a concave down shape
Type I error probability spending for post-market drug and vaccine safety surveillance with binomial data

Ivair R. Silva

First published: 25 September 2017 | https://doi.org/10.1002/sim.7504

Type I Error Probability Spending for Post-Market Drug and Vaccine Safety Surveillance With Poisson Data

Authors

Authors and affiliations
We need a matrix of information: \((z/p, \text{treatment cases, comparator cases})\).

- \(z/p\) represents the probability of a case being in the treatment group under the null hypothesis.
- **Key Innovation**: let \(z\) be a vector not a scalar!
Diagram of the first 7 Looks in a Continuous Sequential Analysis

boxes show the N of pathways to each possible case split, defined by row & column,

red boxes would signal according to an alpha-spending plan, orange boxes can only be observed after a signal

p and q=1-p indicate the chances that the next event will exposed or unexposed
Appendix proof shows a case-centered logistic regression is mathematically equivalent to a stratified Cox proportional hazards model.

**Key innovation:** Treat “survival” data as binary / Binomial data.
Methodological advances to adapt sequential statistical analysis from the context of clinical trials to the context of observational database studies continue:

– Adaptation for the manner in which data arrive.
– Adaptation to cover commonly employed study designs (e.g., propensity score matched analysis with variable matching).
– Continued optimization to minimize expected time-to-signal (i.e., detect a risk as soon as possible).
Implementing near real-time vaccine safety surveillance using the Clinical Practice Research Datalink

Andreia Leite
Implementing near real-time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD)

Andrea Leite, Sara I. Thomas, Nick J. Andrews

Abstract

Introduction: Near real-time vaccine safety surveillance (NRTVSS) using electronic health records is increasingly used to rapidly detect vaccine safety signals. NRTVSS has not been fully implemented in the UK. We aimed to assess the feasibility of implementing this surveillance using the UK Clinical Practice Research Datalink (CPRD).

Method: We studied seasonal influenza vaccine safety data from 2013 to 2015 as an example of a rare outcome and measured time-to-phase (TTP) to report inﬂuenza (COP). We estimated the proportion of cases with TTPs <28 days using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases) using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases) using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases) using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases). We also performed power calculations for detecting increases in additive risk (IRR) from 2.5 to 10.

Results: For influenza cases we estimated the proportion of cases with TTPs <28 days using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases) using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases) using observed data (6384 cases) and compared this with estimates from 6036 cases (6384 cases). We also performed power calculations for detecting increases in additive risk (IRR) from 2.5 to 10.

Conclusions: NRTVSS is a potential data source to implement NRTVSS to achieve large increases in the risk of rare outcomes after seasonal influenza and lower increases in risk for more frequent outcomes.

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Clinical Practice Research Datalink

• CPRD – UK primary care database:
  – 4.4 million active patients by mid-2013;
  – Information on diagnosis, vaccines administered in primary care, referrals/feedback from secondary care;

• CPRD availability and key dates
  – Data is made available monthly to researchers;
  – Practices upload their data some time before that (last collection date, lcd);
Clinical Practice Research Datalink

Key dates

Hypothetical patient

- Study begins
- System date
- Study ends
- Transferred out of practice
- Last collection date
- UTS
- CRD (+1 year)
- Event date
- TOD
- LCD

Current registration date

Up-to-standard
Trial implementations: objectives

• Assess the feasibility of implementing NRTVSS using CPRD:
  – Most appropriate statistical test to detect a signal
  – Adjustment for delays
  – Power to detect an increased risk
## Trial implementation: methods

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccine/outcome pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seasonal influenza/GBS</td>
</tr>
<tr>
<td></td>
<td>MMR/seizures</td>
</tr>
<tr>
<td>Purpose</td>
<td>Rare outcome (background rate – 0.7-4.3/100,000 PY(^1))</td>
</tr>
<tr>
<td></td>
<td>Less rare outcome and positive control</td>
</tr>
<tr>
<td>Statistical test</td>
<td>PMaxSPRT</td>
</tr>
<tr>
<td></td>
<td>PMaxSPRT and BMaxSPRT</td>
</tr>
<tr>
<td>Study population</td>
<td>≥ 65 years, vaccinated</td>
</tr>
<tr>
<td></td>
<td>12-23m, 1(^{st}) MMR dose</td>
</tr>
<tr>
<td>Study period</td>
<td>2013/2014 and 2014/2015</td>
</tr>
<tr>
<td></td>
<td>August 2014 – July 2015</td>
</tr>
<tr>
<td>Historical period (for PMaxSPRT)</td>
<td>2008/09-2012/13 and 2009/10-2013-14</td>
</tr>
<tr>
<td></td>
<td>July 2009 – June 2014</td>
</tr>
<tr>
<td>Risk-window</td>
<td>42 days</td>
</tr>
<tr>
<td></td>
<td>6-21 days</td>
</tr>
<tr>
<td>Control period (for BMaxSPRT)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1-5 and 22-32 days</td>
</tr>
</tbody>
</table>

BMaxSPRT – Binomial maximized sequential probability ratio test, GBS – Guillain-Barré syndrome, m – months, MMR – Measles-mumps-rubella vaccine, PMaxSPRT – Poission maximized sequential probability ratio test, PY – Person-years.

Trial implementation: adjustments

• Number of expected events (PMaxSPRT) adjusted by age and sex. GBS/seizure cases excluded if:
  – Recording delays > 365 days
  – Likely to have been involved in mass transfers.

• Delays (PMaxSPRT):
  – Expected events reduced based on a previously generated delay distribution

• Delays & partially accrued periods (BMaxSPRT):
  – The ratio of the adjusted number of days in the control and risk periods was calculated and used as a matching ratio
Adjustments for data accrual (PMaxSPRT)

Average recording 62.5%
Expected recorded events in the recent data = 2.5
### Adjustments for data accrual and partially accrued periods (BMaxSPRT)

<table>
<thead>
<tr>
<th>Period</th>
<th>Observed</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1 ($c_1$)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Risk</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Control 2 ($c_2$)</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Adjustments
- **Risk window**
- **Control period**
- **Vaccine**
- **Last collection date**
- $r_d$: expected recording $d$ days after the event

#### Example:
- **$c_1$ - 15 days ($r_{15} = 80.0\%$)**
- **$c_2$ - 5 days ($r_5 = 60.0\%$)**
- **Risk - 10 days ($r_{10} = 75.0\%$)**
Power and implementation

• Power to detect a signal calculated for detecting increases in relative risk (RR) from 1.5-10;

• Implementation done graphically, by calculating the log-likelihood ratio test (LLRT) at the time of each CPRD data release (monthly):
  – PMaxSPRT – based on the number of observed and expected events
  – BMaxSPRT – based on the number of observed events in the control and risk periods.

• For influenza/GBS further implementation assuming an increase in risk that should be detected according to power calculations.

• The results from the LLRT were compared with the critical limit. For PMaxSPRT this was done requiring at least 1, 2, and 4 events before raising a signal.

• R Package Sequential version 2.3.1.
### Trial implementation: results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccine/outcome pair</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Influenza/GBS Season 2013-14</td>
<td>Influenza/GBS Season 2014-15</td>
<td>MMR/Febrile seizures</td>
</tr>
<tr>
<td>Number of doses (n)</td>
<td>533,110</td>
<td>477,454</td>
<td>28,249</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>240,884 (45.2)</td>
<td>216,224 (45.3)</td>
<td>14,474 (51.2)</td>
</tr>
<tr>
<td>Female</td>
<td>292,226 (54.8)</td>
<td>261,230 (54.7)</td>
<td>13,775 (48.8)</td>
</tr>
<tr>
<td>Age (years) – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>270,690 (50.8)</td>
<td>242,168 (50.7)</td>
<td></td>
</tr>
<tr>
<td>75-84</td>
<td>188,423 (35.3)</td>
<td>168,160 (35.2)</td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>73,997 (13.9)</td>
<td>67,126 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Age (months) – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>11,460 (40.6)</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td>10,049 (35.6)</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td>3,320 (11.8)</td>
</tr>
<tr>
<td>≥15</td>
<td></td>
<td></td>
<td>3,420 (12.1)</td>
</tr>
</tbody>
</table>

*Age (at time of vaccination) is expressed in years for seasonal influenza/GBS and months for MMR/febrile seizures.

Implementation: influenza vaccine/GBS

No signal detected in any of the seasons
### Power and time to signal: influenza/GBS

<table>
<thead>
<tr>
<th>Minimum events</th>
<th>Season</th>
<th>Data available at</th>
<th>Power (time to signal in months from beginning of surveillance)*</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2013-14</td>
<td>07-04-2014</td>
<td>13 25 40 55 (4) 78 (4) 91 (3) 97 (3) 100 (3) 100 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014-15</td>
<td>06-04-2015</td>
<td>12 23 37 51 (4) 74 (4) 88 (4) 95 (4) 99 (3) 100 (3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2013-14</td>
<td>07-04-2014</td>
<td>14 28 44 60 (4) 82 (4) 93 (3) 98 (3) 100 (3) 100 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014-15</td>
<td>06-04-2015</td>
<td>14 26 41 55 (4) 77 (4) 90 (4) 96 (4) 100 (3) 100 (3)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2013-14</td>
<td>07-04-2014</td>
<td>16 33 50 65 (4) 86 (4) 95 (4) 98 (4) 100 (3) 100 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014-15</td>
<td>06-04-2015</td>
<td>16 31 47 62 (4) 83 (4) 93 (4) 98 (4) 100 (4) 100 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Cells in bold refer to power ≥ 80%. * Time to signal is only displayed for cells where equivalent power ≥ 50%. PMaxSPRT - Poisson-based Maximized Sequential Probability Ratio.
Implementation: influenza vaccine/GBS

Signal detected assuming RR = 4/5
Implementation: MMR/seizures

Only for PMaxSPRT a signal is detected.
### Power and time to signal: MMR/seizures

<table>
<thead>
<tr>
<th>Minimum events</th>
<th>Season</th>
<th>Data available at</th>
<th>Power (time to signal in months from beginning of surveillance)*</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMaxSPRT 06-07-2015</td>
<td>30</td>
<td>73 (5)</td>
<td>95 (4)</td>
</tr>
<tr>
<td></td>
<td>BMaxSPRT 06-07-2015</td>
<td>28</td>
<td>63 (6)</td>
<td>85 (6)</td>
</tr>
<tr>
<td>2</td>
<td>PMaxSPRT 06-07-2015</td>
<td>33</td>
<td>76 (5)</td>
<td>96 (4)</td>
</tr>
<tr>
<td>4</td>
<td>PMaxSPRT 06-07-2015</td>
<td>36</td>
<td>79 (5)</td>
<td>96 (4)</td>
</tr>
</tbody>
</table>

Cells in bold refer to power ≥ 80%. * Time to signal is only displayed for cells where equivalent power ≥ 50%. BMaxSPRT - Binomial-based Maximized Sequential Probability Ratio, PMaxSPRT - Poisson-based Maximized Sequential Probability Ratio.
Trial implementation: summary

- For influenza/GBS we implemented a system in both seasons with no signal detected.
- Power to detect a signal was >80% for RR≥4. Implementation assuming RR=4/5 did signal;

- For MMR/seizures we were able to identify a signal with PMaxSPRT only.
- Power was >80% for RR≥2.5.
Conclusions

• NRTVSS is an option to quickly identify vaccine safety signals;

• Delays exist in CPRD but these are compatible with a near real-time system;

• CPRD can be used to implement NRTVSS, despite limited power to identify signals for a rare outcome.
Prospective Sequential Surveillance
“Regulatory Perspective”

Efe Eworuke, PhD
Presented by: Sarah Dutcher, PhD

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Disclosures

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• No external funding to disclose
FDA’s Sentinel System

Data Partners (DPs) hold data in Common Data Model format:
- Enrollment
- Demographics
- Medical Utilization
- Pharmacy Prescriptions
- Diagnoses
- Procedures
- Laboratory Tests
- Vital Signs

Sentinel Operations Center (SOC)

Queries Distributed to Data Partners (DPs)

Query Results Reviewed and Returned to SOC (all direct identifiers removed)

Data transferred securely
Sequential Analysis in Sentinel

Prospective sequential analyses is one of Sentinel’s Active Risk Identification and Analysis (ARIA) tools
Sequential Surveillance: Regulatory Context

- Formal study design
- Outcomes are checked using a plan that permits termination of surveillance with a determination that:
  - Additional investigation is needed
  - Results support a regulatory action
  - Any observed differences in safety fall within acceptable limits

Why Prospective Sequential Surveillance?

- Characterize hypothesized risk not adequately powered in clinical trials
- Characterize observed risk in populations not adequately covered in clinical trials
  - Patients difficult to recruit (e.g., those with multiple comorbidities)
  - Minority populations
- Detect a potential undesirable exposure-outcome association earlier than a non-sequential analyses
Key Assumptions

Sequential boundaries and sequential test statistics are determined by assuming that:

1. Each new look includes all of the same data from prior looks ("anchoring" assumption)

2. Data are relatively stable and accurate, and therefore, worth anchoring on ("data stability" assumption)
Pilot Test Case in Sentinel

- Angiotensin-converting enzyme inhibitors (ACEI) and angioedema
  - Comparator: beta-blockers
  - Known positive exposure-outcome association

- Surveillance population and study criteria:
  - Claims-based databases in Sentinel
  - Age 18+ years with established new use of any study medication
  - Exclusion criteria: history of angioedema, use of ARB or aliskiren
  - Follow-up: treatment cessation, switch to another study or excluded drug, disenrollment, outcome, death, 60 days, end of study period

- Outcomes monitored:
  - Angioedema (ICD-9: 995.1, ICD-10: T783XXA)
  - Serious angioedema (presence of angioedema diagnosis + inpatient care management)
Implementation Challenges in Postmarketing Settings

• Dynamic Data Environment
  – Investigators have to allow time for corrections to claims data
  – Data lag often differs between Data Partners in a distributed database setting
  – Data lag may complicate prospective sequential surveillance

• Variable outcome risk windows
  – Risk may not be fixed at a single data look
  – Challenge when risk window is variable and spans across data refreshes
Implementation Challenges in Postmarketing Settings

Three surveillance modes to meet anchoring assumptions:

- **Full lock**
  - Requires data to be strictly incremental: matched pair cannot be broken across looks
  - Already-analyzed information cannot be updated in subsequent looks
  - Limitation: Potential misclassification if data is incomplete during an interim analyses

- **Partial lock**
  - Data is added incrementally
  - Allows data for an interim look to be updated if new information comes in from subsequent look
  - Limitation: Incomplete information in prior looks if subsequent look adds information, which can affect test statistic for inferences

- **Re-matching / No lock**
  - Re-do PS estimation and PS matching at each look
  - Uses the most updated information
  - Limitation: Anchoring assumption is not met
Implementation Challenges in Postmarketing Settings

• Multiple outcomes under surveillance
  – Setting the same end of surveillance may be challenging if outcomes under consideration do not occur at the same rate
  – How long do we continue to monitor for each outcome?
    • Use of maximum length of surveillance
    • Follow-up descriptively

• Uptake of product
  – Changes in practice recommendations, guidelines
  – Formulary changes
Implementation Challenges in Postmarketing Settings

• Expected time to signal is an important criterion in postmarketing surveillance
  – Unlike clinical trials, it is often more desirable to detect a signal early (if any) in the post-approval setting
  – Determined by parameter selection
• Trade-off between looking as the data arrive (continuous sequential) vs. looking at intervals (group sequential)
Parameter Considerations for Sequential Analysis

- **Maximum length of surveillance**: Number of outcomes needed to stop surveillance, when the null is not rejected
- **Total type I error**: 0.05
- **Shape of the alpha spending function**: rho can be set at 0.5, 1, or 2
  - To “spend” more alpha in earlier looks, balanced over time, or in later looks
- **Minimum number of events**: Number of outcomes required to begin hypothesis testing
Test Case Parameter Selection

- Surveillance mode: Partial lock
- Propensity score adjustment: Compared stratification and matching
- Assumed mean probability of being exposed: 0.56
- Maximum length of surveillance:
  - Angioedema: 112
  - Serious angioedema: 25
- Total type I error: 0.05
- Shape of the alpha spending function: rho = 0.5
- Minimum number of outcomes: 5
## Test Case Results: Angioedema

<table>
<thead>
<tr>
<th>Exposure Definition</th>
<th>Monitoring Period</th>
<th>New Users</th>
<th>Person Years at Risk</th>
<th>Average Person Days at Risk</th>
<th>Number of Events</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmatched Analysis (Site-adjusted only)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>1</td>
<td>498,360</td>
<td>67,665.43</td>
<td>49.59</td>
<td>530</td>
<td>2.90 (2.40, 3.52)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>381,633</td>
<td>47,898.43</td>
<td>45.84</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>2</td>
<td>620,604</td>
<td>85,792.13</td>
<td>50.49</td>
<td>674</td>
<td>2.96 (2.50, 3.51)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>479,025</td>
<td>61,196.84</td>
<td>46.66</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td><strong>1:1 Matched Unconditional Analysis; Caliper=0.025</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>1</td>
<td>288,908</td>
<td>38,989.41</td>
<td>49.29</td>
<td>349</td>
<td>3.17 (2.54, 3.94)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>288,908</td>
<td>36,195.30</td>
<td>45.76</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>2</td>
<td>362,038</td>
<td>49,777.84</td>
<td>50.22</td>
<td>444</td>
<td>3.35 (2.75, 4.09)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>362,038</td>
<td>46,201.77</td>
<td>46.61</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td><strong>Predefined Deciles Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>1</td>
<td>498,360</td>
<td>67,665.43</td>
<td>49.59</td>
<td>530</td>
<td>3.41 (2.79, 4.17)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>381,633</td>
<td>47,898.43</td>
<td>45.84</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>2</td>
<td>620,604</td>
<td>85,792.13</td>
<td>50.49</td>
<td>674</td>
<td>3.59 (3.00, 4.30)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>479,025</td>
<td>61,196.84</td>
<td>46.66</td>
<td>166</td>
<td></td>
</tr>
</tbody>
</table>
Discussion/Lessons Learned

• Selection of parameters depends on the regulatory question
  – Weigh relative importance of stopping boundaries: expected time to signal vs. maximum length of surveillance

• There are unique challenges when conducting sequential surveillance in observational data
  – Data timeliness depends on the source data
    • Sentinel is based on secondary use of administrative claims
  – Data stability is impacted by claims adjustments, number of contributing sources (Data Partners), refresh rate
Acknowledgements

Many thanks are due to the Sentinel Data Partners who provided data used in the pilot study
Sequential Surveillance Demonstration and Exercise

Judith C. Maro
R Sequential Analysis

Exact Sequential Analysis for Poisson and Binomial Data

www.sequentialanalysis.org

Home

This is a web-based interface for the R Sequential package, with which you can conduct exact sequential analyses for binomial and Poisson data. It allows you to run the R Sequential package online, without installing and managing an R programming environment, and without writing any code in the R programming language. Functions to calculate statistical power, expected time to signal and required sample sizes for performing exact sequential analysis are also provided. All these calculations can be done for either Poisson or binomial data, and for different types of rejection boundaries. In the case of group sequential analyses, the group sizes do not have to be specified in advance.

For complete documentation, please read the R Sequential User Guide and the scientific papers in the reference list.

This site is currently using selected functions from R Sequential version 2.3.2.
R Sequential Features

1. **Signaling threshold functions** – the CV and *Threshold* suite – that help investigators develop optimal statistical stopping boundaries.

2. **Planning functions** – the *Performance* and *SampleSize* suite – that develop statistical power information before you select your parameters for surveillance.

3. **Implementation functions** – the *Analyze* suite – that execute sequential analysis according to the chosen study design.
Performing Sequential Statistical Analysis

- You are performing a study to monitor Outcome Y following new Drug A v. Drug B use with a 1:1 propensity-score matched design.
- You intend to monitor outcomes sequentially.
- For simplicity, in this example, we will assume the matching ratio or probability of exposure is fixed – so if one part of a matched pair censors (i.e., disenrolls, dies, has outcome), the other part of the pair censors too.
- **Recall:** We have two statistical stopping boundaries: 1) the rejection of the null hypothesis in case of a detected elevated hazard ratio and 2) the failure to reject the null hypothesis by the end-of-study.
Tradeoff between Two Stopping Boundaries

Sequential Information Time to detect a Twofold Relative Risk with 90% Statistical Power and Overall Type 1 Error=0.05 (one-sided).

<table>
<thead>
<tr>
<th></th>
<th>Continuous</th>
<th>4 Hypothesis Tests</th>
<th>2 Hypothesis Tests</th>
<th>Non-Sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Sample Size (in Total Events)</td>
<td>112</td>
<td>92</td>
<td>84</td>
<td>78</td>
</tr>
<tr>
<td>Mean Time-to-Signal (in Total Events)</td>
<td>44.2</td>
<td>50.4</td>
<td>57.5</td>
<td>78</td>
</tr>
</tbody>
</table>
Home

This is a web-based interface for the R Sequential package, with which you can conduct exact sequential analyses for binomial and Poisson data. It allows you to run the R Sequential package online, without installing and managing an R programming environment, and without writing any code in the R programming language. Functions to calculate statistical power, expected time to signal and required sample sizes for performing exact sequential analysis are also provided. All these calculations can be done for either Poisson or binomial data, and for different types of rejection boundaries. In the case of group sequential analyses, the group sizes do not have to be specified in advance.

For complete documentation, please read the R Sequential User Guide and the scientific papers in the reference list.

This site is currently using selected functions from R Sequential version 2.3.2.
Browse as Guest and Proceed to Sequential Analysis

Home

You are now browsing as a Guest User. You may interact with the site, but your work will be deleted at the end of the browsing session. To save your work, please convert this temporary Guest account to a permanent User account with the "Convert Guest Account..." button. Clicking the "End Guest Session" button will log you out without saving your work.

Convert Guest Account ➔ User Account  End Guest Session (Work will not be saved!)

This is a web-based interface for the R Sequential package, with which you can conduct exact sequential analyses for binomial and Poisson data. It allows you to run the R Sequential package online, without installing and managing an R programming environment, and without writing any code in the R programming language. Functions to calculate statistical power, expected time to signal and required sample sizes for performing exact sequential analysis are also provided. All these calculations can be done for either Poisson or binomial data, and for different types of rejection boundaries. In the case of group sequential analyses, the group sizes do not have to be specified in advance.

For complete documentation, please read the R Sequential User Guide and the scientific papers in the reference list.

This site is currently using selected functions from R Sequential version 2.3.2.

Proceed to Sequential Analysis
Set-up the Binomial Analysis

Home / Analysis Index

You are now browsing as a Guest User. You may interact with the site, but your work will be deleted at the end of the browsing session. To save your work, please convert this temporary Guest account to a permanent User account with the "Convert Guest Account..." button. Clicking the "End Guest Session" button will log you out without saving your work.

Sequential Analysis

Analyze.Binomial

You have no Analyze.Binomial analyses.
Enter Surveillance Parameters

- N = 100 (Maximum Length of Surveillance in Total Events)
- alpha = 0.05 (Total one-sided Type 1 error)
- AlphaSpendType = Wald (Shape)
- zp = 1 (Matching Ratio)
- M = 5 (Minimum Number of Events to Perform Tests)
- Title = Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)
Enter Setup Parameters For A New Analyze.Binomial Analysis

name

My New Analysis

Name of the analysis.

N

100

Maximum sample size, at which the sequential analysis stops without rejecting the null hypothesis. No default value. (This site allows a maximum value of N=1000.)

alpha

0.05

Overall significance level. Must be in the range (0,0.5]. Default is alpha=0.05.

AlphaSpendType

Wald

The type of alpha spending function to be used. With the Wald option, the Wald type upper rejection boundary is used, which is flat with respect to the likelihood ratio. With the power-type option, the alpha spending uses a power function with parameter rho, with rho defined by the user. This alpha spending setting is automatically used when the Analyze.Binomial function is run, but during the sequential analysis, and before each test, the user can always specify an arbitrary amount of alpha spending to be used up until and including that test.

zp

1

The prediction for z, the expected ratio between cases and controls under the null hypothesis that will be specified in the Analyze.Binomial function. This variable is only used when Alphaspendtype='Wald', and it is used to calculate the appropriate rejection boundary. If the z used in Analyze.Binomial during the actual sequential analysis is different from zp, that is okay, and the sequential analysis will still maintain the correct alpha level. Default is z=1.

M

5

Minimum number of events required before the null hypothesis can be rejected. Must be a positive integer. Default is m=1.
Set-Up is Complete! Now, Time for the Analysis

Analyze.Binomial: My New Study

The analysis files have been created. You may now begin to apply sequential tests.

Apply A Sequential Test  Download Analysis Files  Delete This Analysis
Add Sequential Hypothesis Test #1

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Z (Ratio)</th>
<th>Cases**</th>
<th>Controls**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Knowledge Check: Who knows what’s going to happen?**

**The software refers to “cases” as the number of outcome events that occurs in the exposed or treatment group of interest. The software refers to “controls” as the number of outcome events that occurs in the comparator or referent group of interest.**
For a matched case-control analysis, $z$ is the number of controls matched to each case. For example, if there are 3 controls matched to each case, $z=3$. In a selfcontrol analysis, $z$ is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, $z=7/2$. In terms of $p$, the binomial probability under the null hypothesis, $p=1/(1+z)$, or equivalently, $z=1/p-1$. The parameter $z$ must be a positive number. The default value is $z=1$ ($p=0.5$). If the ratio is the same for all observations, then $z$ can be any positive number. If the ratio is different for different observations, then $z$ is a vector of positive numbers.

**Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.**

**cases**

2

A number or a vector of the same length as $z$ containing the number of cases.

**controls**

2

A number or a vector of the same length as $z$ containing the number of controls.

**AlphaSpend**

no override

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probability) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range $[0,\alpha]$. The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.
Results after Hypothesis Test #1

Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

| Test Cases | Controls | Cases | Controls | E[Cases|H0] | RR estimate | LLR | target | actual | CV | Reject | H0 |
|------------|----------|-------|----------|----------|-------------|-----|--------|--------|----|--------|-----|
| 1          | 2        | 2     | 2        | 2        | 2.00        | 1.00| 0.000000| 0      | 0  | <NA>   | No  |

Parameter settings: N= 100, alpha= 0.05, rho= n, Tailed= 1, and M= 5, H0: RR<= 1. Analysis performed on Tue Aug 21 10:48:58 2018.
**Add Sequential Hypothesis Test #2**

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Z (Ratio)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Test 2</td>
<td>1</td>
<td>21</td>
<td>10</td>
</tr>
</tbody>
</table>

**The software refers to “cases” as the number of outcome events that occurs in the exposed or treatment group of interest. The software refers to “controls” as the number of outcome events that occurs in the comparator or referent group of interest.**
For a matched case-control analysis, \( z \) is the number of controls matched to each case. For example, if there are 3 controls matched to each case, \( z=3 \). In a selfcontrol analysis, \( z \) is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, \( z=7/2 \). In terms of \( p \), the binomial probability under the null hypothesis, \( p=1/(1+z) \), or equivalently, \( z=1/p-1 \). The parameter \( z \) must be a positive number. The default value is \( z=1 \) (\( p=0.5 \)). If the ratio is the same for all observations, then \( z \) can be any positive number. If the ratio is different for different observations, then \( z \) is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.

**cases**

21

A number or a vector of the same length as \( z \) containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.

**controls**

10

A number or a vector of the same length as \( z \) containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.

**AlphaSpend**

no override

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probability) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range \([0,\alpha]\). The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.
**Results after Hypothesis Test #2**

Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

=> Do not reject H0. Proceed to a new test as soon as you have more data.

| Test Cases | Controls | Cases | Controls E[Cases|H0] | RR estimate | LLR target | actual | CV | Reject H0 |
|------------|----------|-------|----------------------|--------------|-------------|--------|----|-----------|
| 1          | 2        | 2     | 2                    | 2.00         | 1.00        | 0.000000| 0.0000| <NA>      | No         |
| 2          | 21       | 10    | 23                   | 17.50        | 1.92        | 1.758216| 0.0343| 0.0205    | 24         |

Parameter settings: N= 100, alpha= 0.05, rho= n,zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Tue Aug 21 10:54:32 2018.
Additional Graphical Output after Test #2
## Add Sequential Hypothesis Test #3

**The software refers to “cases” as the number of outcome events that occurs in the exposed or treatment group of interest. The software refers to “controls” as the number of outcome events that occurs in the comparator or referent group of interest.**

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Z (Ratio)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Test 2</td>
<td>1</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Test 3</td>
<td>1</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>
z

For a matched case-control analysis, z is the number of controls matched to each case. For example, if there are 3 controls matched to each case, z=3. In a self-control analysis, z is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, z=7/2. In terms of p, the binomial probability under the null hypothesis, p=1/(1+z), or equivalently, z=1/p-1. The parameter z must be a positive number. The default value is z=1 (p=0.5). If the ratio is the same for all observations, then z can be any positive number. If the ratio is different for different observations, then z is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

cases

16

A number or a vector of the same length as z containing the number of cases.

controls

9

A number or a vector of the same length as z containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

AlphaSpend

no override

The alpha spending function is specified in the Analyze.SetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probability) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range (0,alpha]. The default value is no override, which means that the function will use the alpha spending plan specified in the Analyze.SetUp.Binomial function.
Results after Hypothesis Test #3

Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

| Test | Cases | Controls | Cases | Controls | E[Cases|H0] | RR estimate | LLR | target | actual | CV | Reject H0 |
|------|-------|----------|-------|----------|---------|-------------|-----|--------|--------|----|-----------|
| 1    | 2     | 2        | 2     | 2        | 2.00    | 1.00        | 0.0000000 | 0.0000 | 0.0000 | <NA> | No        |
| 2    | 21    | 10       | 23    | 12       | 17.50   | 1.92        | 1.758216  | 0.0343 | 0.0205 | 24   | No        |
| 3    | 16    | 9        | 39    | 21       | 30.00   | 1.86        | 2.742032  | 0.0414 | 0.0306 | 39   | Yes       |

Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Thu Aug 23 18:29:00 2018.
Additional Graphical Output after Test #3
Add a Non-Sequential Version of My New Analysis

You are now browsing as a Guest User. You may interact with the site, but your work will be deleted at the end of the browsing session. To save your work, please convert this temporary Guest account to a permanent User account with the "Convert Guest Account..." button. Clicking the "End Guest Session" button will log you out without saving your work.

Convert Guest Account ➔ User Account  End Guest Session (Work will not be saved!)

Sequential Analysis

<table>
<thead>
<tr>
<th>Name</th>
<th>Number of Tests</th>
<th>Created</th>
<th>Last Updated</th>
<th>R Sequential Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>My New Analysis</td>
<td>4</td>
<td>Aug. 21, 2018</td>
<td>Aug. 21, 2018</td>
<td>2.3.2</td>
</tr>
</tbody>
</table>
Enter Setup Parameters For A New Analyze.Binomial Analysis

**name**

Non-Sequential Version Of My New Analysis

Name of the analysis.

**N**

100

Maximum sample size, at which the sequential analysis stops without rejecting the null hypothesis. No default value. (This site allows a maximum value of N=1000.)

**alpha**

0.05

Overall significance level. Must be in the range (0,0.5]. Default is alpha=0.05.

**AlphaSpendType**

Wald

The type of alpha spending function to be used. With the Wald option, the Wald type upper rejection boundary is used, which is flat with respect to the likelihood ratio. With the power-type option, the alpha spending uses a power function with parameter rho, with rho defined by the user. This alpha spending setting is automatically used when the Analyze.Binomial function is run, but during the sequential analysis, and before each test, the user can always specify an arbitrary amount of alpha spending to be used up until and including that test.

**zp**

1

The prediction for z, the expected ratio between cases and controls under the null hypothesis that will be specified in the Analyze.Binomial function. This variable is only used when Alphaspendtype=Wald, and it is used to calculate the appropriate rejection boundary. If the z used in Analyze.Binomial during the actual sequential analysis is different from zp, that is okay, and the sequential analysis will still maintain the correct alpha level. Default is z=1.

**M**

5

Minimum number of events required before the null hypothesis can be rejected. Must be a positive integer. Default is m=1.

**title**

Non-Sequential PSM 1:1 Outcome Y

Title for the results shown in the output tables and the illustrative graphics. Can be any text string. Default is no title.
Same Surveillance Parameters as BEFORE

- N = 100 (Maximum Length of Surveillance)
- alpha = 0.05 (Total Type 1 error)
- AlphaSpendType = Wald (Shape)
- zp = 1 (Matching Ratio)
- M = 5 (Minimum Number of Events to Perform Tests)
- Title = Non-Sequential PSM 1:1 Outcome Y
Analyze.Binomial: Non-Sequential Version of My New Analysis

The analysis files have been created. You may now begin to apply sequential tests.

+ Apply A Sequential Test  Download Analysis Files  Delete This Analysis
## Add Non-Sequential Hypothesis Test #1

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Z (Ratio)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Test 2</td>
<td>1</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Test 3</td>
<td>1</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Test 4</td>
<td>1</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Non-Sequential</td>
<td>1</td>
<td>67</td>
<td>33</td>
</tr>
</tbody>
</table>
Analyze.Binomial: My Non-Sequential Analysis - Add Test (#1)

\[ z \]

For a matched case-control analysis, \( z \) is the number of controls matched to each case. For example, if there are 3 controls matched to each case, \( z=3 \). In a self-control analysis, \( z \) is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, \( z=7/2 \). In terms of \( p \), the binomial probability under the null hypothesis, \( p=1/(1+z^2) \), or equivalently, \( z=1/p-1 \). The parameter \( z \) must be a positive number. The default value is \( z=1 \) (\( p=0.5 \)). If the ratio is the same for all observations, then \( z \) can be any positive number. If the ratio is different for different observations, then \( z \) is a vector of positive numbers.

**Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.**

**cases**

\[ 67 \]

A number or a vector of the same length as \( z \) containing the number of cases.

**controls**

\[ 33 \]

A number or a vector of the same length as \( z \) containing the number of controls.

**Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.**

**AlphaSpend**

\[ \text{no override} \]

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probability) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range \([0,\alpha]\). The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.

![Add Test Button](82)
Analyze.Binomial: My Non-Sequential Analysis

Non-Sequential PSM 1:1 for Outcome Y

=> Reject H0. No further sequential analyses are needed.

| Test Cases | Controls | Cases | Controls | E[Cases|H0] | RR estimate | LLR   | target | actual CV | Reject H0 |
|------------|----------|-------|----------|----------|-------------|-------|--------|-----------|-----------|
| 1          | 67       | 33    | 67       | 33       | 50.00       | 2.03  | 5.896854| 0.0500    | 0.0443    | 59        | Yes      |

Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Thu Aug 23 18:38:34 2018.

Compare with the sequential test version below. Note the difference in the information time required to signal (100 total outcomes v. 60 total outcomes).
• We looked at a 3-test sequence that reached a stopping boundary with 60 total outcomes accumulated (39/21 split with $p=0.5 / z=1$)

• What if our first bolus of data had those 60 outcomes with the same split?
  – Would you reach the stopping boundary?
  – Will the number of treatment group outcomes needed to reach the stopping boundary be a) higher? b) lower? or c) the same?

Knowledge Check

Compare with the sequential test version below
What if you need an answer NOW?

- Let’s rewind and go back to Test #1 in our sequential analysis when we still had not signaled.
- Despite the best-laid plans, low uptake means that you will not be able to monitor Outcome Y for the rest of the planned surveillance – you will need to terminate surveillance at Test 2. What do you do?

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Z (Ratio)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Test 2</td>
<td>1</td>
<td>21</td>
<td>10</td>
</tr>
</tbody>
</table>
For a matched case-control analysis, \( z \) is the number of controls matched to each case. For example, if there are 3 controls matched to each case, \( z=3 \). In a self-control analysis, \( z \) is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, \( z=7/2 \). In terms of \( p \), the binomial probability under the null hypothesis, \( p=1/(1+z) \), or equivalently, \( z=1/p-1 \). The parameter \( z \) must be a positive number. The default value is \( z=1 \) (\( p=0.5 \)). If the ratio is the same for all observations, then \( z \) can be any positive number. If the ratio is different for different observations, then \( z \) is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.

**cases**

21

A number or a vector of the same length as \( z \) containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.

**controls**

10

A number or a vector of the same length as \( z \) containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. ‘1,2,3’. Do not add spaces or any other characters. Do not wrap vector data with ‘c()’ as if you were using the R functions directly; the system does that for you.

**AlphaSpend**

0.05

The alpha spending function is specified in the AnalyzeSetUp:Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probability) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range \( (0,\alpha) \). The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp:Binomial function.
Test Results after Alpha Override to Force-Quit Surveillance

Analyze.Binomial: My New Analysis - Finished Early

---

| Test Cases | Controls | Cases | Controls | E[Cases|H0] | RR estimate | LLR | target | actual | CV | Reject | H0 |
|------------|----------|-------|----------|----------|-------------|-----|--------|--------|----|--------|-----|
| 1          | 2        | 2     | 2        | 2.00     | 1.00        | 0.000000 | 0.0000 | 0.0000 | <NA> | No     |     |
| 2          | 21       | 10    | 23       | 17.50    | 1.92        | 1.758216 | 0.0500 | 0.0448 | 23   | Yes    |     |

Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
**Important Takehomes**

- Hitting an early stopping boundary means that you identified a potential elevated risk worthy of additional scrutiny.
  - It occurs prior to the total sample size you had planned (consider 60 outcomes instead of 100 outcomes) – there is less information there (and hence, more uncertainty in the risk estimate).

- You **don’t** have to stop monitoring. You can continue to collect data on the outcome, verify the existing data, and/or perform additional investigations.

- You **do** have to stop performing sequential hypothesis tests in the current analysis, but you can continue to develop risk estimate information.
Other R Sequential Analysis or R Functions

- Poisson Analysis is also available
  - As Andreia discussed, Poisson functions compare observed outcomes to expected outcomes where expected outcomes are given by a flat rate that increments as follow-up time among the observed group accrues.

- More Complex Functions are available in R: [https://cran.r-project.org/web/packages/Sequential/index.html](https://cran.r-project.org/web/packages/Sequential/index.html)
  - Includes Conditional Poisson Analysis.
  - Includes a more sophisticated suite of equations to find optimal alpha spending plans.
Recall Case-Centered Logistic Regression Paper

- It is possible for $Z$ to be a summation over multiple risk sets (e.g., different matching ratios, different amounts of contributed time)

- EXAMPLE:

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Z (Ratio)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>(1,2)</td>
<td>(2,0)</td>
<td>(1,1)</td>
</tr>
<tr>
<td>Test 2</td>
<td>(1,2)</td>
<td>(19,2)</td>
<td>(7,3)</td>
</tr>
</tbody>
</table>
R Sequential Features

1. **Signaling threshold functions** – the CV and *Threshold* suite – that help investigators develop optimal stopping boundaries.

2. **Planning functions** – the *Performance* and *SampleSize* suite – that develop statistical power information before you select your parameters for surveillance.

3. **Implementation functions** – the *Analyze* suite – that execute sequential analysis according to the chosen study design.
Calculate Sample Size for Binomial Data

Samplesize.Binomial

You have no Samplesize.Binomial analyses.

Samplesize.Poisson

You have no Samplesize.Poisson analyses.
Enter Several Relative Risks and Powers

- RR = 1.5, 2, 3
- alpha = 0.05
- Power = 0.90, 0.85, 0.80
- M = 5
- z = 1
Enter Parameters For A New Sample Size: Binomial Analysis

**name**

My New Analysis

Name of the analysis.

**RR**

1.5, 2.3

A target vector of relative risks to be detected with the requested statistical powers.

*Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.*

**alpha**

0.05

The significance level. The default value is "alpha=0.05". Must be in the range (0, 0.5).

**power**

0.90, 0.85, 0.80

The target vector of overall statistical powers to detect an increased risk of the relative risk (RR). The default value is "power=0.90".

*Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.*

**M**

5

The minimum number of events needed before the null hypothesis can be rejected. It must be a positive integer. The default value is "M=1".

**z**

1

For a matched case-control analysis, z is the number of controls matched to each case under the null hypothesis. There is no default value.
While that’s running...

Samplesize.Binomial: My New Analysis

<table>
<thead>
<tr>
<th>Target</th>
<th>RR</th>
<th>Target</th>
<th>power</th>
<th>Sample Size</th>
<th>Critical value</th>
<th>Type I Error prob.</th>
<th>Actual power</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1,]</td>
<td>1.5</td>
<td>0.80</td>
<td></td>
<td>254</td>
<td>3.75651</td>
<td>0.04998989</td>
<td>0.8016928</td>
</tr>
<tr>
<td>[2,]</td>
<td>1.5</td>
<td>0.85</td>
<td></td>
<td>291</td>
<td>3.80962</td>
<td>0.04995446</td>
<td>0.8527304</td>
</tr>
<tr>
<td>[3,]</td>
<td>1.5</td>
<td>0.90</td>
<td></td>
<td>340</td>
<td>3.85490</td>
<td>0.04998340</td>
<td>0.9004340</td>
</tr>
<tr>
<td>[4,]</td>
<td>2.0</td>
<td>0.80</td>
<td></td>
<td>84</td>
<td>3.46574</td>
<td>0.04617813</td>
<td>0.8062950</td>
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<tr>
<td>[5,]</td>
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<td>0.8551184</td>
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<tr>
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<td></td>
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<td>0.9057856</td>
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<tr>
<td>[7,]</td>
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<td></td>
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<td>0.04880955</td>
<td>0.8090669</td>
</tr>
<tr>
<td>[8,]</td>
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<td>0.85</td>
<td></td>
<td>41</td>
<td>3.46574</td>
<td>0.03705363</td>
<td>0.8562287</td>
</tr>
<tr>
<td>[9,]</td>
<td>3.0</td>
<td>0.90</td>
<td></td>
<td>49</td>
<td>3.46574</td>
<td>0.03880460</td>
<td>0.9084408</td>
</tr>
</tbody>
</table>
While that’s running...
Summary and Audience Questions

- Today, we wanted to talk about:
  - Sequential Statistical Theory
  - Applied Uses in Research and Regulatory Settings
  - How to do an analysis, thereby developing intuition with it

- Audience Questions