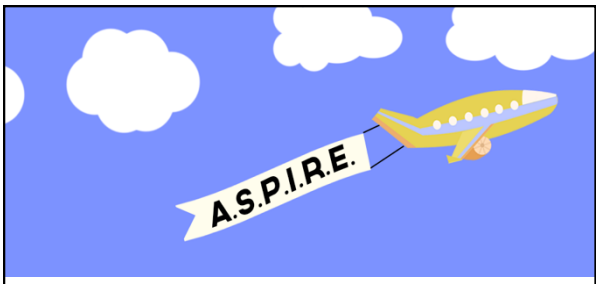

ASPIRE Workshop 5: Application of Biostatistics

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What to Expect Today

- Review biostatistic principles
- Hands on application
- Questions related to your research project

Example Study: Statin Letter Intervention

Among patients with DM eligible for statin therapy, does an intervention involving a letter, a pre-ordered statin prescription, and pharmacist counseling increase statin initiation compared to no intervention (i.e., usual care)?

- Primary Objective: Compare statin-start rate (i.e., purchase of a statin Rx within 3 months after mailing date) between groups.
- How do you decide which statistical test should be used to test this objective?

Statin Letter Intervention

- What is a rate?
- What type of data are rates?
- Based on the study design (i.e., quasi-experimental, two groups), what potential bias/confounding variables need to be considered?
- What statistical test will you use?

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Statin Letter Intervention

- What is a rate?
  - Rate = The proportion of a population that experiences an outcome in a specified period of time.
- What type of data are rates?
  - Percentages (yes/no experienced the outcome) so are binomial data.
- Based on the study design what potential bias/ confounding variables need to be considered?
  - Selection bias: Patients in the intervention clinic are more engaged in health behaviors.
  - Confounding: Patients in the intervention clinic are older & sicker.

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Selecting a statistical test

	Type of Data			
Goal	**Measurement (from Gaussian Population)**	**Rank, Score, or Measurement (from Non-Gaussian Population)**	**Binomial (Two Possible Outcomes)**	**Survival Time**
Compare two unpaired groups	Unpaired *t* test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel*
Compare two paired groups	Paired *t* test	Wilcoxon test	McNemar's test	Conditional proportional hazards regression*
Compare three or more unmatched groups	One-way ANOVA	Kruskal-Wallis test	Chi-square test	Cox proportional hazard regression**
Compare three or more matched groups	Repeated-measures ANOVA	Friedman test	Cochrane Q**	Conditional proportional hazards regression**
Quantify association between two variables	Pearson correlation	Spearman correlation	Contingency coefficients**	
Predict value from another measured variable	Simple linear regression or Nonlinear regression	Nonparametric regression**	Simple logistic regression*	Cox proportional hazard regression*
Predict value from several measured or binomial variables	Multiple linear regression* or Multiple nonlinear regression**		Multiple logistic regression*	Cox proportional hazard regression*

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Statin Letter Intervention

- What statistical test will you use?
  - To assess differences in rates between two groups: Chi-square test of association since outcome is binary (yes/no started a statin) and these are large groups
  - To adjust for any potential selection bias: stratification on presence/non-presence of biasing factor
  - To adjust for any potential confounding: logistic regression since outcome is binary (yes/no started a statin)

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Statin Letter Intervention

- Secondary Objectives: Between the intervention and control groups
  - Compare statin persistence rate (i.e., statin purchase 1 year after mailing date +/- 45 days) between groups
  - Compare abnormal CK (>600) or ALT (>200) rate (i.e., at least one abnormal lab result within 6 months after mailing date) between groups
- What statistical tests will you use for these secondary objectives?

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Selecting a statistical test

	Type of Data			
Goal	**Measurement (from Gaussian Population)**	**Rank, Score, or Measurement (from Non-Gaussian Population)**	**Binomial (Two Possible Outcomes)**	**Survival Time**
Compare two unpaired groups	Unpaired *t* test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel*
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Statin Letter Intervention

- What statistical tests will you use for these secondary objectives?
  - Persistence is a binary outcome (yes/no persistent with a statin) and these are large groups so chi-square test of association
  - Abnormal CK is a binary outcome (yes/no) but the rate of these are low (i.e., a rare outcome) so Fisher's exact test is likely appropriate

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An Examination of the Association Between Therapeutic Anticoagulation Control and Glycemic Control for Patients with Diabetes on Oral Anticoagulation Therapy

- Purpose: To assess the relationship between A1c% and percent time in therapeutic INR range (TTR) for patients with diabetes receiving warfarin
  - A1c% are normally distributed interval level data
  - TTR are skewed interval level data
- Study Design: Retrospective cohort
- What statistical test will you use to quantify the relationship?
- What statistical test will you use if A1c% is categorized as >=8% & <8%?

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Selecting a statistical test

	Type of Data			
Goal	**Measurement (from Gaussian Population)**	**Rank, Score, or Measurement (from Non-Gaussian Population)**	**Binomial (Two Possible Outcomes)**	**Survival Time**
Compare two unpaired groups	Unpaired *t* test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel*
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- A good way to develop a plan for statistical analysis is to think about what your Subject/ Patient Characteristic table is likely to look like…
- Which variables do you think should be adjusted for in logistic regression modeling of the relationship between A1c<8% & TTR?

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Table 1. *Subject Characteristics*

Characteristic	A1C ≥ 8 ($n = 216$)	A1C < 8 ($n = 695$)
Mean Percent of Time in INR Range (SD)	60.3 (31.2)	60.3 (28.9)
Mean Percent of Time above INR Range (SD)	15.8 (23.3)	15.4 (21.2)
Mean Percent of Time below INR Range (SD)	22.9 (28.6)	23.2 (26.3)
Mean Age in Years (SD)	67.6 (10.5)[†]	71.1 (9.3)
Female (%)	41.2	41.4
Diet Interaction (%)	2.8	4.3
Drug Interaction (%)	6.5	7.8
Non-Adherent with Anticoagulant Therapy (%)	53.2	45.9
Thromboembolic Event during the 90 Days Prior to A1C Reading (%)	0.9	1.0
Mean Frequency of INR Testing during the 90 Days Prior to A1C Reading (SD)	4.6 (2.6)[‡]	5.0 (2.7)
Primary Diagnosis for Anticoagulation Therapy (%)	45.4	48.2
Atrial Fibrillation		
Pulmonary Embolism/Venous Thrombosis	7.4	8.2
Mechanical Heart Valve	4.2	4.9
Stroke/CVA	8.3	6.2
Other	34.7	32.5

[†] $p < 0.001$.
[‡] $p = 0.049$.
INR-international normalized ratio, CVA—cerebrovascular accident, SD—standard deviation.

- This is a logistic regression model of A1c>=8%.
- Which of the variables in the table appear to be associated with having an A1C value ≥8%?
- How would you interpret the odds ratio associated with 'Age in Years'?

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Table 2. *Multivariate Logistic Modeling of A1C Value ≥ 8*

Explanatory Variable	Odds Ratio	95% CI
Percent of Time in INR Range	1.00	0.99, 1.01
Age in Years	0.97	0.95, 0.99
Frequency of INR Testing during the 90 Days Prior to the A1C Reading	0.91	0.85, 0.97
Gender		
Male	0.94	0.69, 1.29
Female	1.00	–
Diet Interaction		
Yes	1.02	0.49, 2.14
No	1.00	–
Drug Interaction		
Yes	0.87	0.47, 1.62
No	1.00	–
Thromboembolic Event during the 90 Days Prior to the A1C Reading		
Yes	1.14	0.22, 5.85
No	1.00	–
Adherent with Anticoagulant Drug Therapy		
No	1.21	0.88, 1.65
Yes	1.00	–
Primary Diagnosis for Anticoagulation Therapy (%)		
Atrial Fibrillation	1.03	0.72, 1.47
Pulmonary Embolism/Venous Thrombosis	1.27	0.73, 2.20
Mechanical Heart Valve	0.73	0.33, 1.62
Stroke/CVA	1.32	0.72, 2.42
Other	1.00	–

CI—confidence interval, INR—international normalized ratio, CVA—cerebrovascular accident.

A Randomized Controlled Trial of Empiric Warfarin Dose Reduction with the Initiation of Doxycycline Therapy

- Purpose: To evaluate the utility of preemptive warfarin dose adjustment for preventing non-therapeutic INR following doxycycline+warfarin co-administration
- Primary outcome: Proportion of subjects with an INR increase ≥1 point over INR goal range upper limit
- Study Design: Randomized controlled trial
- Results: Primary outcome was reached in 0/21 intervention group subjects and 2/18 control group subjects (p = 0.201)
- What statistical test was used to generate the above p-value?
  - Interpret this finding using layman's terms
- Is there a need for regression analysis?

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Selecting a statistical test

Goal	Type of Data: Measurement (from Gaussian Population)	Rank, Score, or Measurement (from Non-Gaussian Population)	Binomial (Two Possible Outcomes)	Survival Time
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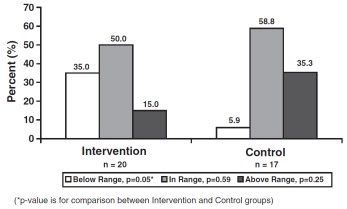
A Randomized Controlled Trial of Empiric Warfarin Dose Reduction with the Initiation of Doxycycline Therapy



(*p-value is for comparison between Intervention and Control groups)

Fig. 1. Dispositions of INR Values Recorded within 7 Days of Doxycycline Initiation by Study Group.

- **With only 37 patients, is it possible that this study was underpowered to detect a difference in the % of subjects with a 'Below Range' follow up INR?**

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Assessment of the Impact of Medication Therapy Management Delivered to Home-Based Medicare Beneficiaries

- **Purpose: To assess the impact of an MTM program on mortality, healthcare utilization, and prescription medication costs and to quantify drug-related problems (DRPs) identified during MTM**
- **Study Design: Retrospective cohort with patents who were targeted for MTM but did and did not consent to receiving MTM**
- **Outcomes: All-cause death (binomial, primary outcome), hospitalization (binomial), and emergency department visit (binomial) rates and medication costs (ratio) in the 180 days following MTM targeting**

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Assessment of the Impact of Medication Therapy Management Delivered to Home-Based Medicare Beneficiaries

Table 1. Patient Characteristics at Baseline

Characteristic	Patients Who Opted In (n = 459)	Patients Who Opted Out (n = 336)	p Value
Age, y (mean ± SD)[a]	68.8 ± 10.7	68.9 ± 11.3	0.949
Chronic Disease Score, mean ± SD	8.8 ± 3.1	8.2 ± 3.5	0.016
Male, %	43.4	45.5	0.541
Preperiod utilization[b]			
inpatient hospitalization, %	20.7	29.2	0.006
inpatient hospitalizations, mean ± SD	0.3 ± 0.7	0.5 ± 1.0	0.003
ED visit, %	23.5	23.2	0.917
ED visits, mean ± SD	0.3 ± 0.8	0.3 ± 0.8	0.956
Mean preperiod medication cost, $[a] (median; IQR)	4465 (3149; 2378–4806)	5197 (3186; 2363–5123)	0.525

ED = emergency department; IQR = interquartile range.
[a]As of date of targeting for medication therapy management.
[b]In the 180 days prior to targeting for medication therapy management.

- Do you think the outcome 'Pre-period Medication Cost' is normally distributed?
- What statistical test should be used to compare this variable between groups?

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Selecting a statistical test

Goal	Type of Data: Measurement (from Gaussian Population)	Rank, Score, or Measurement (from Non-Gaussian Population)	Binomial (Two Possible Outcomes)	Survival Time
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Table 3. Unadjusted and Adjusted Odds Ratios[a]

Event	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[b]
Death	0.5 (0.3 to 0.9)	0.5 (0.3 to 0.9)[c]
Inpatient hospitalization	1.3 (0.9 to 1.9)	1.4 (1.1 to 2.0)[d]
ED visit	0.9 (0.7 to 1.3)	0.9 (0.6 to 1.3)[d]
Increase in medication cost	1.5 (1.1 to 2.0)	1.4 (1.1 to 1.9)[e]

ED = emergency department; MTM = medication therapy management.
[a]Post-MTM targeting, 180-day odds ratios.
[b]Patients who opted out are comparator group.
[c]Adjusted for age, sex, Chronic Disease Score, and presence/absence of a baseline ED visit and inpatient hospitalization.
[d]Adjusted for age, sex, Chronic Disease Score, and specific baseline utilization.
[e]Adjusted for age, sex, Chronic Disease Score, and baseline medication cost.

- What type of statistical test was used to generate this table?
- Why was it necessary to do an adjusted analysis?
- For which variable did the adjusted analysis make a difference in the outcome?
- Interpret the finding related to death in layman's terms

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Assessment of the Association Between Colchicine Therapy and Serious Adverse Events

- **Purpose: To quantify the association of colchicine therapy with myotoxicity and blood dyscrasias in a cohort of insured patients**
- **Primary outcome: Colchicine exposure**
  - **What would be the true outcome?**
- **What study design would be best for accomplishing the purpose of this study?**

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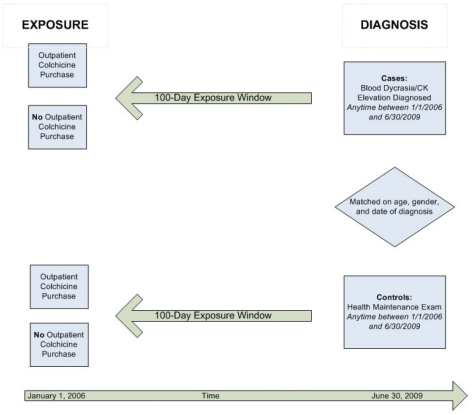

Figure 1. Schematic of the case-control study design.

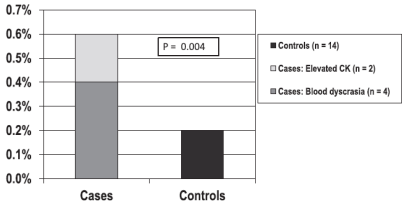

Figure 2. Colchicine exposure rates in the 954 cases and 9007 controls.

- **The odds ratio (OR) for exposure to colchicine for cases was 17.7 (95% confidence interval [CI] 2.4 to 128.2)**
- **When the analysis was limited to patients with diagnosis of gout the OR was 4.6 (95% CI 1.2 to 16.3)**
- **Which of these OR's is more precise?**
- **Interpret these OR's using layman's terms**

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Questions regarding your studies?

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