Center for Collaboration on Research, Design and Analysis (CCORDA)

Jane Meza, Ph.D., Director
Lynette Smith, M.S., Associate Director
Overview

• Coordinate services provided by faculty and staff in the College of Public Health
• Make resources more easily accessible to investigators
• Faculty and staff of the College of Public Health will become an integral part of the research team.
Vision and Mission

- **Vision:** Advance clinical, basic science, translational and public health research at UNMC and in the community and region.
- **Mission**
  - Provide expertise in the quantitative and qualitative sciences, including
    - Biostatistics
    - Epidemiology
    - Health Services Research (GIS, survey, observational studies)
    - Clinical Research Ethics
    - Information technology
    - Coordinate the collaborative design, planning, conduct, analysis and interpretation of laboratory, clinical, and public health research studies.
    - Provide educational training opportunities for quantitative sciences graduate students and educational opportunities for public health, clinical, and translational investigators.
History

• Department of Preventive and Societal Medicine, James Anderson, chair
• Collaborative support in biostatistics, epidemiology and health services research and administration.
• Educational degree programs: MSIA program, participated in development of an MPH degree program.
• Other educational activities: lectures, seminars and workshops in research design and analysis for students, faculty and staff.
College of Public Health

• Opportunities for new, multidisciplinary collaborative relationships.
• Faculty and staff of the College of Public Health have been active collaborators, providing core support in research design and analysis for many centers, research groups, and investigators across UNMC and in the community.
• Need expansion of and enhanced coordination of research design and data analysis expertise.
• Effective research programs often require multi-disciplinary approaches.
Administrative Core

• Jane Meza, Ph.D., Director
• Lynette Smith, M.S., Associate Director
• Gene Boilesen, Data Manager
• Matt Anderson, Data Manager
• Mary Morris, Administrative support
CCORDA Services

• Research Design
  – Participate in protocol and grant development
  – Study design
    • Laboratory based studies
    • Clinical Trials
    • Epidemiological studies
    • Observational and qualitative studies
    • Survey sampling
  – Study conduct
  – Sample size calculations
  – Statistical analysis plans
  – Protocol coordination
  – Randomization sequences
  – Design of secondary analyses of complex survey data
  – Design of experiments producing high-dimensional genomic data.
Benefits of involvement in design stage

- Identify sources of bias
- Explore design options
- Estimate and justify sample size
- Optimum use of resources
CCORDA Services

• **Data Acquisition and Management**
  – Data acquisition
    • Clinical trials
    • Surveys
  – Data management
  – Data monitoring
  – Data query reports
  – Develop, monitor and manage study databases
  – Develop web-based surveys
  – Develop case report forms
  – Develop web-based data entry programs
  – Program scannable case report forms
  – Perform complex data acquisition, merging and processing
CCORDA Services

• Analysis
  – Statistical analysis and interpretation
  – Participate in manuscript writing
  – Secondary analyses of complex survey data
  – Geographic Information System (GIS)
  – Economic evaluation of health care
  – Needs assessment and evaluation
  – Qualitative analysis
Online Requests for Services

• Indicate important time deadlines (abstracts etc.)
• Reason for deadline:
  □ grant submission □ abstract □ presentation □ manuscript
  □ other
• Project title:
• Type of support requested:
  □ Research Design/Development
  □ Database development
  □ Data Acquisition and Management
  □ Clinical research ethics
  □ Data Analysis/Statistical Support

Brief goals and description of the project
When to contact the CCORDA

• When you need expertise in these areas
• The expertise and knowledge of the CCORDA members can supplement your area of expertise and enhance the quality, integrity and validity of your study or project.
Initial consultation

• Your research hypotheses.
• The data file, with identifying information removed.
• A printed example of your the data is also useful for discussion.
• Please make sure you have IRB approval.
• Relevant papers from the literature.
• Your written research proposal or draft of your manuscript if available.
CoPH Center for Collaboration on Research Design and Analysis

- [www.unmc.edu/publichealth/ccorda/](http://www.unmc.edu/publichealth/ccorda/)

- Director: Jane Meza, Ph.D.
  - [jmeza@unmc.edu](mailto:jmeza@unmc.edu)
  - 559-6825

- Associate Director: Lynette Smith, M.S.
  - [lmsmith@unmc.edu](mailto:lmsmith@unmc.edu)
  - 559-8114
Statistical Considerations

- Data analysis plan
- Sample size justification
Analysis plan needs to account for Study Design

- Phase I
- Phase II
- Phase III
- Cross sectional
- Case-control
- Longitudinal
- Pilot
- Feasibility
- Matching
- Clustering
Hypotheses and Objectives

• What are the hypotheses to be tested?
• What is the primary endpoint?
• What groups will be compared?
• What are the secondary endpoints and associations of interest?
Analysis plan: Populations

- Intent-to-treat - Patients are analyzed according to the assigned treatment, regardless of treatment received.
- Treated – participants who never received treatment or never provided follow-up data are excluded
Analysis plan: Descriptive statistics

• Describe the summary measurements (mean, median, SD, range, frequency, percentage)
  – Outcomes
  – Patient characteristics
  – Comparison groups
  – Baseline and each time point
Analysis plan: Pilot study

• Objective: Estimate a parameter for one or more groups in order to estimate the effect size for planning a “fully” powered randomized trial

• State the parameter to be estimated and the subpopulations

• State how the parameter will be summarized, how variance and or CI will be calculated
Analysis plan: Testing a hypothesis

• Univariate analysis
  – Statistical hypothesis to be tested (effect of treatment on outcome)
  – Statistical test to be used
  – Alternative tests if assumptions are violated
  – Level of significance
  – One-sided vs. two-sided tests
Analysis plan: Testing a hypothesis

• Multivariate analysis
  – Still interested in effect of treatment on outcome
  – Adjust analyses for potential imbalances in patient characteristics
  – Which potential confounders will be examined? (age, sex, stage, etc)
  – Model to be used (linear regression, logistic regression, Cox proportional hazards regression)
  – Interactions to be tested
  – Variable selection methods
  – Assessment of model fit
Analysis plan template

• Objectives
• Analysis populations
• Analysis of baseline data
• Analysis of primary objectives
  – Descriptive statistics
  – Univariate analysis
  – Multivariate analysis
• Analysis of secondary endpoints and objectives
• Other planned analyses such as subgroup analyses
Example

• Randomized, double-blinded controlled trial designed to determine if study drug reduces incidence of severe oral mucositis (World Health Organization [WHO] Grade 3 or 4), compared to placebo
Example: Study Design

• Phase III
  – Randomized
  – Placebo controlled
  – Double blind
Example: Hypotheses and Objectives

• What are the hypotheses to be tested?
  – HO: Incidence of severe oral mucositis is the same for study drug and placebo
  – HA: Incidence of severe oral mucositis is different for study drug and placebo (two-sided)

• What is the primary endpoint?
  – Incidence of WHO Grade 3 or 4 oral mucositis

• What groups will be compared?
  – Study drug vs. placebo

• What are the secondary endpoints and associations of interest?
  – Other mucositis scales, safety of study drug, …
Example: Populations

- Intent-to-treat
  - Analysis of efficacy endpoints will follow the intention-to-treat paradigm.

- Treated
  - Analysis of safety endpoints will be conducted using all patients who received at least one dose of study medication.
Example: Descriptive statistics

- The incidence of oral mucositis will be descriptively summarized for each treatment group using frequencies, percentages and 95% confidence intervals.
Example: Univariate Analysis

- Statistical hypothesis to be tested (effect of treatment on outcome)
- Statistical test to be used
- Alternative tests if assumptions are violated
- Level of significance
- One-sided vs. two-sided tests
  - For the primary outcome measure, the incidence of WHO Grade 3 or 4 mucositis will be compared between groups using a two-sided Chi-square test or Fisher’s Exact test if the data do not follow the assumptions for the Chi-square test. A p-value > 0.05 will be considered statistically significant.
Example: Multivariate analysis

• Still interested in effect of treatment on outcome
  – Adjust analyses
  – Which potential confounders will be examined?
  – Model to be used
  – A logistic regression model will be used to adjust for potential confounders of age and treatment regimen.
Importance of Careful Study Design

• Goal of sample size calculations:
  – Adequate sample size to detect meaningful differences
  – Ethical use of resources

• Important to justify sample size early in planning stages

• Examples of inadequate power:
  – Of 71 “negative” trials, 70% had >10% chance of missing a true 50% reduction
  – *NEJM* 299:690-694, 1978
Type of Outcome

- Sample size calculations depend on type of outcome variable, sampling method and method of analysis
  
  - Continuous response
    - Example: cholesterol, weight, blood pressure
  
  - Dichotomous response
    - Example: yes/no, presence/absence, success/failure
  
  - Sampling Method
    - Example: SRS, cluster sampling
  
  - Method of analysis
    - Example: 2 group comparison, > 2 group comparison, regression
Effect Size

• What is the minimal, (scientifically) significant difference between groups we would like to detect?

• Pilot studies may indicate magnitude

• Example:
  – In previous studies, 60% of placebo treated patients developed Grade 3 or 4 oral mucositis.
  – Detect a reduction of 25% in the incidence of severe oral mucositis
Variability in Response

• To estimate sample size for a continuous outcome, in addition to the mean, we need an estimate of the variability of the response in the population

• Estimate variability from pilot or previous, related study
Summary

• To estimate the sample size, we need
  – Primary endpoint
  – Comparison groups
  – Significance level
  – Power
  – Effect size that reflects a scientifically meaningful difference
  – Historical values of estimates of the parameters (mean and SD, proportions)
Example – Dichotomous Response

• If a reduction of 25% in the incidence of severe oral mucositis is considered clinically meaningful, (i.e., 60% of placebo treated patients and 35% of palifermin treated patients), 180 randomized patients will provide at least 90% power to detect such a difference with a two-sided alpha level of 0.05.
Example - Continuous Response for 2 groups

- A total of 230 participants (115 in each group) will provide 90% power at the two-sided 0.05 significance level, to detect a **3 mm Hg difference** in blood pressure level with where the standard deviation has been estimated to be **7 mm Hg**.
Adjustments to Sample Size

• Dropouts will decrease the effective sample size
  – Adjust the sample size for dropouts
  – A simple adjustment to calculate sample size for dropout rate is
    
    \[
    \text{Adjusted total size} = \frac{\text{Calculated size}}{1 - \text{dropout rate}}
    \]
  – Example: The calculated total sample size is 230 and the dropout rate is expected to be 10%. The adjusted total sample size is \(230/0.9 = 256\), or 128 in each group.
Adjustments to Sample Size

• Multiple comparisons
  – Multiple comparisons result in an increased probability of detecting a difference in treatments by chance alone, that is, an increased probability of a Type I error
  – Adjust the significance level $\alpha$, by dividing it by the number of multiple comparisons