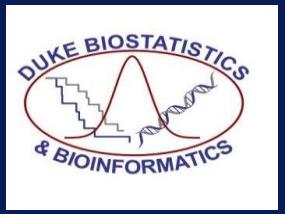
Biostatistics Core
HCS Research Collaboratory
Are we on the right track?

Grand Rounds

April 19, 2013

The Core Team

- Elizabeth Delong, Duke School of Medicine
  - Comparative Effectiveness
- Andrea Cook, Group Health Research Institute
  - Longitudinal and Correlated Data
- Lingling Li, Harvard Medical School
  - Causal Inference
- Yuliya Lokhnygina, DCRI
  - Randomized Trials, Adaptive Designs
- Tammy Reece – DCRI – Project Leader



WG members and Affiliations

Study	PI	Statistician/ Group Member	Acronym
Hypertension Nighttime dosing of Anti-Hypertension Medications	Rosenthal	Bridget Zimmerman Eric Eisenstein	
Strategies and Opportunities to Stop Colon Cancer	Coronado	Bill Vollmer	STOP CRC
Lumbar Image Reporting with Epidemiology	Jarvik	Patrick Heagerty Bryan Comstock	LIRE
Collaborative Care for Chronic Pain in Primary Care	DeBar	Bill Vollmer	PPACT
Maintenance hemodialysis: Time to Reduce Mortality in ESRD	Dember	Richard Landis Peter Yang	TIME
Pragmatic Trial of Population Based programs to prevent Suicide	Simon	Rob Penfold	
Decreasing Bioburden to Reduce Healthcare-Associated Infections and Readmissions	Huang	Ken kleinman	ABATE

Means of Interaction

- Initial conference call on January 24
  - Discussion
    - » General statistical issues among the seven projects
    - » Potential deliverables
  - Schedule
    - » Monthly update calls
    - » Series of initial weekly calls to become familiar with each other and the projects

Outcome of first call

- Created three working subgroups
  - » Power - Liz
  - » Blocking and stratification for cluster randomized trials - Andrea
  - » Ascertainment of outcomes - Lingling
- Decided to become oriented by having individual project overviews
  - – Two presentations per week
  - – Focusing on power assessments/ assumptions

Potential Deliverables

- Initial report on issues related to calculation of power
- Possible white papers on common elements and lessons learned
- Eventual manuscripts with original work

Study Template (Ken Kleinman)

- Study name:
- Study description (one sentence):
- Setting (what are the subjects, what population do they represent):
- Design:
- Intervention (what are the arms of the trial):
- Outcomes:

Study Template (Ken Kleinman)

- Ascertainment:
- Planned Analysis:

- (Above captured in one page or less)

- Power Assessment:
- Concerns

Presentations

Study	PI	Presenter	Acronym	Power Presentation
Hypertension Nighttime dosing of Anti-Hypertension Medications	Rosenthal	Bridget Zimmerman		2/22
Strategies and Opportunities to Stop Colon Cancer	Coronado	Bill Vollmer	STOP CRC	2/12
Lumbar Image Reporting with Epidemiology	Jarvik	Bryan Comstock	LIRE	3/15
Collaborative Care for Chronic Pain in Primary Care	DeBar	Bill Vollmer	PPACT	3/15
Maintenance hemodialysis: Time to Reduce Mortality in ESRD	Dember	Peter Yang	TIME	2/22
Pragmatic Trial of Population Based programs to prevent Suicide	Simon	Rob Penfold/ Greg Simon		3/29
Decreasing Bioburden to Reduce Healthcare-Associated Infections and Readmissions	Huang	Ken kleinman	ABATE	2/12

Common theme

- Cluster randomization- Impact on power (randomized unit is starred)
  - ABATE – wards within 57 hospitals*
  - LIRE – providers (2-~150) within clinics* within health system
  - STOP CRC – providers within clinics* within Health Services organizations
  - PPACT – providers** within clinics* within Sites
  - TIME – patients within hemodialysis facilities* within dialysis provider organizations

Interesting statistical issues

- When randomizing clusters, widely varying cluster sizes
  - To use weighting mechanism or to confine to a narrower range?
  - How does the jacknife estimate of variance compare to either of these
- The ICC
  - Obtaining preliminary estimates
  - Intuitive meaning for dichotomous outcomes

Interesting statistical issues

- Frailty model versus random effects logistic model – relative power
- Robust variance versus frailty model to account for clustering

Blocking/Stratification call

- Andrea summarized randomization approaches from the seven PTs
- Two plan individual randomization
  - Nighttime dosing – anticipate little contamination because dosing will be protocol- not physician driven
  - Suicide prevention – intervention mostly online
  - Easier to create balance with individual randomizatoin

Blocking/stratification call

- Typical cluster randomization scheme randomizes at the clinic level, with varying number of providers
  - LIRE plans a nice step wedge design, stratifying each wave by site and clinic size (small, medium, large)
  - STOP CRC and PPACT will use simulation strategy to create balance among several covariates
  - ABATE will create matched pairs

Interesting common issues

- Stratifying by size of cluster within Site or Health Service Organization
  - EG – define tertiles of size across entire distribution
  - Or define tertiles of size within the larger entity
  - Or use absolute numbers
- Pairing versus stratifying

“Constrained Randomization”

- Simulation to balance among several covariates
- “Selecting an appropriately balanced randomization scheme from all possible allocations of clusters to treatments”*
- Question: How to ensure enough adequate possibilities from which to randomly select

Outcome ascertainment call

- Lingling summarized potential simulation study to assess impact on analysis of:
  - False positive codings in EHR
    - » Adding noise to analysis results
    - » Possibly introducing bias
  - Possible false negatives
    - » Harder to determine
    - » Due to missing data

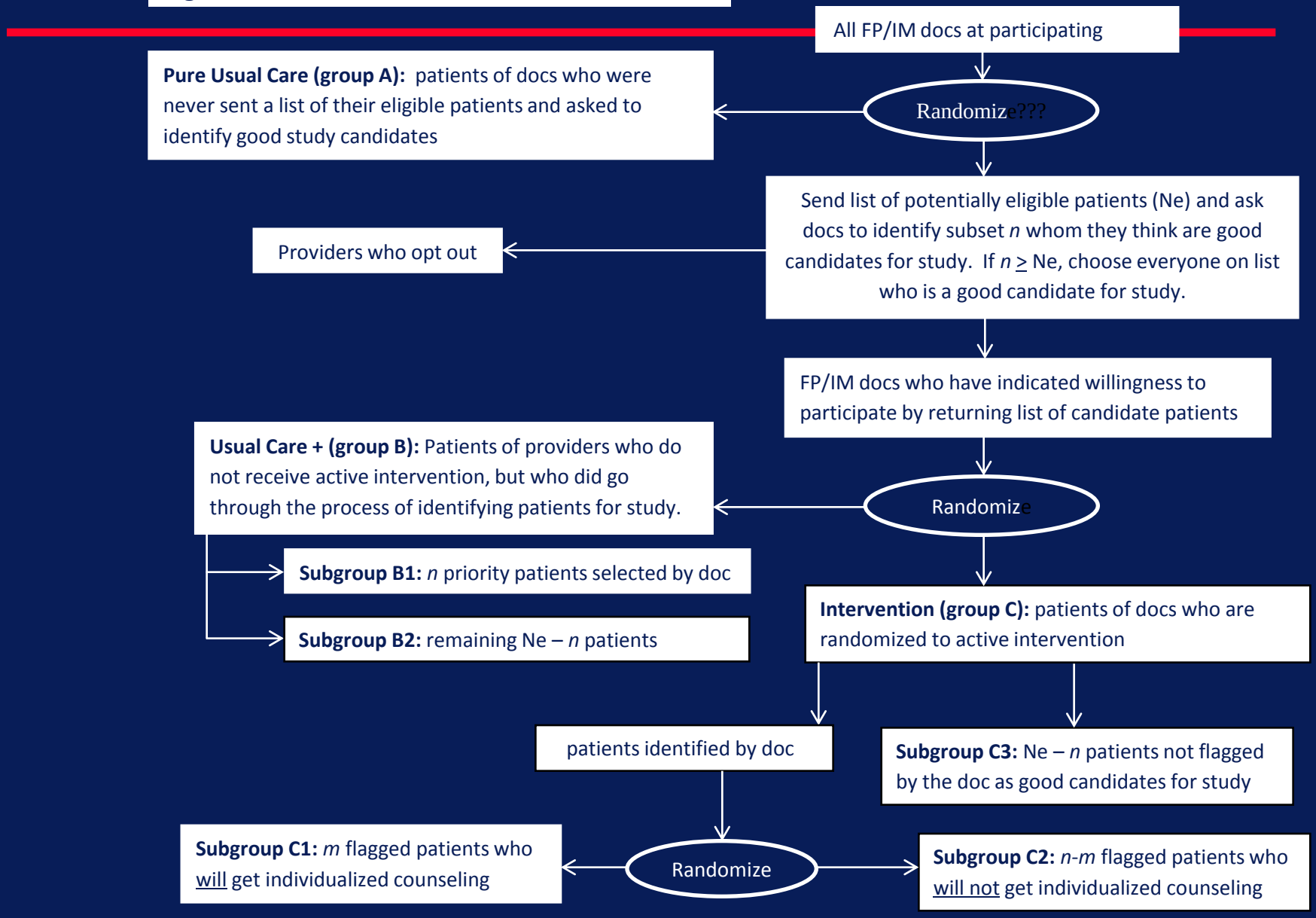
Other interesting statistical issues

- ABATE trial on multi-drug resistant organism
  - Outcome assessed based on ordering of tests – no test, no outcome measurement
  - Within hospital denominator?
    - » total number of subjects
    - » OR number of subjects tested
- STOP CRC trial – how to incorporate rolling time window into assessment

Other interesting statistical issues

- PPACT trial
  - Originally randomizing clusters of 24 patients per clinic, 20 clinics for each of 2 treatment arms
  - Newly proposed design proposed by Bill Vollmer – to be discussed on call today
    - » Randomize at provider level rather than clinic level
    - » Double randomization:
      - True control (no contact) vs ranking list of eligible patients
      - Within responding providers, randomize to treatment

Figure 1. Randomization Flowchart



Back to Deliverables

- As conversations progressed, consensus was:
  - Much information already exists
  - Regurgitating known information might not be productive
  - Original work – adding to the literature would be more interesting and more valuable to the Collaboratoy, and future pragmatic trials

Preferences for studying

	Core 1	NIH	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7
Stratification vs pairing	1			1					
Varying cluster size	4	1	4	2	2				
Intuitive ICC	3	4	3	3	1				
Uneven drop-out	2	5	6	4					
Robust variance vs frailty model	4	2							
Relative power frailty model vs logistic	5								
Missing EHR data			1		3				
Simulations – ensuring enough possibilities		3	2						
Defining quantiles			5						

Results of the survey

- The Work Group will do some original work to
  - Study impact of varying cluster size on power and analyses
  - Create an intuitive demonstration of the ICC
- A graduate student at Duke will help with simulations

Some level of push-back

- Calls have been well-attended
- Participants have been engaged and constructive
- BUT – for those not on the Core, their real job is to work on their own studies
  - They have little time to contribute to other work
  - They are somewhat confused regarding their role in this group

Where to go from here

- Many from the working group will attend the face-to-face meeting April 29
- What are the expectations of this group?
- What would best serve the Collaboratory?