Delirium: Building the Research Enterprise

E. Wesley Ely, MD, MPH
Professor of Medicine and Critical Care
Associate Director of Aging Research, GRECC
Vanderbilt University Medical Center

"As some of your material on ICU delerium suggests, the experience of having been a 'chronic' delerious ICU patient was terrifying in the extreme. But for me has been exceeded by the ongoing ordeal of facing friends - close friends, along with spouses and siblings, who have not even the slightest clue that such medical conditions exist and that the l ongterm repercussions are real and ongoing. I do not believe in alien abductions. However, the terrified fear that such alleged abductees speak of seems not at all unlike the way I feel about my ICU experiences.

The difference between alien abductees and delirious ICU survivors is that the former have the benefit of a widespread network of support groups. ICU survivors seem not to receive support or belief or sympathy that they have any medical condition at all now that they have allegedly recovered (aka not died). You must, in addition to the reserach you do, design a public education program which at the very least leaves chronic ICU survivors with the feeling that at least the occasional person OR PHYSICIAN has a clue as to why something should continue to feel so wrong for so long a time."

Mr. BAK

Research Success

- Time
- Cross Talk
- “Use what we already know”
- 2020 scientists must be 1990 scientists first, then become excellent 2030 scientists

Considering Scope of Research Along Different Axes

1. Axis based on types of clinical and translational research
2. Axis based on specific clinical disciplines
3. Axis based on methodological foci

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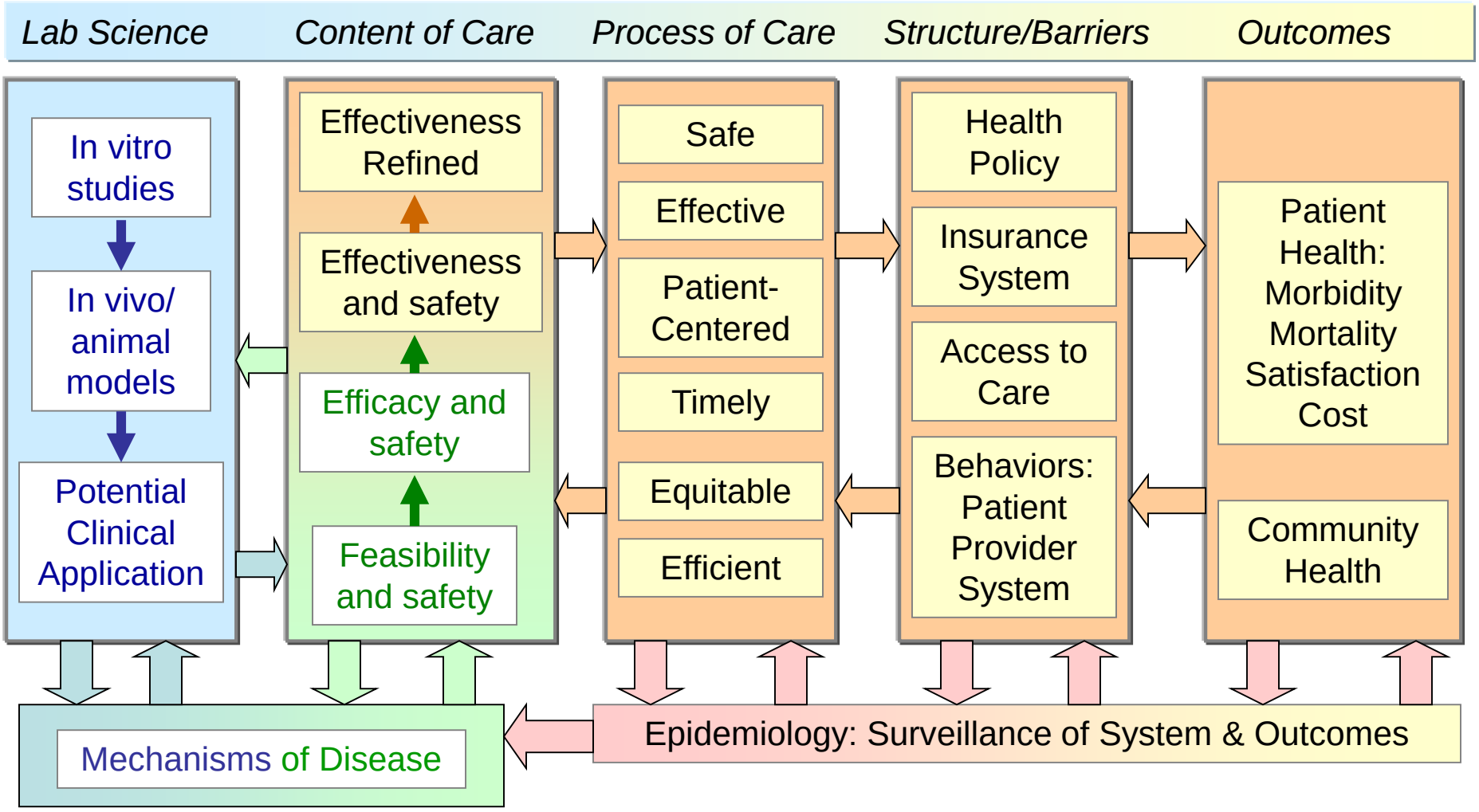
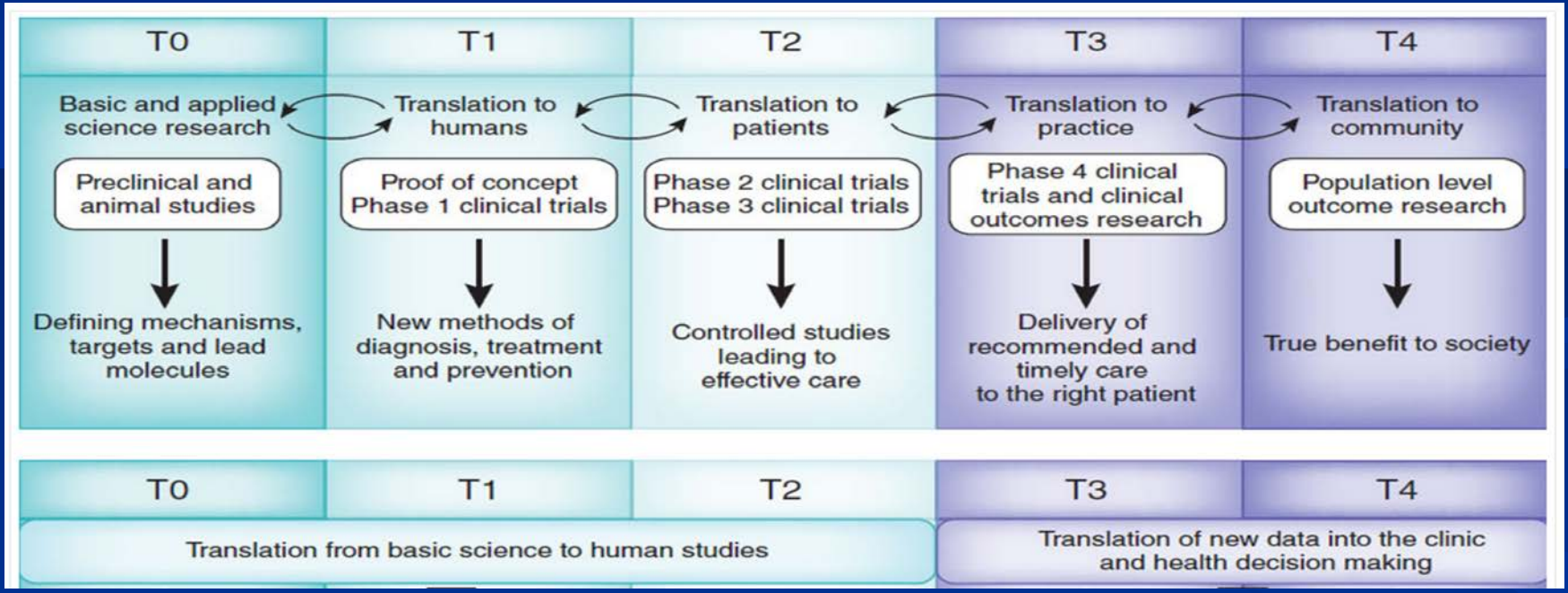
Continuum of Clinical & Translational Research to Improve Health and Healthcare



T0 to T4 Research



Blumberg RS. Nature Medicine 2012;18, 35–41, doi:10.1038/nm.2632

Careers in Translational Clinical Research

- 11% of U.S. medical school graduates plan careers significantly devoted to research (n=1600)
- Clinical researchers are considered by some to be an endangered species
- “Serious doubts about the viability of careers based on patient-oriented research”
- Without such research, we can’t close the loop on discovery and advancement

Nathan D, JAMA 2000;287:2424-2427

Perils of Clinical Researcher

- Goldstein J, ***J Clin Invest*** 1997;992803-12
- Culliton B, ***Nature Med*** 1995;1:281
- Schrier R, ***Acad Med*** 1997;72:589-94
- Thompson J, ***JAMA*** 1997;278:241-45
- Shine K, ***JAMA*** 1997;278:245-46
- Schulman L, ***Acad Med*** 1996;71:362-63
- Williams G, ***JAMA*** 1997;278:227-31
- Moy E, ***JAMA*** 1997;278:217-21
- Nathan D, ***Nature Med*** 2000;6:1201-04
- Kelley W, ***National Academy Press*** 1994

Clinician affects patient of today

Clinical Researcher affects patient of tomorrow

Considering Scope of Research Along Different Axes

1. Axis based on types of clinical and translational research
2. Axis based on specific clinical disciplines
3. Axis based on methodological foci

“Do you see what I see? The epistemology of interdisciplinary inquiry”

H. G. Petrie. The Journal of Aesthetic Education 1976;10:29-43

Axis based on specific clinical disciplines and levels of training

- Neurology
- Critical Care
- Geriatrics
- Nursing
- Radiology
- Psychiatry/Psychology
- Pharmacology
- Anesthesiology
- Surgery
- Sleep Medicine
- Psychometrics
- Social Work
- Students to Post Docs
- Others….

Clinical Research...
...the path to success

1. Protected time
2. Tool box formation
3. The mentor
4. Developing the ??s
5. Building the team
6. IRB issues
7. Consent
8. Study Design
9. Funding
10. Other issues

The job description

- Get protected time
  - 80/20, 50/50, 20/80
- Use it!
- “Fill up the jar with large rocks first”… the pebbles, sand, and water will kill your research efforts (Covey)
- High Butt : Chair ratio
  (sitzfleisch – the ability to sit through and tolerate)

Tool box formation

- Seek formal training early on, or surround yourself with those who have it
  - MPH, MSCI, etc
  - Career development awards
- Center for Health Services Research concept (e,g, variable degrees/training door to door)
- Federal and foundational funding agencies

The mentor as a catalyst

- Reality - not all will have a favorable mentor
- 7 Roles of the Mentor
- Teacher, sponsor, advisor, agent, role model, coach, confidante
  - Needs to “walk the talk”

Tobin M, AJRCCM 2004

Hypothesis-driven research questions

- Patient care arena is the lab (ICU, wards, out patient facility, etc)
- Observe and ask practical questions
- 2 Guiding Principles:
  1. "Study what you have a lot of"
  2. "Either answer matters" to advance care
- Develop, refine, and test your hypothesis


RASS SCALE
PHILIPS
92/61 (68)

Building the team:

- Membership must include
  - Mavens
  - Connectors
  - Salespersons
- Membership will fluctuate over time
- Cut losses to make gains

Building the team: restating the obvious?

- Research infrastructure
  - Nurses, Therapists, PharmD, Administrators, Statisticians, Physicians, etc
- Research “extra” structure
  - Expert consultants
- Key Features:
  - Bring energy and passion
  - Collaboration
  - Diligence
  - Manners and openness
  - Selling yourself and your idea

Building the Research Enterprise

- In both single center and multi-center investigations, the TEAM is the key
- The Principal Investigator is the quarterback for the team
- The team is the coordinating center and more

Teamwork

(sometimes requires “holding”…)

Vanderbilt/VA ICU Delirium & Cognitive Impairment Study Group

HUGE ISSUES
in team building

- What wall is the ladder against?
- Are you putting the big rocks in first?
- (carry in my wallet for remembrance)
- “As iron sharpens, so one man sharpens another”
- “A cord of three is not easily broken”

SO...load the bus with the right people

Major Concepts

- The guiding principle MUST BE the patient
- That means it is not career, money, promotion, getting a specific grant, etc
- Driven by passion
- Decide in what area you can be THE BEST
- Determine how you'd feel if you failed; why would that matter to you?

Clinical Research is a pathway of discovery. You must follow the leads…for example…

“Dig the break” Dubin

Projects that are totally safe (easy) have less chance of making a big difference than projects with a distinct chance of failure.

Fear of failure would mean death of progress.

The Road Not Taken

Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth
Then took the other…

Robert Frost (1874–1963)

Considering Scope of Research Along Different Axes

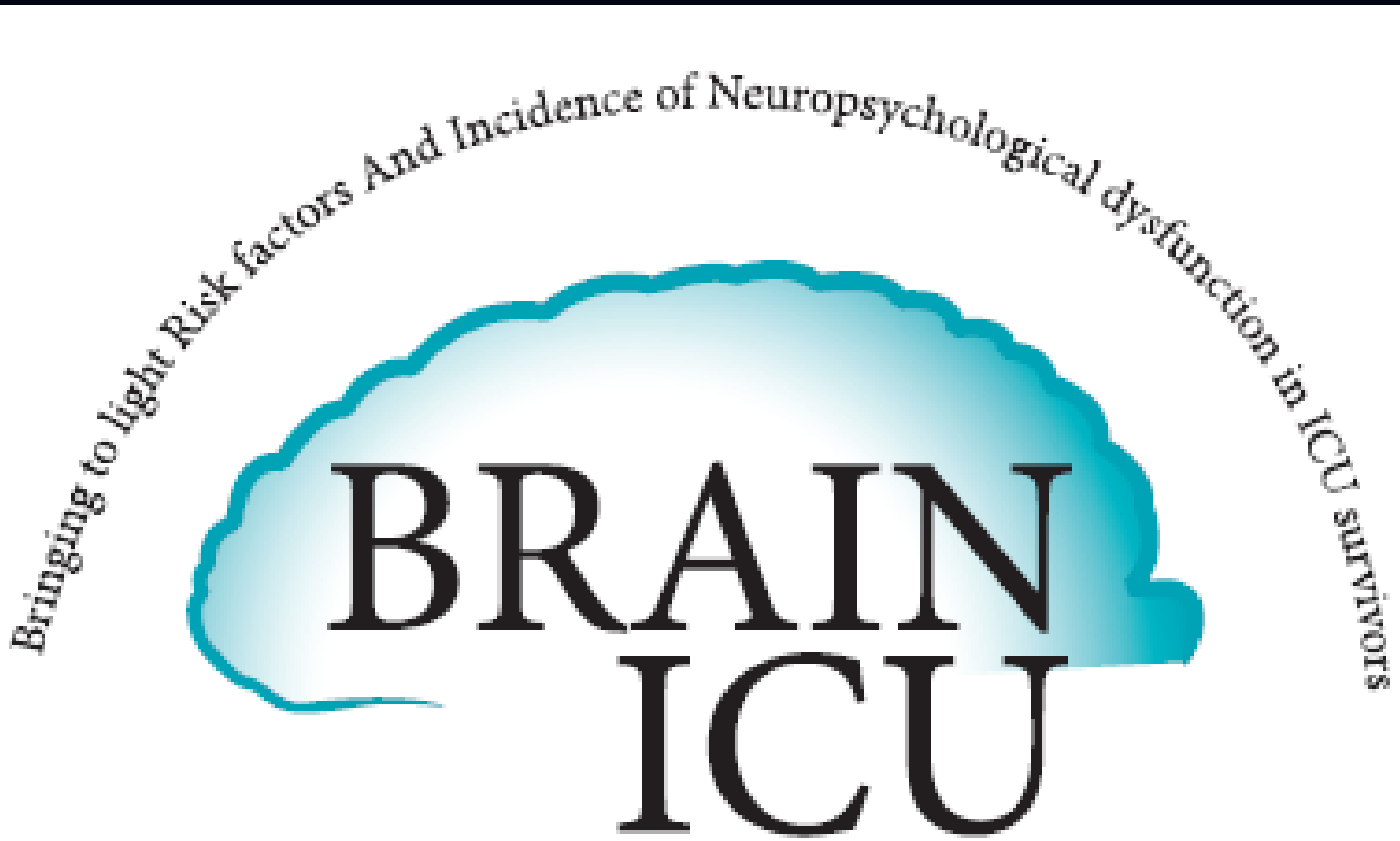
1. Axis based on types of clinical and translational research
2. Axis based on specific clinical disciplines
3. **Axis based on methodological foci**
   - Design (e.g., cohort, RCT)
   - Measurement (e.g., tools, scores, metrics)
   - Analysis (e.g., not reporting univariate data, incorporating time-varying covariates, frequentist vs. Bayesian)

Another Axis for Types of clinical research

- Quantitative
  - Establish incidence, prevalence, determine treatment effectiveness, measure risk
- Qualitative (Users' Guide - JAMA 2000;284:478-482)
  - Describe phenomenon, understand thinking or behavior, "why" treatments do or don't work
  - Rigorously done qualitative research provides insights that quantitative research can not
  - Poorly done, qualitative research is as useless as poorly done quantitative research
- Quality Improvement
  - when does it become research?

Conducting and Analyzing Cohort Studies

- Intensely interdisciplinary and technical
- Many things can never be randomized, such as “delirium group” vs. “no delirium group”
- Attributing cause and effect is limited yet robust predictor methodology is available
- Key methodological issues must be considered such as time-immortal bias


Bringing to light Risk factors And Incidence of Neuropsychological dysfunction in ICU survivors
BRAIN
ICU

Organizational Chart
DRAFT Last edited 01-26-07

BRAIN-ICU Project

NIH BRAIN-ICU Study

St Thomas
Site PI: Canonico
RN: Jan Dunn
NPC: Venice Anderson

Meharry
Site PI: Trochtenberg
RN: CRC Nurse
NPC: Venice Anderson

VUMC
Site PI: Pandharipande
RN: Joyce Okahashi & Kate van der Heijden
NPC: Venice Anderson

Veterans' MIND-ICU Study

TN Valley VA
Site PI: Ely/Cotton
RN:Kate van der Heijden
NPC: Sharon Gordon
CC: LaJuana Fleming
Vincent Messina

Puget Sound VA
Site PI: Martin, Goodman
RN: Gail Rona & Melissa Hutchinson
NPC: TBA

SLC VA
Site PI: Wasserstein & Elstad
RN: Nichole Pace
NPC: TBA

Study Site Coordination

Advisory Council Consultants
Bill Hazzard
Edward Koo
Ramona Hopkins
Daniel Laskowitz
Carl Moons
George Martin

Senior Advisors
Robert Dittus
Gordon Bernard
Ted Speroff
Frank Harrell

Coordinating Center

Project Manager
Brenda Pun

Project Administrator
Meredith Gambrell

Neuropsychological Coordinators
Sharon Gordon
Jim Jackson

Principal Investigator
Project Director
Wes Ely

Epidemiology
Carl Moons

DNA Core Lab
Cara Sutcliffe

Biostatistics
Ayumi Shintani
Robert Greevy
Jennifer Thompson
Dale Plummer

Data Support & Analysis

Specialty Projects

Clinical Pharmacology
Mike Stein
Usha Nair
Pratik Pandharipande

Biomarker Analyses
Tim Girard
Lorraine Ware
Nancy Wickersham
BIOSITE

Brain Perfusion
Pratik Pandharipande

Imaging
Russ Miller
Chris Gatenby
John Gore

Sleep
Paula Watson
Rich Tyson
ASPECT

BP and Pulse Ox
Bryan Cotton

Epidemiology

- Changing delirium rates
- Subtypes of delirium (septic, pharm, etc)
- Relationship with LTCI
- Dementia type (amnestic vs. non-amnestic, vascular vs. AD)

Tools

- Clinical instruments
  - ICDSC and CAM-ICU
  - Severity scales
- EEG, fronto-temporal
- Neuroimaging (MRI, fMRI, PET)
- Biomarkers

Understanding/Predicting Outcomes (examples)

- Clinical prediction rules for both delirium and LTCI
- Caregiver burden
- Inter-relationships with other psychiatric illnesses such as depression, PTSD, dementia

Planning an RCT

1. Ensure that similar studies aren't ongoing or haven't been completed
2. If possible, undertake RCT as part of broader research program
3. Simple rather than complex designs (2 parallel arms vs. factorial)
4. "Minimal data" collection strategies are often regretted

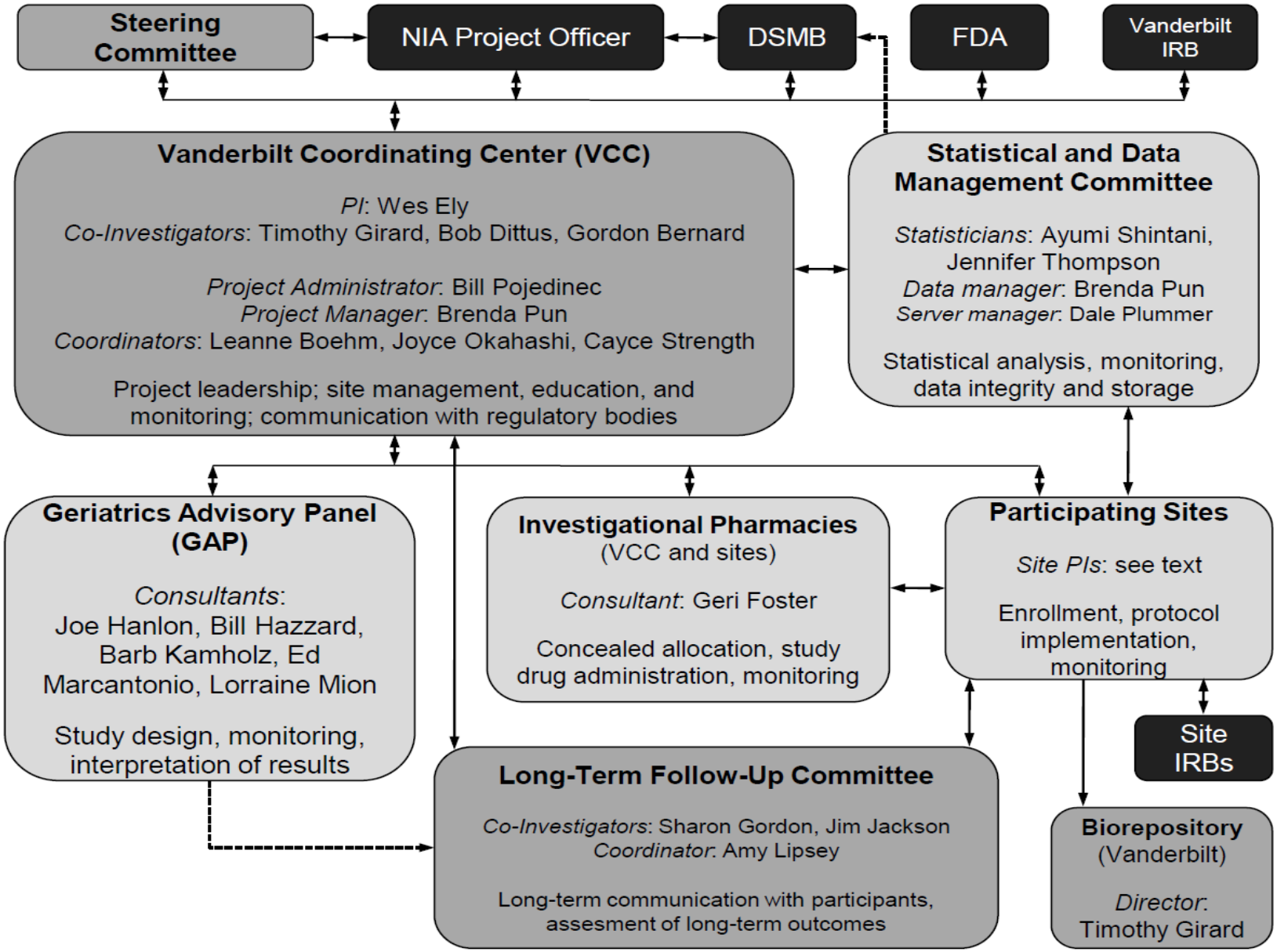
Planning an RCT

5. Primary Outcome - patient-oriented rather than surrogates or biological markers
6. Answer questions that clinicians consider important
7. Select an achievable goal (sample size)
8. Involve experienced trialists, biostatisticians, and multiple pertinent disciplines

Clinical Trials

- Pharmacological interventions
  - Sedation and analgesia
  - Antipsychotics
  - Anticholinergic modulation
- Sleep optimization and modification
- Multi-component interventions
- Physical/cognitive rehabilitation

Example RCT Organizational Chart



Publications…quality

- **“Anyone who reads journals widely and critically is forced to realize that there are scarcely any bars to eventual publication. There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print.”**

Rennie, D. JAMA 1986;256:2391-2392

On Leadership

- Humility and Will (level 5 leadership)
- Screwtape Letters, #14 (CS Lewis)
- The window and the mirror
- By example, you must be a work horse, not a show horse

Good to Great – Jim Collins

As Researchers…

- We are not satisfied with status quo
- We ask questions and find answers
- Driven by the desire to improve the lives of both our own patients and those whom we'll never meet
- So this is YOUR study, YOUR time, and YOUR vocation

The Aging Mind: Opportunities in Cognitive Research

“the study of the aging mind is highly interdisciplinary and this exciting research area would benefit from collaborative work in many disciplines...”

The National Research Council of NIH 2000

Miscellaneous issues critical to ensure success

- Database and statistical analysis
- Publish (write, write, and write)
- Tips for Discussion section:
  - Horton R, (editor of Lancet). JAMA 2002;287:2775-2778
- Authorship
- Formulate next questions
- Modify team for next study

“It can not be done”

“According to recognized aerotechnical tests, the bumblebee cannot fly because of the shape and weight of his body in relation to the total wing area. But the bumblebee doesn’t know this, so he goes ahead and flies anyway.”

Ann Intern Med. 2007; 146:753-754

Institutional Review Board (IRB)

- Know your IRB personnel
- Rules are now in evolution and somewhat of a moving target

Institutional Review Board (IRB)

- Know your IRB personnel
- Rules are now in evolution and somewhat of an improving target
- HIPAA* (health insurance portability and accountability act of 1996), as you know, changed everything!
- Never assume you “don’t need an IRB approval”

* http://ohrp.osophs.dhhs.gov/humansubjects

Informed Consent in Critically Ill

- Incompetent patient and surrogate consent
- Waived consent
- Participation of the family
  - They'll be under stress
  - Obtaining a 2nd consent form
- Implied (presumed) consent in Emergency Setting (vasopressin and CPR)
- Reconsenting the patient
- Is consent required for quality improvement projects?

Funding pros and cons

- NIH
  - K awards (K23 and K08)
  - Loan repayment *
  - RO1
- VA
- Industry
- Foundation
- Talk to the institute or granting agency
- Grant writing is a “team effort”

* Ley T, N Engl J Med 2002;346:368-72
* Natahan D, N Engl J Med 2002;346:372-374

Components of a Grant – selling your idea

1. We have the following specific aims
2. The reason we think this is important is because
3. In response to this issue, we, the investigators have already conducted the following germane areas of work
4. Our plan has the following components
5. Pros/cons/caveats/timeline

No degree of grantsmanship will turn a bad idea into a good one, but there are many ways to disguise a good idea.

The one way to guarantee that you won’t get a grant is...

“The one way to guarantee that you won’t get a grant is...

...not to apply!