Delirium: Building the Research Enterprise

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“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 longterm 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 research 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

Lab Science
- In vitro studies
- In vivo/animal models
- Potential Clinical Application
- Mechanisms of Disease

Content of Care
- Effectiveness
- Refined
- Effectiveness and safety
- Efficacy and safety
- Feasibility and safety

Process of Care
- Safe
- Effective
- Patient-Centered
- Timely
- Equitable
- Efficient

Structure/Barriers
- Health Policy
- Insurance System
- Access to Care
- Behaviors: Patient Provider System

Outcomes
- Patient Health: Morbidity Mortality Satisfaction Cost
- Community Health

Epidemiology: Surveillance of System & Outcomes
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

- Thompson J, *JAMA* 1997;278:241-45
- Shine K, *JAMA* 1997;278:245-46
- Williams G, *JAMA* 1997;278:227-31
- Moy E, *JAMA* 1997;278:217-21
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”

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, outpatient 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
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
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

Vanderbilt Coordinating Center (VCC)

*Pl: Wes Ely*
*Co-Investigators: Timothy Girard, Bob Dittus, Gordon Bernard*
*Project Administrator: Bill Pojedinec*
*Project Manager: Brenda Pun*
*Coordinators: Leanne Boehm, Joyce Okahashi, Cayce Strength*

Project leadership; site management, education, and monitoring; communication with regulatory bodies

Geriatrics Advisory Panel (GAP)

*Consultants:*
*Joe Hanlon, Bill Hazzard, Barb Kamholz, Ed Marcantonio, Lorraine Mion*

Study design, monitoring, interpretation of results

Investigational Pharmacies (VCC and sites)

*Consultant: Geri Foster*

Concealed allocation, study drug administration, monitoring

Long-Term Follow-Up Committee

*Co-Investigators: Sharon Gordon, Jim Jackson*
*Coordinator: Amy Lipsey*

Long-term communication with participants, assessment of long-term outcomes

Statistical and Data Management Committee

*Statisticians: Ayumi Shintani, Jennifer Thompson*
*Data manager: Brenda Pun*
*Server manager: Dale Plummer*

Statistical analysis, monitoring, data integrity and storage

Participating Sites

*Site.Pl: see text*

Enrollment, protocol implementation, monitoring

Biorepository (Vanderbilt)

*Director: Timothy Girard*
“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:
- 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”

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!