Clinical Research: “The Nuts and Bolts”

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Depts. Of Pediatrics and Anesthesiology
Disclosures

• Financial interests: None

• Clinical research involvement:
  
  • Current co-investigator for the NIH Pediatric Heart Network
  • Past principal or co-investigator for:
  • FAER
  • AHA
  • NIH
  • Site-PI for Industry Initiated studies:
    Fenoldepaam, iNO, Dexmedetomidine
Outline

• What is “clinical research?”

• How does clinical research fit into a career in Peds Anesthesia?

• Take-home points
Why is Clinical Research Important?

• Enhances our understanding of human physiology and pathophysiology.

• Translates basic research into medical care.

• Informs and drives basic research.

• Improves diagnostic tools and preventive care.

• Improves human health!
What Can Clinical Research Accomplish?

• Research in human physiology and pathophysiology translates basic research into knowledge of disease mechanisms and medical therapeutics.

• Clinical trials establish safety and efficacy of new interventions.

• Epidemiological and behavioral research identify high risk populations with potential to benefit from prevention, early detection, or therapeutic intervention.

• Outcomes and health services research assess the health impact and cost-effectiveness of interventions.
Clinical Trials

• Research that prospectively assigns human subjects to intervention and concurrent comparison/control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. (International Committee of Medical Journal Editors).

http://clinicaltrials.gov/ct/info/whatis#types
Clinical Trial Phases

• **Phase I trials**: First-time test of intervention in a small group of people (20-80) to evaluate safety, determine appropriate dosage, and identify side effects.

• **Phase II trials**: Intervention given to a larger group (100-300) to evaluate effectiveness and safety.

• **Phase III trials**: Intervention given to large groups (1,000-3,000) to confirm effectiveness, monitor side effects, compare to other treatments, and collect information that will allow it to be used safely.

• **Phase IV trials**: Post marketing studies determine additional information including risks, benefits, and optimal use of an intervention.
Population Research

• Epidemiology and behavioral research to identify high risk populations with potential to benefit from prevention, early detection, or intervention of established disease processes.

• Outcomes and health services research to assess the health impact and cost-effectiveness of an effective intervention in a population or community setting.
Basic and Clinical Research are Interdependent

Basic Research

Translation from basic science to human studies

Clinical Research

Translation of new knowledge into clinical practice

Improved Health

Adapted from Sung et al. (2003) JAMA, 289, 1278-89.
Helping Newborns Breathe

• Tens of thousands of babies died annually from a mysterious respiratory ailment. Clinical investigators characterized the patients and studied infant respiration and human lung physiology.

• Separately, basic studies of surface tension and pulmonary physiology allowed researchers to identify and characterize pulmonary surfactant.

• With this information in mind, clinical and basic scientists determined that the deaths were due to a lack of surfactant, which caused the alveoli, or air sacs in the lungs, to collapse.

• Treatments were then developed in the lab and tested in and applied to patients with great clinical success.

How do I begin doing clinical research?

• Find a question/issue/patient group that interests you

• Find a research mentor

• Review what is known on this group
  - Retrospective study
  - Meta-analysis
  - Database searches

• Get funding
Who Funds Clinical Research?

• Federal Government
  - National Institutes of Health
  - Department of Veterans Affairs
  - Centers for Disease Control and Prevention
  - Agency for Health Care Research and Quality
  - Department of Defense

• State and Local Governments

• Private Organizations
  - Foundations and other not-for-profits
  - Industry
Sponsors of Biomedical Research (Basic and Clinical)

Moses et al. (2005) JAMA, 294, 1333-42

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Industry vs. Investigator-Initiated Clinical Trials

• Industry
  - Regulatory hurdles
  - Recruitment
  - Funding based on enrollment

• Investigator-initiated
  - Protocol development
  - Data management / analysis
  - Funding must be secured
  - Preliminary data at departmental expense
Clinical and Translational Science Awards

- Transforms academic health centers into definable academic homes for clinical and translational science, which work together to improve the conduct of clinical research.

- Subsumes some General Clinical Research Centers (GCRC).

- 38 academic health centers currently participating.

- Funded from existing clinical research programs and Roadmap dollars.

- No funds are taken from basic research.

http://ctsaweb.org/about.html
## PhRMA Spending on Research in 2006

<table>
<thead>
<tr>
<th>Research area</th>
<th>Dollars (in billions)</th>
<th>Percent of total spending</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-human and Pre-clinical</td>
<td>11.8</td>
<td>27.2</td>
</tr>
<tr>
<td>Phase I</td>
<td>2.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Phase II</td>
<td>5.7</td>
<td>13.1</td>
</tr>
<tr>
<td>Phase III</td>
<td>12.2</td>
<td>28.1</td>
</tr>
<tr>
<td>Phase IV</td>
<td>5.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Uncategorized</td>
<td>2.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Total R&amp;D</td>
<td>43.4</td>
<td>100</td>
</tr>
</tbody>
</table>

How is Clinical Research Regulated?

• **Office of Human Research Protections**
  - Protects the rights, welfare, and well-being of subjects involved in research conducted or supported by the Department of Health and Human Services.

• **Food and Drug Administration**
  - Regulates the approval process and assures the safety, efficacy, and security of drugs, biological products, medical devices.

• **Local Institutional Review Boards**
  - Conducts initial review of research proposals.
  - Ensures participants are not exposed to unreasonable risks and that they give informed consent.
  - Conducts continuing review of approved research to ensure that human-subjects protections remain in force.
Challenges Faced By Clinical Researchers

• Difficulty balancing patient care and research responsibilities.

• Expensive medical training; lower salaries compared to private clinicians.

• Long training time compared to medical school peers.

• Burdensome regulations and paperwork.

• Insufficient mentoring due to competing pressures.

• Low success rate for clinical R01s.
Addressing the Challenges

• Assess clinical research career development awards to optimize retention of clinical researchers.

• Promote effective mentoring by senior clinical researchers.

• Implement loan forgiveness programs to boost retention in the research track.

• Streamline, standardize, and simplify regulatory requirements.

• Include reasonable “protected time” requirements in grants to ensure sufficient time for research.

• Ensure adequate representation of clinical researchers on review panels for clinical research grants.

Academic Pediatric Anesthesiology

• Outstanding clinical experience.

• Research lags behind educational and clinical performance in many specialties.

• Excellence in education, clinical operation and research can lead to departmental status at the university.
Comparing National Institutes of Health Funding of Emergency Medicine to Four Medical Specialties

Sara C. Bessman, MS, Noah O. Agada, MB, MPH, Ru Ding, MS, Wesley Chiang, Steven L. Bernstein, MD, and Melissa L. McCarthy, ScD

Abstract

Objectives: The purpose of this study was to compare National Institutes of Health (NIH) funding received in 2008 by emergency medicine (EM) to the specialties of internal medicine, pediatrics, anesthesiology, and family medicine. The hypothesis was that EM would receive fewer NIH awards and less funding dollars per active physician and per medical school faculty member compared to the other four specialties.

Methods: Research Portfolio Online Reporting Tools (RePORT) were used to identify NIH-funded grants to 125 of the 133 U.S. allopathic medical schools for fiscal year 2008 (the most recent year with all grant funding information). Eight medical schools were excluded because six were not open in 2008, one did not have a website, and one did not have funding data available by medical specialty. From RePORT, all grants awarded to EM, internal medicine, family medicine, anesthesiology, and pediatric departments of each medical school were identified for fiscal year 2008. The authors extracted the project number, project title, dollars awarded, and name of the principal investigator for each grant. Funds awarded to faculty in divisions of EM were accounted for by identifying the department of the EM division and searching for all grants awarded to EM faculty within those departments using the name of the principal investigator. The total number of active physicians per medical specialty was acquired from the Association of American Medical Colleges’ 2008 Physician Specialty report. The total number of faculty per medical specialty was collected by two research assistants who independently counted the faculty listed on each medical school website. The authors compared the total number of NIH awards and total funding per 1,000 active physicians and per 1,000 faculty members by medical specialty.

Results: Of the 125 medical schools included in the study, 84 had departments of EM (67%). In 2008, NIH awarded over 9,000 grants and approximately $4 billion to the five medical specialties of interest. Less than 1% of the grants and funds were awarded to EM. EM had the second-lowest number of awards and funding per active physician, and the lowest number of awards and funding per faculty member. A higher percentage of grants awarded to EM were career development awards (26%, vs. a range of 11% to 19% for the other specialties) and cooperative agreements (26%, vs. 2% to 10%). In 2008, EM was the only specialty of the five not to have a fellowship or T32 training grant. EM had the lowest proportion of research project awards (42%, vs. 58% to 73%).

Conclusions: Compared to internal medicine, pediatrics, anesthesiology, and family medicine, EM received the least amount of NIH support per active faculty member and ranked next to last for NIH support by active physician. Given the many benefits of research both for the specialty and for society, EM needs to continue to develop and support an adequate cohort of independent investigators.

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Table 1
Total NIH Grants Awarded and Total Funding per Active Physician and Faculty Member by Medical Specialty for 2008

<table>
<thead>
<tr>
<th>Medical Specialty</th>
<th>Total Awards</th>
<th>Total Funding</th>
<th>No. of Active Physicians</th>
<th>Awards/Physician*</th>
<th>Funding/Physician</th>
<th>No. of Faculty</th>
<th>Awards/Faculty*</th>
<th>Funding/Faculty</th>
</tr>
</thead>
<tbody>
<tr>
<td>All five specialties</td>
<td>9,237</td>
<td>$4,004,993,788</td>
<td>423,876</td>
<td>22</td>
<td>$9,449</td>
<td>69,126</td>
<td>134</td>
<td>$57,938</td>
</tr>
<tr>
<td>EM</td>
<td>66</td>
<td>$21,027,187</td>
<td>30,742</td>
<td>2</td>
<td>$684</td>
<td>4,313</td>
<td>15</td>
<td>$4,875</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>278</td>
<td>$87,840,107</td>
<td>38,724</td>
<td>7</td>
<td>$2,269</td>
<td>7,164</td>
<td>39</td>
<td>$12,261</td>
</tr>
<tr>
<td>Family medicine</td>
<td>154</td>
<td>$44,089,393</td>
<td>103,315</td>
<td>1</td>
<td>$427</td>
<td>6,651</td>
<td>23</td>
<td>$6,629</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>6,575</td>
<td>$3,033,590,842</td>
<td>193,851</td>
<td>34</td>
<td>$15,649</td>
<td>37,331</td>
<td>176</td>
<td>$81,262</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>2,164</td>
<td>$818,446,259</td>
<td>57,244</td>
<td>38</td>
<td>$14,298</td>
<td>13,667</td>
<td>158</td>
<td>$59,887</td>
</tr>
</tbody>
</table>

*Per 1,000 active physicians and per 1,000 faculty members.

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Survey of Anesthesiology Residency Program Directors and Residents

31% response rate (41/131)

94% of programs provided support for research training:
  funding
  mentorship

Greatest challenge - “no time to do research”.
Improving Clinical Research in the Field of Pediatric Anesthesiology - How Do We Get There?

- Obstacles
  - Too busy
  - No training in research
  - Too few mentors/role models
  - No interest
Improving Research

How Do We Get There?

• Solutions
  - 1) Recruit researchers
  - 2) Develop researchers

  - Personal and academic investment

  - Expose residents and fellows to advantages of academic career

  - Funding through grants and career development awards
Research Training During Residency

• Start early (CA1)

• Develop own idea

• Develop that idea with a faculty mentor
  - avoid doing research for them
  - find mentors with common interest

- Research curriculum and support to facilitate project development

• Research Director- support and direction of clinical research mission
Research During Fellowship

• Train residents and fellows to appreciate research efforts, critically evaluate a study
  - Study design, methodology, statistics

• Exposure to opportunities for an academic career

• Some will decide to do research fellowships and pursue academic medicine
Research Curriculum

Structure and Support to Develop Your Idea

• Utilize a Research Curriculum:

- 12 hours – 6 sessions with core reading and homework designed to develop a project and integrate with resources at institution.

• Textbook
  - “Designing Clinical Research” - Hulley and Cummings
  - small paperback readable

• Help identify mentors and sources of data
The Five Page Protocol

*Goal for the Research Curriculum*

- Concise protocol
  - More concise than an NIH submission, but often sufficient for small intramural grants
  - Discipline approach to planning the study
  - Provide the materials and answers for IRB submission
  - Completed by the end of first year
  - Implement in years 2 and 3
Organization

The Five Page Protocol

• Page One
  - Title, Specific objectives, significance

• Pages 2-5
  - Overview of design (RCT, observational cohort/ cross sectional, case/control)
  - Study subjects: selection criteria, exclusions, accessible populations, plans for sampling and recruitment
  - Measurement – predictor and outcome variables
  - Statistical issues – sample size, proposed analysis
  - Quality control and data management
  - Timetable
  - Ethical considerations
Advanced Second Year Fellowship Training in Pediatric Anesthesiology in the United States

Dean B. Andropoulos, MD, MHCM,*† Scott G. Walker, MD,†§ C. Dean Kurth, MD,¶¶ Randall M. Clark, MD,### and Desmond B. Henry, MD††††

Table 1. Survey Results for Chairs, Chiefs, and Program Directors: Fellowship Skills ($n = 53$)

<table>
<thead>
<tr>
<th>What skills are desired in some or all of fellowship graduates?</th>
<th>Percent answering affirmatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent general clinical care</td>
<td>96</td>
</tr>
<tr>
<td>Formally trained educator</td>
<td>62</td>
</tr>
<tr>
<td>Formally trained researcher</td>
<td>44</td>
</tr>
<tr>
<td>Formally trained in quality and outcomes improvement</td>
<td>44</td>
</tr>
<tr>
<td>Subspecialty trained and qualified, e.g., cardiac, pain, ICU</td>
<td>37</td>
</tr>
<tr>
<td>Formally trained in leadership and management</td>
<td>33</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Which skills does the core clinical ACGME fellowship provide?</th>
<th>Percent answering affirmatively</th>
<th>Actual – desired skills (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent general clinical care</td>
<td>100</td>
<td>+4</td>
</tr>
<tr>
<td>Formally trained educator</td>
<td>23</td>
<td>-29</td>
</tr>
<tr>
<td>Subspecialty trained and qualified, e.g., cardiac, pain, ICU</td>
<td>21</td>
<td>-16</td>
</tr>
<tr>
<td>Formally trained in quality and outcomes improvement</td>
<td>14</td>
<td>-30</td>
</tr>
<tr>
<td>Formally trained researcher</td>
<td>12</td>
<td>-32</td>
</tr>
<tr>
<td>Formally trained in leadership and management</td>
<td>0</td>
<td>-33</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the pediatric anesthesia workforce for the future being trained through the ACGME fellowship (clinical subspecialties, research, quality, education, leadership)?</th>
<th>Percent answering affirmatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>47</td>
</tr>
</tbody>
</table>

Actual minus desired skills represents the percent answering affirmatively to question 2 minus percent answering affirmatively to question 1.
ACGME = Accreditation Council for Graduate Medical Education; ICU = intensive care unit.
Collaboration

“it takes a village to raise a child”

Many Pediatric Anesthesiology clinical Departments/Divisions are:
1) Financially isolated
2) Physically isolated from residency programs and adult group
3) Have larger groups of trained investigators in other specialties
4) Lack the critical mass of mentors

Potential Barriers:
1) Not enough non-clinical time
2) Lack of financial support from Department
3) Inability to develop a pathway to independence
Mentoring:

“Success gives rise to success”

#1 influence on research path

Characteristics of a research mentor:

- Have time to mentor you
- Have ongoing research
- Have prior success with other mentees
- Help you develop a plan for your independence
Research Development

Residents/Fellows

- Institutional: Resident Research Grants - $5,000
- Institutional: Research Fellowships - $75,000
- T and F awards from NIH

Faculty

- Career development awards

FAER, ISRA, AHA, K awards from NIH
What is a Career Development Award?

- Funding to protect your time so that you can develop your research skills
- Protected time
- Extra Training
- Step towards independence
- New relationships
- Research may be:
  - Clinical
  - Basic Science
Research Options

• Basic Science

• Translational Research

• **Clinical Research**
  - Large database analysis
  - Retrospective reviews
  - Clinical trials/Prospective cohorts
Summary

• Pediatric Anesthesiology is the youngest medical sub-specialty and is growing.

• Clinical Research is an integral part of this growth.

• Getting current and future Pediatric Anesthesiologist involved in clinical research is essential for the future success of the specialty.

• Find a mentor, get started, and have fun!!!
Thank You