

The ultimate success of pediatric clinical and translational research will depend on the training of a new generation of clinical researcher in addition to the implementation of new technology infrastructure as indicated above. Pediatric subspecialty training will be refocused to concentrated training in clinical research techniques, bio-informatics, biostatistics and epidemiology, and genomic analysis. Children's hospital will take the lead nationally in developing appropriate technology and training the next generation of clinical and translational pediatric researchers.

## Training Physicians in Clinical Research in Pediatrics

Thomas B. Newman, MD, MPH  
Professor of Epidemiology and  
Biostatistics and Pediatrics  
University of California, San  
Francisco

## TN's job

- Clinical pediatrics (urgent care and newborn nursery) ~25%
- My own research (mostly jaundice and infections in newborns) ~35%
- Teaching clinical research and clinical epidemiology and mentoring others doing research (including writing texts) ~30%
- Miscellaneous administration and consulting ~ 10%

## Overview

- Importance of clinical research and clinical research training
- Integrating research training into clinical training
- UCSF approach

## What is Clinical Research?

- *Clinical Research*: primary goal is helping guide the practice of medicine
  - Human subjects or samples
  - Prevention, diagnosis, treatment, prognosis, etc.
- *Basic Research*: primary goal is *understanding* biology, biochemistry, etc.
  - Humans, animals, cells, molecules
  - Pathophysiology, cell biology, microbiology, anatomy, pharmacology, etc.
- *Translational research*: goal is translating basic advances to improve clinical care

## Need for Clinical Research

- Basic science necessary but not sufficient
  - Allows one to tell what tests and treatments *might* be helpful
  - Leaves unclear in which patients the benefits of treatments justify risks and costs

## Case study #1: Premature ventricular contractions (PVCs) after myocardial infarction (MI)

- PVCs after MI associated with sudden death
- Anti-arrhythmic drugs decrease these PVCs
- Recommended by > 50% of University cardiologists\*
- But 2 such drugs (encainide and flecainide) tripled the rate of sudden death ( $P < 0.001$ ) when used for this indication\*\*
- >50,000 deaths in the US\*\*\*

\* Vlay SC. Am Heart J. 1985;110:904-12

\*\* Cardiac Arrhythmia Suppression Trial (CAST) Investigators. NEJM 1989; 321:406-412

\*\*\*Moore TJ. Deadly Medicine. Why tens of thousands of patients died in America's worst drug disaster. NY: Simon andSchuster, 1995

### Case study #2: Jaundice in Newborns

- Kernicterus (brain damage) is caused by very high bilirubin levels
- 1980-83: Exchange transfusion for bilirubin > 20 mg/dL
- Beginning of AIDS epidemic, HIV in blood supply
- We now know no almost all of these exchange transfusions were not needed

### Importance of clinical research training 1: Greater quantity of research

- Makes doing research more satisfying -> more people choose careers in research
- Better understanding of methodology -> More competitive for funding
- Investigators more efficient -> more productive

### Importance of clinical research training 2: Greater quality of research

- Better questions
- Better answers
- Better understanding of limitations
  - "What gets us into trouble is not what we don't know. It's what we know for sure that just aint so. -- Mark Twain

### Importance of clinical research training 3: Helps clinicians

- Less reliance on "eminence-based medicine"
- More comfortable and discriminating consumers of peer-reviewed original research
  - Are answers valid?
  - Are they applicable to my patients?
- Less deterioration over time and reliance on industry reps

### Example: Singulair<sup>®</sup> for Persistent Asthma in Children 2-5 Years\*

- RCT, 93 centers 5 continents, N=689
- "... montelukast administered as a 4-mg chewable tablet produced significant improvements compared with placebo."
- P = 0.003
- Effect size
  - 0.12 points on a 6-point symptom scale
  - 9% fewer courses of oral steroids over 12 weeks
- ~\$3000 per course of oral steroids prevented
- Sponsored by Merck

\*Knorr et al. PEDIATRICS Vol. 108, September 2001, p. e48

### Integrating Clinical Research Training into Clinical Training

- Case conferences
- Journal club
- Culture change – encourage questions!

### Case conferences 1. Traditional format

- Case presentation by trainees
- Formal discussion by prepared trainees and faculty
- Most of group is passive; some are asleep
- Correct answers based upon faculty authority

### Alternative case conferences -1

- Interactive discussions -- encourage questioning WHY?
- Identify areas of controversy, disagreement, or ignorance
- "I don't know" is OK for students AND faculty, as long as it is followed by "Let's find out."

### Journal Club – a way of teaching clinical research

- Choose article based on real case, prescription for learning, or new research
- Trainee meets with faculty, then leads
- Article distributed in advance
- Review "History and Physical" of the article before critique

### History and Physical Exam of a journal article

- Authors and funding source
- Research question
- Study design
- Subjects
- Predictor variable(s)
- Outcome variable(s)
- Results
- Conclusions

### Leading the journal club

- Emphasize use of chalk board, interaction
- Consider each element of the study
- Need to decide on *importance* and *direction* of possible biases
- Detailed instructions: Google Tom Newman Documents

### Randomized trial of Antibiotic Prophylaxis after Acute Pyelonephritis

- RQ: Does antibiotic prophylaxis reduce pyelonephritis or scarring in children with vesicoureteral reflux (VUR)?
- Study design: Randomized (unblinded) trial
- Subjects: Children 1-18 yr following pyelonephritis
- Predictor: Antibiotics (Trimethoprim-sulfa or Nitrofurantoin; MD choice) or no antibiotics
- Outcome: Recurrent pyelonephritis, scarring on DMSA scan

Garin et al., Pediatrics 2006;117:629

Randomized trial of Antibiotic Prophylaxis after Acute Pyelonephritis -- Results

	Patients With VUR		P
	Prophylaxis (N=55)	No Prophylaxis (N=58)	
Pyelonephritis (%)	7 (12.9)	1 (1.7)	.03
Renal scars, n (%)	5 (9.0)	2 (3.4)	.21

Garin et al., Pediatrics 2006;117:629

Randomized trial of Antibiotic Prophylaxis after Acute Pyelonephritis – Possible biases and effects on results

- No "intention to treat" analysis
  - 92% follow-up
  - If all 8% (5 children) lost were in no prophylaxis group and all got pyelo, still no benefit from treatment and trend towards harm
- Antibiotic treatment not standardized
  - Both commonly used
  - Benefit must be small because pyelonephritis and scarring were rare in control group

Randomized trial of Antibiotic Prophylaxis after Acute Pyelonephritis -- Results

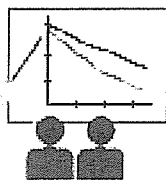
	Patients With VUR		P
	Prophylaxis (N=55)	No Prophylaxis (N=58)	
Pyelonephritis (%)	7 (12.9)	1 (1.7)	.03
Renal scars, n (%)	5 (9.0)	2 (3.4)	.21

Garin et al., Pediatrics 2006;117:629

Culture change

- Move from eminence-based medicine to evidence-based medicine
- Increase funding, prestige and accountability for clinical researchers, teachers, and clinicians
- Encourage questioning of current practice and finding ways to improve it
  - Albuterol vs Isoproterenol for severe asthma--Dr. Maekawa
  - Evaluation of infants with Failure to Thrive --Dr.Otah

UCSF Approach: Google TIGR



Training In Clinical Research

UCSF Approach

- Small group teaching
- Relevant homework problems
- Financial support to faculty for teaching through tuition and grants
- Continuous improvement based on teaching evaluations
- "Missionary" enthusiasm

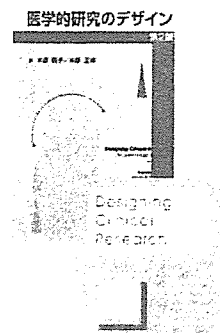


## UCSF TCR Program

- TCR: Summer courses
  - Designing Clinical Research
  - Research ethics
  - Building an Academic Career
  - Introduction to statistical computing
- Advanced Training in Clinical Research (ATCR): 1 year certificate program
- Masters in Clinical Research (MCR): 2-year program leading to Master of Advanced Studies in Clinical Research

## Designing Clinical Research

- 7 sessions
- 1 hour lecture, 2 hour small group
- Weekly homework
- Text: DCR
- Final session: review of protocols



## Homework assignments: Building a protocol

- Week 1: Research question, literature review and background
  - Characteristics of good RQ
  - Context
  - Review by group
- Week 2:
  - 1-page outline of study
  - Detailed sampling, recruitment, retention plans

## Week 3 Homework

- Sample size estimation
  - Specify hypotheses, types of variables
  - Produce sample size estimate for your own study
  - Justify assumptions
  - Moved early in course in case RQ needs to change

## Small Group sessions

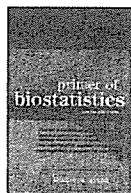
- About 12 students per group
- Small group leaders mostly MCR/ATCR grads
- Students divide into pairs, critique each others' homework
- Small group leader reviews illustrative examples in class and reads and returns all homework

## Final Protocol review

- Protocol 5 pages, single spaced + references and appendices
- New groups created: 2 students + 1 faculty with similar interests
- 90 minute session
- Students review each other's protocols

## ATCR/MCR Required Courses

- Summer– TIGR
- Fall
  - Epidemiologic methods
  - Clinical epidemiology
  - Biostatistics 1
  - Work-in-progress seminar



## ATCR/MCR Required courses

- Winter
  - Clinical trials
  - Database management
  - Biostatistics 2
  - Work-in-progress seminar
- Spring
  - Systematic reviews
  - Publishing and presenting clinical research
  - Biostatistics 3
  - Work-in-progress seminar



## Clinical Research Training is Expensive!

- Tuition
  - Summer DCR workshop \$1000 (¥117,000)
  - ATCR \$7425 (¥868,725)
  - MCR \$17,500 (¥2.05 million)/yr x 2
    - ~50% discount for full time UCSF fellows and faculty
    - Further discount if teaching assistant
- Most tuition paid by training grants or departments
- Tuition supports faculty teaching

## Clinical Research Training Requires “Protected Time” and Mentoring

- ATCR/MCR Application requirements:
  - Supervisor’s written promise of ≥ 70% protected time for classes and research
  - Access to a research mentor in trainee’s home department.

## NIH “Roadmap”

- K grants to bridge gap between fellowship training and ability to compete as independent investigator
- Multidisciplinary research encouraged
- 70% protected time for research x 3-5 years
- Additional training plans included in application
- Mentoring required

## Strategies for improving mentoring

- Salary support for mentor
- Salary support for trainee based partly on commitment and track record of mentor
- Training program for mentors
- Addition of mentoring section to CV, used for promotion
- “Mentor of the Year” awards

## Unresolved Issues

- Long term job security on “soft money”
- Research agenda underemphasizes public health, over emphasizes development of marketable products
- Tight funding due to money being spent on “war on terrorism”

## Take-home messages

- Training in clinical research requires a significant commitment in time and money
- Value for improving research and also improving clinical care and teaching
- Explore the UCSF courses by typing TIGR into Google.



Final Report  
June, 1992

## I. ACADEMIC

### A. Goals

1. To acquire an understanding and working knowledge of clinical epidemiology and biostatistics and to gain skills in their application in health services research.
2. To broaden and strengthen my knowledge of effective health care delivery to vulnerable populations of children; health care systems that permit universal access to quality health care at reasonable cost; and preventive medicine and public health practice.
3. To develop skills in quantitative and qualitative research design, data collection, statistical analysis using computer systems, and effective communication of research findings.

### B. Courses Completed

Health Services 505	Topics in Preventive Medicine
Biostatistics 511	Medical Biometry I
Biostatistics 512	Medical Biometry II
Environmental Health 590B	Environmental and Occupational Health
Epidemiology 512	Epidemiologic Methods I
Epidemiology 513	Epidemiologic Methods II
Health Services 501	Public Health Practice
Health Services 510	Theory & Methods in Social & Behavioral Sciences: Poverty and Health
Health Services 534	International Health Care Systems
Health Services 590B	Introduction to Health Services
Health Services 590E	Clinical Scholars
Health Services 590H	Applied Data Analysis
Health Services 592A	Health Services Seminar
Health Services 592B	Clinical Scholars Seminar
Health Services 592D	Preventive Medicine Seminar
Health Services 600	Research Methods Minicourse/Independent Study/Research
Health Services 700	Masters Thesis

C. Master's Thesis Completed

"Health Care Utilization Patterns and Health Expenditures  
Among Foster and Nonfoster Children in Washington State"

II. CLINICAL

A. Goals

1. To maintain and improve my skills in clinical pediatrics.
2. To maintain and improve my skills in clinical teaching.

B. Activities

1. Harborview Pediatric Clinic -- one half day per week
2. Pediatric Grand Rounds weekly.
3. Research Seminar/Division of General Pediatrics
4. Journal Reading
5. Certification in Pediatric Advanced Life Support (July, 1991)

III. RESEARCH

A. Goals

1. To understand the health problems and health care of children in foster care.
2. To develop my interests and growing knowledge base in disease prevention, health care delivery systems, health behavior, cross-cultural medicine and international health care systems into relevant and feasible research questions.
3. To explore the role of outreach programs in improving access to quality health care by vulnerable and disenfranchised populations.
4. To learn appropriate language and skills required to analyze large secondary data sets on a mainframe computer.
5. To contribute to the understanding of salutatory factors in the prevention of poor health outcome in vulnerable populations.

A. Goals (cont.)

6. To translate research results into policy statements that can lead to meaningful solutions to difficult problems in health services.

B. Activities

1. Health Conditions and Health Care Utilization Patterns Among Foster and Nonfoster Children on Medicaid

- a) What is the cost of health care for foster children?  
The cost of health care is much higher for foster children compared to nonfoster controls. Foster children utilize more mental health and specialized services (visiting nurses, physical therapy and medical equipment); a small subpopulation with behavioral problems and chronic neurologic conditions account for a large proportion of health care expenditures. While the cost is high, we do not know the nature of the health services provided. Given the circumstances that contribute to foster care placement, the need for health care may be much greater among foster children than in the general population. We, therefore, suggest that these health services be examined more closely before any decisions are made to cut costs.

Findings have been presented at the western regional (February 1992) and National Ambulatory Pediatrics Association meetings (May 1992); and also at the Children's Information Exchange of the Department of Social and Health Services, Olympia, Washington (April 22, 1992).

- b) Prevalence of chronic illness among foster children  
Perinatal and congenital conditions are much more prevalent among foster children compared to nonfoster controls. These conditions range from respiratory distress syndrome and fetal alcohol syndrome to congenital brain anomalies and musculoskeletal deformities.

B. Activities (cont.)

The relationship between these medical conditions and foster care placement is complex. Some of the conditions, such as FAS, may be associated with pre-existing family dysfunction that eventually results in foster placement. Others, such as brain anomalies, may provoke financial and emotional stress which, in turn, lend to abuse and neglect. These conditions are identified at birth, providing an opportune time and place for instituting programs to prevent abuse, neglect, and future foster placement.

2. "History of Foster Care" Lecture presented at Harborview Medical Center Pediatric Resident Conference on August 30, 1991.
3. Health Care System in Japan: Balancing access, health and cost. Work-in-Progress given on March 16, 1992. I am writing a paper for publication on the health care system in Japan with special emphasis on the role of its national health insurance in providing access to universal health care and controlling health care expenditures.
4. Infant Mortality Prevention Network  
I have become interested in community program development and evaluation to improve obstetric and pediatric access to quality health care for "the most difficult to reach" families in King County. Through the infant mortality prevention network, we have attempted to improve the outreach component of access. We have provided forums for outreach providers to network with each other, discuss aspects of barriers to access with representatives of health care institutions, and explore their own cultural biases that prevent effective communication with both clients and providers. I have helped assemble a guidebook of outreach and specialized services in Seattle/King County for various providers of care. The impact of such interventions has not been evaluated.

V. IMPACT STATEMENT

Caring for the vulnerable population, the poor and the sick in this society, is a difficult and trying process. Important in this quest is to understand not only the problems but the culture of this population. The Clinical Scholars Program has provided me with a language to define the health problems, methods to explore the causes and effects, and the perspectives to understand the relationship of health care systems with the triad of culture, circumstances, and health.

I am beginning to understand some of the problems faced by foster children and their families. I am appreciating the role outreach programs play in assuring primary prevention and early intervention for disenfranchised populations. Finally, I am learning about how different health care systems balance cost of health care, access to quality services, and individual and population health outcomes.

As I develop my education and research, I hope to continue to rely not only on those newly learned tools and perspectives but on the individuals that are helping to nurture my growth in the realm of scientific inquiry. I also want to work to convert the knowledge into some meaningful contribution to the status of health services for children and families.

VI. ADVISORY COMMITTEE

Thomas S. Inui, Sc.M., M.D.  
Fred Connell, M.D., M.P.H.  
Fred Rivara, M.D., M.P.H.  
Donald Patrick, Ph.D.

## I. ACADEMIC

### A. Goals

1. To acquire an understanding and working knowledge of clinical epidemiology and biostatistics and to gain skills in their application in health services research.
2. To broaden and strengthen my knowledge about the cross-cultural issues of prematurity and infant mortality; and the delivery of effective health care to children in foster care.
3. To develop skills in data collection and computerized statistical analysis.

### B. Courses Completed

Biostatistics 511	Medical Biometry I
Health Services 590E	Clinical Scholars
	Program in Administration
Health Services 600	Research Methods Minicourse

### C. Courses in Progress

Epidemiology 512	Epidemiologic Methods I
Health Services 590H	Applied Data Analysis
Health Services 592B	Clinical Scholars Seminar
Health Services 592D	Health Services Seminar

## II. CLINICAL

### A. Goals

1. To maintain my skills in clinical pediatrics.
2. To maintain and improve my skills in clinical teaching.

### B. Activities

1. Harborview Pediatric Clinic -- one half day per week
2. Journal Club
3. Medical Grand Rounds weekly.
4. Journal Reading

### III. RESEARCH

#### A. Goals

1. To contribute to the understanding of salutatory factors in the prevention of poor health outcome in vulnerable populations.
2. To develop skills necessary to pursue research in health behavior, cross-cultural medicine, and health care delivery.
3. To improve my understanding of the impact of poverty and related factors on the birth of infants and the growth and development of children.

#### B. Activities

1. I am currently developing a research project to explore the roles of salutatory factors in the prevention of premature birth and infant mortality in vulnerable populations. This project will initially attempt to identify salutatory factors and then determine the role of those factors on health outcome by the use of surveys, in-depth interviews, and medical records.
2. I will do a literature review on the history and evolution of foster care in the United States; and describe the current health status and needs of foster children in the state of Washington.

### IV. IMPACT STATEMENT

The clinical scholars program has had a tremendous impact on me. It has provided me with the tools to explore my interests and the framework to view my interests from varying vantage points. Caring for the poor and the sick in this society is often a difficult and frustrating process. In my past clinical experience I had begun to realize the need for innovative methods in prevention and early detection in order to most effectively serve this sub-population. As I begin to further define and solidify those ideas, I hope to continue to rely not only on those newly learned tools and perspectives, but on the individuals that directed me towards those instruments.

IV. ADVISORY COMMITTEE

Thomas S. Inui, Sc.M., M.D.  
Fred Connell, M.D., MPH  
Fred Rivara, MD, MPH  
Donald Patrick, Ph.D.



## ROBERT WOOD JOHNSON CLINICAL SCHOLARS PROGRAM

## RESEARCH METHODS MINI-COURSE

Course Outline, 1990

Course Co-Directors: Bill Carter and Jim Stout

DATES: July 23 - August 3  
 TIME: 8:30-9:50 AM  
 PLACE: T-663 Health Sciences Building

SESSION DATE	SPEAKER	TOPIC
7/23 #1	Bill Carter	Practical Issues in Research Design - I
7/24 #2	Tom Koepsell	Practical Issues in Research Design - II
7/25 #3	Mike Gordon	From an Idea to a Research Question
7/26 #4	Bill Carter	Collecting Data with Questionnaires
<del>7/27 #5</del>	Fred Connell	Using Existing Data Sets
7/30 #6	Eric Larson	Developing an Overall Research Strategy
7/31 #7	Bruce Psaty	Writing: Grammar and Subterranean Theory of Work
8/1 #8	Marc Miller	Qualitative Research Methods and Analyses
8/2 #9	Erika Goldstein	Clinical Applications of Qualitative Methods/Analysis
8/3 #10	Tom Koepsell	Quantitative Data Analysis - An Overall Strategies for Clinical Investigators

Large Data Set: Secondary

## SESSION 3

**RESEARCH WORKBOOK:****A guide for initial planning  
of clinical, social, and behavioral  
research projects**

Michael J. Gordon, PhD

**Introduction**

Research has often been described as organized curiosity. But the skills and techniques of organizing one's curiosity seldom come naturally. The purpose of this workbook is to provide the clinician-researcher with an explicit approach to thinking about and recording each element in the initial development of a unique research plan.

The workbook is not a do-it-yourself manual for inexperienced researchers. It will provide useful

questions, suggestions, and approaches to guide and stimulate the inventive thinking of the researcher, but it provides no answers, no assistance in making decisions, and no technical expertise. For these essentials, the clinician-researcher must rely on colleagues and competent research consultants.

An earlier version of the workbook has been used productively by numerous family practice residents, faculty, and other health science students. The current version has been included in this monograph at the suggestion of family physicians who were delighted to find that a simple, nontechnical aid, in conjunction with their own professional training, experience, and resourcefulness, could take them so far in organizing their curiosity.

---

Dr. Michael J. Gordon is Research Assistant Professor, Department of Family Medicine, University of Washington, Seattle, Washington.

0094-3509/78/0703-0145\$04.00  
© 1978 Appleton-Century-Crofts

THE JOURNAL OF FAMILY PRACTICE, VOL. 7, NO. 1: 145-160, 1978

145

### I. SELECT A RESEARCHABLE QUESTION

Begin by stating a question of great interest to you in a simple, nontechnical interrogative sentence.

---

---

---

---

As you complete the workbook exercises from this point through the development of your hypothesis (section IV), you will find it useful to rewrite your research question several times. Each revision should reflect greater precision and probably narrower scope in your search for an answer.

The research will require access to these resources.

1. _____	4. _____
2. _____	5. _____
3. _____	6. _____

Is the research feasible?    Yes\_\_\_ No\_\_\_

Define the important terms in your statement of the research question.

<u>Terms</u>	<u>Definitions</u>
1. _____	1. _____ _____
2. _____	2. _____ _____
3. _____	3. _____ _____
4. _____	4. _____ _____
5. _____	5. _____ _____

**II. SEARCH FOR RELATED WORK**

List questions you hope are already answered by previous research.

---

---

---

---

---

---

---

List relevant theories or models.

---

---

---

---

---

---

---

Other background information you could use.

---

---

---

---

---

---

---

---

---

---

Likely sources of information  
(not necessarily in journals).

---

---

---

---

---

---

---

Likely sources of information.

---

---

---

---

---

---

---

Likely sources of information.

---

---

---

---

---

---

---

---

---

---