Lost in Translation: The Path from Scientific Discovery to the Clinic

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Disclaimer: The following are the author's opinions and do not represent the position of the Food and Drug Administration

THESE THOUGHTS ARE THE RESULT OF 30 YEARS OF OBSERVING THOUSANDS OF ATTEMPTED DRUG DEVELOPMENT PROGRAMS (COMMERCIAL AND ACADEMIC) WHILE WORKING AT FDA

MY THESIS:

DESPITE ITS MANY TRIUMPHS IN EXTENDING AND ENHANCING LIFE, THE BIOMEDICAL RESEARCH ENTERPRISE IS SURPRISINGLY INEFFECTIVE AT IMPROVING HEALTH AND TREATING DISEASE, GIVEN OUR LEVEL OF INVESTMENT IN IT

MULTIPLE SYSTEMIC FLAWS IMPEDE GENERATION OF KNOWLEDGE

IN PARTICULAR, MEDICINE MUST TAKE BACK OWNERSHIP OF CLINICAL EVIDENCE DEVELOPMENT

IN THIS PRESENTATION, I WILL USE DRUG DEVELOPMENT AS AN EXAMPLE, SINCE I KNOW IT WELL AND IT IS EXTENSIVELY DOCUMENTED. BUT IT IS A MICROCOSM OF THE OVERALL STATE OF AFFAIRS

Drug Development: Many Decades of Hearing the Same Narratives

- Standards to get to market are too low
- FDA suppresses innovation with unattainable standards and should be radically reformed
- Greedy drug companies charge exorbitant prices
- The pharmaceutical industry model is financially unsustainable
- Patients wait too long for new treatments
- Patients can't afford new therapies

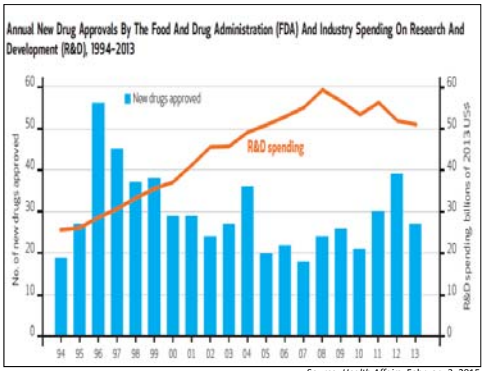
But these Narratives Get Us Nowhere, Except More Media Stories

- Should we have higher drug approval standards to get more information?
- Or lower standards to stimulate innovation?
- Should drugs cost less, so they are affordable?
- Or should they cost what the market will bear, to support R&D?
- What does it really cost to develop a drug?
- Should we get rid of the pharmaceutical industry, since NIH funds all discoveries anyway?
- We've been hearing these arguments for at least 40 years--what is the **real** problem?

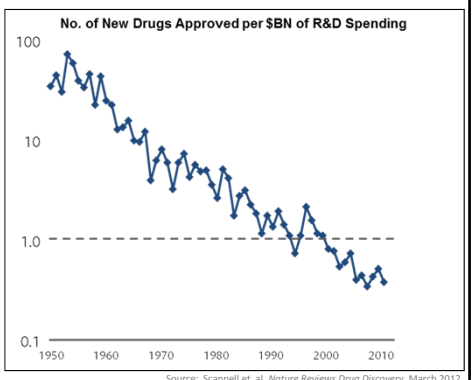
Fact: The Pharmaceutical Industry Experiences a Huge Failure Rate

- Only about 10% of commercial entrants into the clinic make it to approval
- The pace of introduction of innovative therapies has changed little over decades, despite massive increases in R&D investment
- Around 40-50% of Phase 3 programs fail, the majority for lack of effectiveness
- In the face of huge scientific progress, the productivity of the industry is at an all-time low
- It currently costs over a billion dollars to develop a single new drug, effectively shutting many players out

Decreasing Productivity



Source: *Health Affairs*, February 3, 2015



Source: Scannell et. al, *Nature Reviews Drug Discovery*, March 2012.

10

Is this because drug developers are dumb?

- They come from the major universities around the world, many from the august institutions represented here today
- Much of the data comes from “biotech” startups=academic spinoff companies
- In a “produce or die” environment they are highly motivated and work exceptionally hard
- Pharmaceutical development is an extremely risky business

And it is additionally true that, despite all this effort…

- When a novel drug goes on the market, often much of the information you would like to know in order to use it in practice is not available—for example, how its outcomes compare to those of other drugs, or in whom to use this particular drug, or its long-term performance characteristics. The trial participants may not resemble the actual patients very closely
- It takes up to 30 years after publication of the first discovery of an actionable target for a drug to come on the market targeting it (Nobel Prizes for researchers many many decades after publication)
- There are still huge unmet medical needs

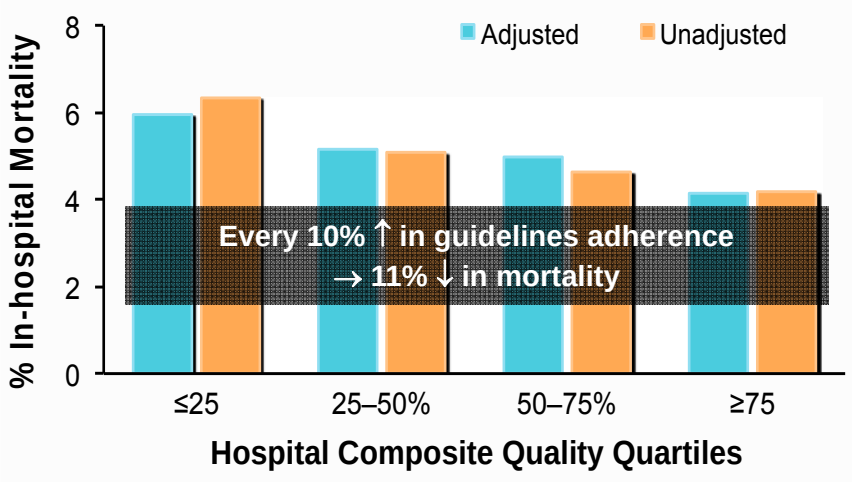
These Shortcomings Are Largely the Result of Three Systemic Problems in Biomedical Research

1. There is a lack of reliable basic scientific information to create generalizable knowledge and support development programs
2. There is no robust translational infrastructure for developing and assessing tools and drug candidates
3. Clinical medicine has not been able to evolve efficient and effective systems for evidence generation

Lost in Translation

- These three problems, taken together, lead to the high failure rate, the extraordinary costs of drug development and the lack of evidence to guide clinical practice
- Because of these problems, a large number of promising investigational interventions are abandoned every year, particularly those intended to treat smaller populations or that would be administered briefly (e.g., antibiotics, vaccines)
- For drugs that are developed, it is increasingly unclear whether society will be willing to pay for them. The “application to practice” phase of translation is becoming increasingly fraught.
- And many prescribers do not adopt new best practices, further weakening the impact of research on health

Consequences: The Link Between Overall ACC/AHA Guidelines Adherence and Mortality



Peterson et al, ACC 2004

We Are at an Inflection Point: Great Opportunity and Great Uncertainty

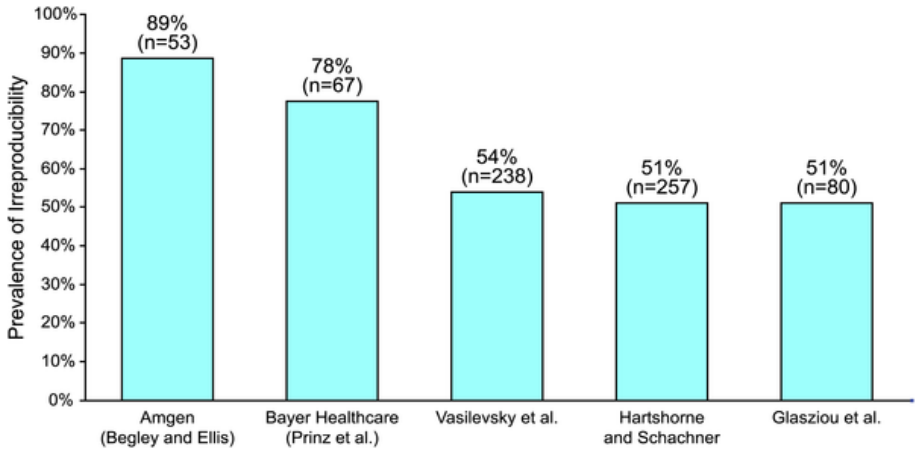
- Basic biomedical science is producing information at an unprecedented rate
- The system we have successfully operated for many years is under severe stress
- Transformative change is needed
- New structures and technologies provide opportunities
- But before considering them, what are the current problems?

1. The Problem Starts with the Basic Sciences

Step A in drug discovery: identify a "target"

- Use information from biomedical literature
- Further develop with data generated in-house
- But there is a catch…..

Fig 1. Studies reporting the prevalence of irreproducibility.



Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLoS Biol 13(6): e1002165. doi:10.1371/journal.pbio.1002165
http://journals.plos.org/plosbiology/article?id=info:doi/10.1371/journal.pbio.1002165

PLOS | BIOLOGY

BUT THE PROBLEMS IN TRANSLATIONAL SCIENCE ARE MUCH MORE SEVERE

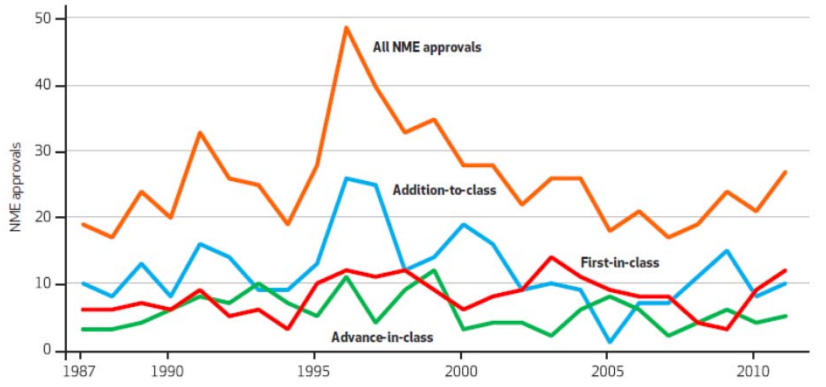
2. Translational Science: example

- Step B in drug development: “target validation”
- What does that mean?
- Ideally, this means that you “know” that if you impact the target in a certain way, that it will lead to a clinical benefit (disease prevention or treatment for example)
- How do you find this out? Or at least diminish the uncertainty around it? Often, you don’t

Rate of Successful New Targets Relatively Constant Over Time

EXHIBIT 1

New Molecular Entity (NME) Approvals, By Innovation Category, 1987–2011



SOURCE Food and Drug Administration drug-approval data. NOTE Innovation categories are defined in the text.

Example: Alzheimer's Disease

- Estimated current US financial toll: $215B
- No disease-altering treatment or preventive
- At least 25 failed efficacy trials worldwide—in part, implies "wrong" target chosen. How to "validate" targets?
- ADNI (Alzheimer's Disease Neuroimaging Initiative): Public-Private Partnership at FNIH
  - Begun in 2005
  - $40M initial budget
  - Longitudinal imaging and biomarker collection in people with presumed Alzheimer's Disease and controls
  - Now expanded to Mild Cognitive Impairment
  - Adding genetic sequencing data
  - Huge amount of information coming out of the collaboration

AMP (Accelerating Medicines Partnership) Alzheimer's: PPP

- FNIH Administered NIH/FDA/Pharmaceutical Industry/Foundations Partnership
- Seeks to find new targets and "validate" known targets via use in ongoing clinical trials
- Also explore biomarkers in Alzheimer's
- Current budget $129M over 5 years

These are the types of large-scale efforts needed to further understand, in the clinic, the meaning of discoveries coming out of the laboratory, e.g., biomarkers, biochemical pathways, targets

One might argue that the above efforts are way too small, given the economic burden of the disease and the amount of laboratory research dedicated to it

"Translational" Science

- As seen in the above example, "target validation" is not strictly a laboratory activity, nor is the knowledge gained solely of interest to drug developers. Knowing a target is valid would reflect a deep understanding of a disease's pathophysiology, in humans
- This is fundamentally the province of biomedicine, not drug development, but generally has been left to the pharmaceutical industry to do, or has not been done at all

Osteoarthritis

- Huge source of morbidity and economic loss
- "Osteoarthritis Initiative": PPP Observational Study
  - 5000 subjects with knee osteoarthritis with serial clinical, imaging and biochemical markers recorded. Enrolled 2004-2006
  - Followed over a decade
  - Specimen and data repository created
- Biomarker Consortium PPP (2014-15)
  - Undertook correlation of the imaging and biochemical markers with clinical outcomes in the knee ($3.5M)
  - Biochemical markers likely NOT predictive, despite years of study
  - After over 10 year program of study, but will need additional clinical work to see if any of the imaging biomarkers are usefully predictive
  - Best Pract Res Clin Rheumatology 2014 Feb; 28(1); 61-71

General Translational Infrastructure Needs for Any Disease

- Disease cohorts (large and small depending on prevalence) that are followed longitudinally along with controls
- Characterized clinically ("phenotyped") with standardized measures and ideally genotyped
- Analytically valid biomarkers (including imaging) for correlation with clinical course including safety biomarkers
- Construction of disease models including biomarker data—allows for modeling of future clinical trials

Disease- or Intervention-specific Translational Needs

- Animal models if reflective of humans
- For drugs—pharmacodynamic measures to provide early indication of whether the drug is working
  - Indicators of mechanism of action
  - Downstream pharmacodynamic measures
- Stable funding of network of disease experts who collaborate to establish SOC and research questions
- Tight links between laboratory researchers and clinical community

Duchenne Muscular Dystrophy

- Uncommon, fatal x-linked muscle disease of children
- Initiated by lack of the protein “dystrophin”, that functions to stabilize muscle
- Various strategies to restore dystrophin production are being tested pre-clinically or in people
- There is no reference standard for dystrophin and no established, well-validated assay to accurately quantitate it in human muscle tissue at low levels

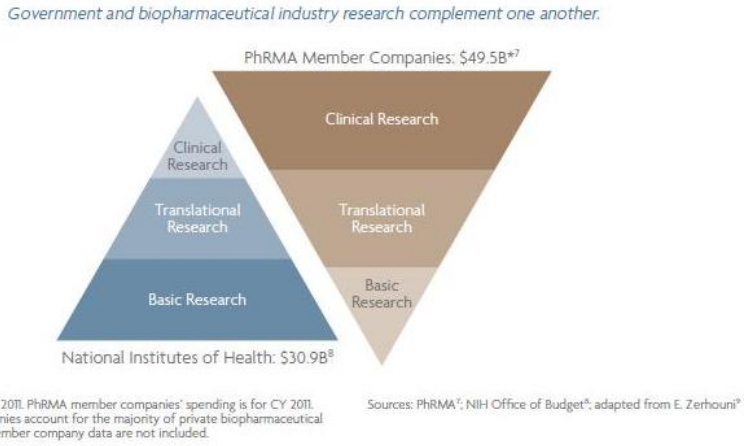
Without Robust Translational Framework

- No clear understanding in early-mid clinical development about whether a drug candidate is having an impact
- Forced to use large, empirical RCTs as initial evaluation of efficacy
- Root cause of many expensive failures, increasing cost
- Also using RCTs this way limits the amount of information obtainable, for example, figuring out optimal dosing and regimen, or order of therapy
- Not too many steps away from traditional medicine—try willow bark for various ailments

3. Generating Evidence in the Clinic

- Clinical trials are the most expensive part of drug development, and costs have been rising rapidly over the last decade
- Most trials still one-off hypothesis testing of a single question (or several closely related questions such as dose-response) related to an investigational drug, taking 1-2 years just to initiate and usually multiple years to conduct.
- Such trials frequently provide population mean information with little insight into individual responses, and often enroll populations not representative of people who will ultimately take the drug
- Huge amount of inefficiency and lost time in the system
- Pharmaceutical companies fund a large proportion of clinical research being conducted in the US
  - In many cases, investigators are basically “service providers” who are contributing patients and assessments on a per-patient fee basis

Most Clinical Research is Currently Funded by, and Conducted on Behalf, of Industry

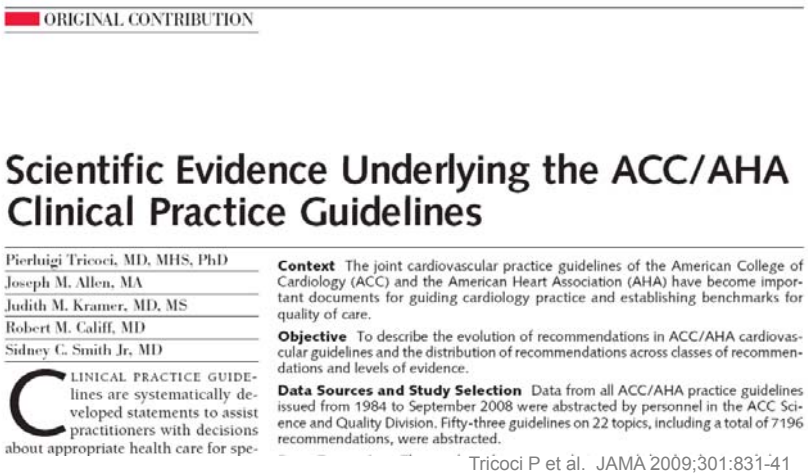


Clinical Trials, as Currently Conducted, are a Huge Barrier to Medical Progress

- Exorbitantly expensive, extremely slow and generally capable of only answering one question at a time
- The needs of “precision” medicine, not to mention “evidence based” medicine, cannot be met with such a blunt instrument
- And even worse, most of the community of practitioners are completely cut out of this effort, or utilized as service providers
- It is no surprise that adoption of evidence-based practices is slow, given that the research is not part of the fabric of medicine, but is perceived as being done by “others”

Where is the evidence?

High-Quality Evidence is Scarce; < 15% of Guideline Recommendations Supported by High Quality Evidence



ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Tricoci P et al. JAMA 2009;301:831-41

33

ADVANCES IN BASIC SCIENCE AND THE NEEDS OF EVIDENCE BASED MEDICINE LEAD TO A HUGE NUMBER OF QUESTIONS THAT NEED TO BE ANSWERED EFFICIENTLY TO BENEFIT HUMAN HEALTH

HOW CAN WE DO THIS?

OPPORTUNITIES FOR TRANSFORMATIONAL CHANGE

1. Basic Sciences

- NIH, Journal editors and the scientific community are beginning to address the reproducibility issue
- Clearly, a strong and creative basic biomedical research sector is absolutely needed
- Structural problems with the current model are being surfaced: "Rescuing US biomedical research from its systemic flaws". Alberts B, Kirschner M, Tilghman S, Varmus H. PNAS, 111, 16, 5773-7

2. Translational Science

- Translational science work needs to be **goal-directed** and **results-oriented;** studies should be large enough to yield **actionable results**
- Not useful to end each paper with "more research needed"
- Example: David Fajgenbaum, MD
  - Medical researcher at Penn
  - Also patient with Castleman Disease, to which he has almost succumbed twice
  - After completing his training, he has embarked on an effort to understand and effectively treat this disorder

Dr. Fajgenbaum's Experience

- "Fragmentation of research is the greatest barrier and ..so much research ends up only published and never utilized"
- Everyone seems to want to run the marathon themselves instead of working as a relay team. For Castleman disease, we've brought the full community together, leveraged their collective knowledge to prioritize research… and (are) taking a laser-focused approach to …do the right studies now.
- One of the greatest reasons for our success is that patients and family members of deceased patients are at the table…this gets everyone focused on impact and …less about the order of authorship or protecting data"
- The Castleman Disease Collaborative Network has brought together laboratory and clinical researchers, inventoried the literature, set up a natural history study, and has resulted in published findings in a short amount of time. It is disease-focused, and goal oriented.

Groups with Disease-Focused Model Get Results

- Cystic Fibrosis Foundation
  - Centers of Excellence for care
  - Active participant in robust pipeline of drugs
- Multiple Myeloma Research Foundation
  - Data bank (a form of natural history)
  - Research collaborations
  - Conducts clinical trials ("60% faster than average")
- Gates Foundation
  - Disease focus, such as malaria and TB

Strengthening Translational Efforts

- The EU has a large translational science PPP ongoing: The "Innovative Medicines Initiative", "IMI 2" funded at 3.3B Euros
- MOST translational research must be conducted, at least in part, in the clinic, and thus should actually be a part of the clinical research enterprise
- Where patient advocates exist, they can be the most effective advocates for disease-focused translational work:
  - Research networks and data sharing
  - Longitudinal cohorts of volunteer patients
  - Target discovery and validation
  - Exploration and development of biomarkers, imaging techniques, and disease models
  - Development of outcome measures, including PROs
  - Exploring patient B/R assessments
  - These activities are important whether or not a drug pipeline exists

3. Clinical Research

- Despite all the rhetoric to the contrary, the current system is NOT focused on preventing, treating, or curing diseases; rather, each sector is driven (of necessity) by other incentives:
  - Pharmaceutical sector: development of marketable molecules with patent protection
  - Academic sector: publications/discovery research leading to continued grants
  - Community medicine: patient care, paperwork, requirements, complying with regulatory requirements

Clinical Research

- Should be a continuum from studying disease (e.g. “target validation”, natural history) and evaluating investigational products through finding the best interventions and disease management, closely linked to the relevant laboratory research communities
- Should be focused on diseases, and on continuous improvement in managing those diseases, not on a single intervention
- Should be owned and operated by the clinical community, as a part of medicine, not by other parties
- Should include the broad clinical community, not just the academic sector

Continuous Improvement in Treating a Disease

- Means that experience and outcomes of the disease improve (from the patient’s point of view) over time
- Fundamental concept (from other disciplines) is that you measure the results and try to make them keep getting better
- We now have an unprecedented opportunity to record diseases and outcomes and see how we are doing
- Ideally, every patient and every caregiver should be able to contribute to knowledge about the disease, and participate in improving the disease outcomes, through clinical trials. This, more than any other intervention, will improve adoption of best practices
- Reflects “learning healthcare system” per the IOM

How Can This be Done?

- Availability of EHR's—despite their current challenges—provides a great opportunity
- Potential to identify people with a disease and conduct natural history studies, translational research and randomized interventional studies in a completely new way, using the EHR as the source documentation
- Include community of practice and patients in the research endeavor, including feedback on results
- Dramatically decrease the time and cost involved in learning more about diseases and their treatments, and improving outcomes

Steps in This Direction

- FDA "Sentinel Network": claims data for drug safety analyses; almost 200M lives; some EHRs; can rapidly perform analyses that previously took years and millions of dollars
- PCORNET: Linked network of EHR holders, conducting ADAPTABLE trial to compare two doses of aspirin to prevent MI and stroke
- NIH Collaboratory: testing important questions in healthcare and learning about doing this sort of research

NIH Collaboratory

- ~$7M total costs per trial
- Average cost per patient= $1500
- Range per patient= $25-7300

Source: Kevin Weinfurt, PhD, Professor, DCRI, Duke University

Trial	N	Setting
Manage PTSD & Other Conditions	**1,000**	**24 Level I Trauma Centers**
Manage Chronic Pain	**1,000**	**200 pract in 3 HCS**
ESRD Care	**6,400**	**400 HD Units**
DM,HTN & CKD Care	**12,000**	**80 Clinics in 4 HCS**
Suicide Prevention	**16,000**	**Primary Care in 3 HCS**
Colon Ca Screening	**20,000**	**26 Clinics in OCHIN**
Nursing Home Care	**152,160**	**230 NH in 2 NH Corp.**
Back Pain Imaging	**250,000**	**100 Sites in 4 HCS**
Hospital Infections	**285,000**	**50 Hospitals in HCA**

New Ways to Study Investigational Drugs

- Concept is to set up trials around improving disease, not studying a particular candidate
- I-SPY 2: “Neoadjuvant” breast cancer setting
  - Screening trial for investigational drugs in newly diagnosed high-risk breast cancer; adaptive design
  - Matches drugs with biomarkers
  - Drugs with superior results on pathologic CR “graduate” to definitive studies
- LungMAP: squamous cell lung cancer, multiple randomized arms based on biomarker status
- Drug-resistant organisms: proposal to set up trial based on the organisms not the antimicrobials

Alzheimer’s Disease: EPAD Project

- Innovative Medicines Initiative (EU): PPP with industry, academia and government
- EPAD= European Prevention of Alzheimer’s Dementia Consortium 63M Euros
- Recruit 24,000 Europeans into registry
- 6,000 for testing and follow up
- Develop high-risk cohort for entry into early, adaptive clinical trial that can screen multiple agents

Transformation of Clinical Research Would be Challenging, with Many Obstacles

- Above early examples show feasibility, but is this workable on a large scale?
- What about current incentive structures?
  - For academic researchers
  - For community practitioners
- Who would pay?
  - Would insurers consider evidence development worthwhile?
  - Would product developers help support?
  - Would healthcare systems participate?

But the Payoff Might be Worth It

- Rapid and efficient clinical evidence generation
- Involvement of the community of practice and patients in the clinical research enterprise as active participants
- Integration of translational research into healthcare
- More effective, efficient and clinically relevant evaluations of new products and other interventions

THESE MAY NOT BE THE RIGHT SUGGESTIONS

BUT THE CURRENT SYSTEM JUST ISN'T SUSTAINABLE

CAN THE BIOMEDICAL RESEARCH COMMUNITY COME TOGETHER TO CREATE A FUTURE WHERE SCIENTIFIC DISCOVERIES CAN RAPIDLY TRANSLATE TO BETTER HEALTH?