SHADES OF GRAY: CONFLICTS OF INTEREST IN RESEARCH

Ross McKinney, Jr, MD

Overview

- Define Conflicts of Interest
- Consider the ubiquitousness of COI
- Clinical Research – there are problems…
- Bayh-Dole
- Personal and Institutional COI
- Can we truly manage conflicts of interest?

Don't get the wrong message

- In health care, almost no good idea will affect significant number of patients if it isn't commercialized
- Pharmaceutical & device companies don't take care of patients – they need advice from people who do
- Conflict of interest isn't intrinsically bad – it's a normal part of life
- As academics, we should encourage working with industry (as distinct from for industry)

Definition

- A conflict of interest exists when a primary interest or responsibility is (unduly) affected by a secondary interest or responsibility

Examples

- The aged tooth
- Basketball

Example

- An obvious charge - ignored...

Interpretation

- We all saw the same data, but our impressions of the validity of the referee's calls were interpreted in light of certain pre-set expectations

COI is part of every day life

- Human beings are very aware of COIs
- Every sales encounter
- All fee-for-service medical encounters

The Human Response

- We consider the paradigm, past history
- We consider the secondary influences we can identify
- Can we trust the provider?
- If we break that trust as medical providers, what happens?
  - Decreased adherence / worse outcomes
  - Poor word-of-mouth
  - Malpractice cases

Key Points

- COI is ubiquitous in life
- Human beings "get it" and incorporate COI considerations into decision making
- An important trap is the situation where a COI exists but isn't acknowledged
  - To manage this, in research we expect disclosure
  - Disclosure is a mixed proposition
- In human subjects research, some COIs may be too great to allow

Clinical Research

Clinical Research

- In science, reproducibility is the key test
- In clinical research, trials are often too expensive to reproduce
- Each clinical study may introduce risk, and it's not fair to expose people to risk unnecessarily
- Bias may introduce risk for HSR participants
- Can we afford COI biased studies designed to achieve an end?

Industry Incentives

- Prime incentive is to develop data that leads to increased product use
- Studies that might disadvantage a product are rarely performed
- Rich history of industry hiding inconvenient information

Industry Research

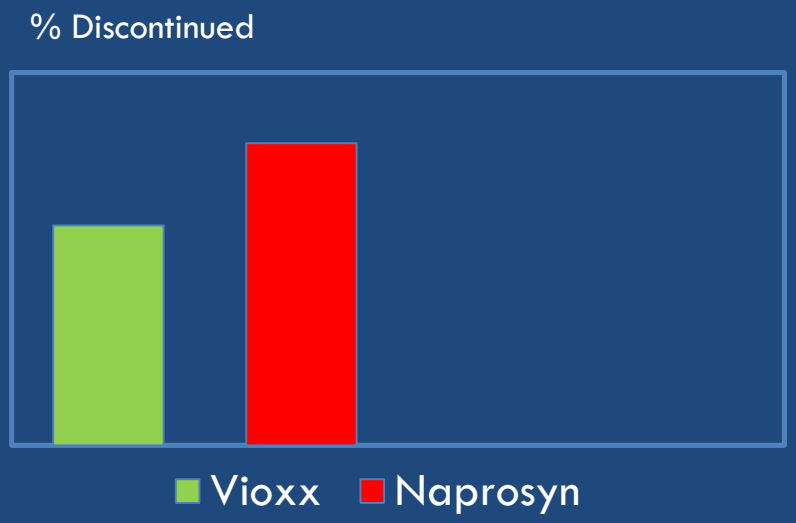
- More than 60% of published drug trials are industry sponsored, 14% NIH, 23% Foundations or other non-profits
  - Positive results in publications:
    - Industry 85%
    - NIH 50%
    - Non-profits 72%
  - Bourgeois et al; Ann Intern Med 2010:158

NEJM Study - 2008

- Studies of 12 anti-depressants, 12,564 patients
- 37 with positive FDA results were published, 1 not published
- 33 with negative FDA results
  - 22 not published
  - 11 published with data selection to appear positive
- In literature, 94% of publications were positive

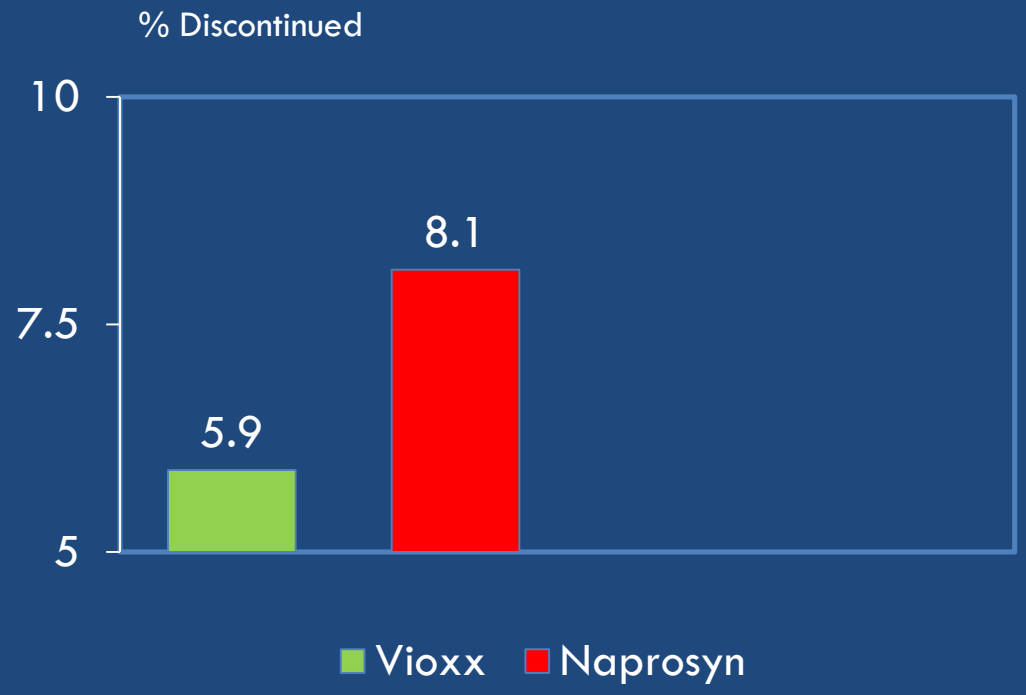
Merck's ADVANTAGE study - 2003

- ADVANTAGE study: Assessment of Differences between Vioxx and Naproxyn to Ascertain Gastrointestinal Tolerance and Efficacy
- After 3 months, 27% more people stopped taking Naproxyn than Vioxx



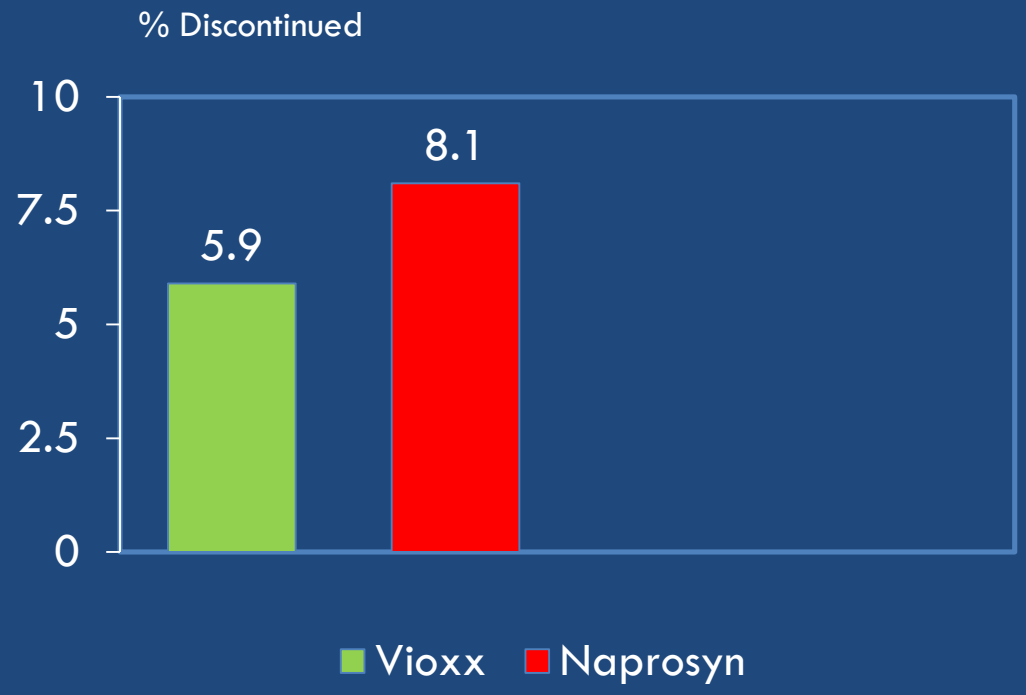
Brief Illustration

- After 3 months, 27% more people stopped taking Naproxyn
  - Of course, that was 5.9% vs 8.1%



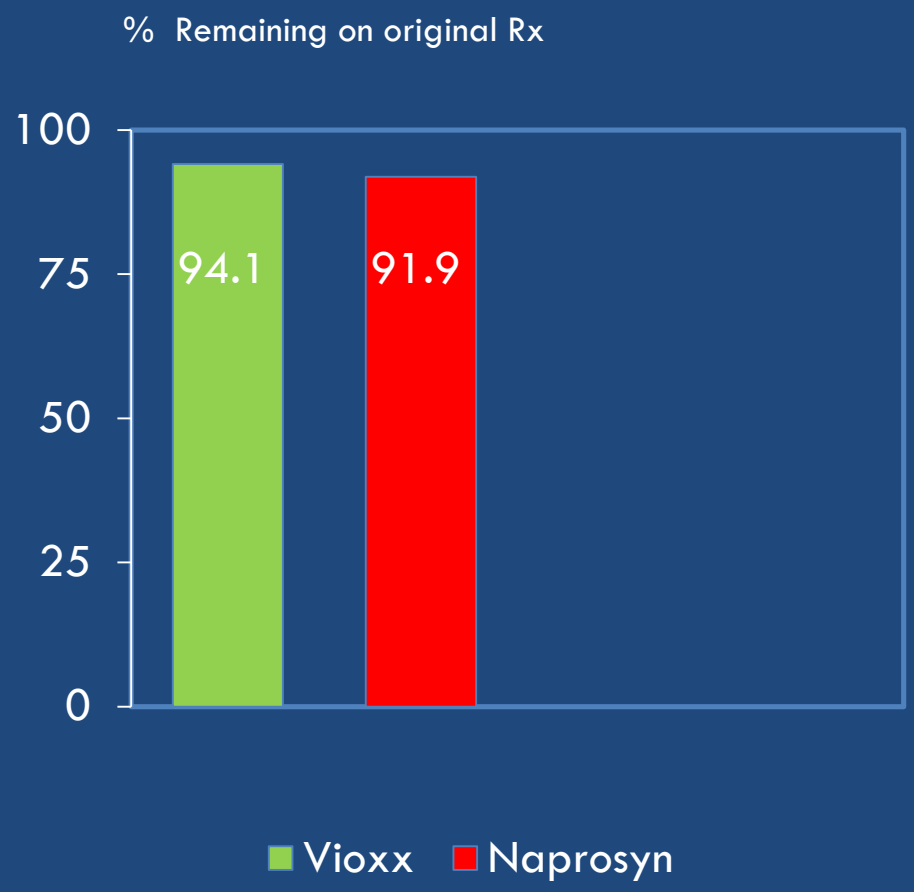
Brief Illustration

- After 3 months, 27% more people stopped taking Naproxyn
  - Of course, that was 5.9% vs 8.1%



Brief Illustration

- or better, 94% vs 92% tolerance



Seeding Study

- ADVANTAGE was designed by the marketing department at Merck
- Real subjects were the MDs
  - Did use of study increase prescription rate?
  - Complimented enrolling doctors
  - Used many primary care sites, rather than a few high enrolling centers

Vioxx and VIGOR

- A study was published in the NEJM in 2000
- Data was provided supporting a claim rofecoxib (Vioxx) only increased cardiovascular risk in high risk individuals
- NEJM found a deleted figure on the submitted floppy disk that included data on heart attacks for three low risk patients (the deletion 2 days before submission to NEJM), making Merck's claim suspect.
- Vioxx removed from the market in September 2004

VIGOR

- Compared rofecoxib (Vioxx) to naproxen for rheumatoid arthritis
- 8076 patients
- Similar symptomatic efficacy
- Confirmed GI events: rofecoxib 2.1/100 pt-years
  - Naproxen 4.5/100 pt-years
- Noted MI's were less common in naproxen group (0.1% vs 0.4%)

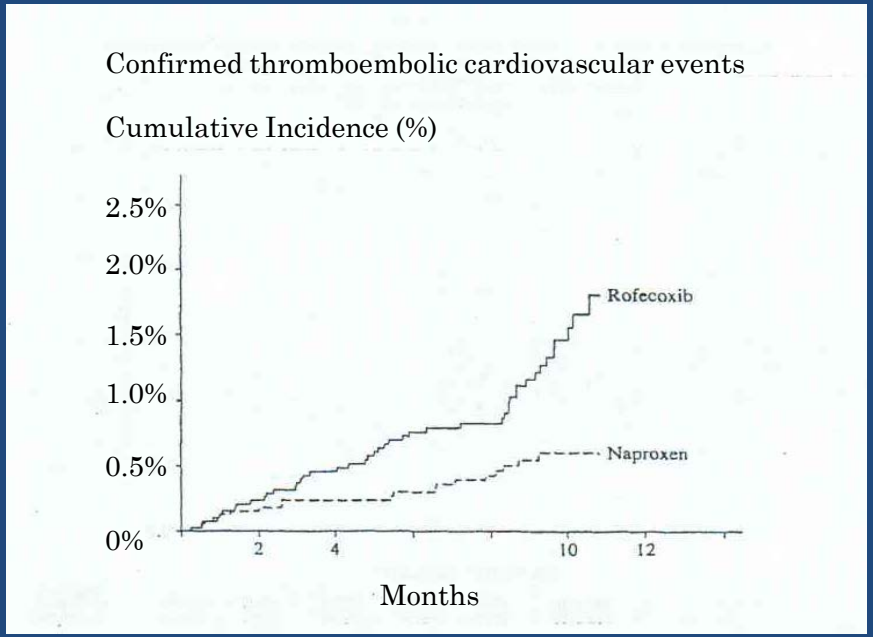
Supplemental information

Data not included in the VIGOR report

Serious events:

Rofecoxib 47

Naproxen 20



Net: prevented 65

Upper Gi events at

Cost of 27 thromboembolic events

What are the big issues?

- Integrity of the research
  - Unbiased interpretation of the data
- Safety of Human Subjects
  - Are safety and efficacy decisions being made by fair judges?
- Perception
  - When you read the list of authors & conflicts, is there a fair broker?

Case Study

- Avandia (rosiglitazone) – SmithKline Beecham (later GSK) received FDA approval in 1999
- Used to treat type 2 diabetes
- 2007 – Steven Nissen published in NEJM that Avandia increases heart attack rate by 43% (based on meta-analysis of 42 trials posted on GSK web site)

Case Study

- Also in 1999, Takeda Pharmaceuticals receives approval for Actos (pioglitazone)
- Both drugs develop markets of ~$3B per year – fairly evenly split (slightly more Avandia prior to Nissen's study)

How to decide?

- Public should want a comparative study

How to decide?

- Public should want a comparative study
- Winkelmayer, et al, Arch Int Med 2008
  - Avandia patients 15% more likely to die and 13% to have CHF than Actos (30,000 patient study)
  - Retrospective study using Medicare records
  - No difference in heart attack or stroke rate
- Very similar result (also using Medicare records) in JAMA in June, 2010 – 1.68 excess events/100 patient-years with Avandia (MI, stroke, heart failure, death)

What did GSK know?

- SmithKline Beecham did a study (Study 175) of Actos only (Takeda's drug)
  - Found that Actos had better lipid profiles, similar effect on glucose

Date: 03/29/2001 08:08:18 (GMT-05:00)

There was no Avandia v Actos study performed in exSB. Study 175 was an Actos only study performed to give us enough info using historical comparison to make a decision about large scale H-H. This was done for the US business, way under the radar and we lost both in terms of LDL and Tgs. Per Sr Mgmt request, these data should not see the light of day to anyone outside of GSK.

Head to Head comparison

- GSK eventually funded a head-to-head comparison with piaglitazone, but the study was terminated early because it was perceived rosiglitazone was clearly inferior, less safe, even without data from the study, and it wasn't fair to put people at risk
- The FDA recently severely restricted the use of rosiglitazone, which will make it a non-factor in the larger market of anti-diabetic drugs
- GSK set aside $2.4B to pay for litigation costs

What are the lessons?

- In our current day, for pharmaceutical companies profit is often held as a higher value than the best interests of patients and the Public
- We need to change systems to incentivize making the Public's interest (and Public Health) the primary goal

Context

- In this context where the motivations of pharmaceutical and device manufacturers are perceived to be suspect
  - Congressional concern
  - Public respect for pharmaceutical companies has plummeted
  - How should academics relate?

Priority Contrast

- Universities are supposed to generate knowledge
  - Publications & presentations
  - Disclosure of discoveries in time so that the collaborative scientific process can occur
- Commercialization model values:
  - Unique ideas
  - Proprietary protection of Intellectual Property
  - Patent first, publish later…

New NIH/Federal Rules

Sunshine & Tighter Controls

NIH Rules Changed: August 2011

- $5,000 threshold for management and reporting to the NIH
  - All cases of research overlap of $5K or more.
  - Determination by the Institution
- Must report all sponsored travel (other than government, universities, and medical centers)
- Require review of all personal COIs prior to any NIH grant expenditures (even on renewal)
- Web site to post all COIs linked to grants

Physician Sunshine Act

- As of 2012, all payments from biomedical companies to physicians and academic medical centers must be reported to the federal government
  - Threshold is $10/gift or $100 cumulative/year
- A publically accessible web site will go on line with all of those data in 2013 (can see an incomplete model at www.propublica.com)

Institutional COI

Bayh-Dole and Societal Priorities

Layers of conflict

- There is intrinsic tension in the competition between current best practices and innovation
- There is a tension in the tax-exempt mission of universities (to serve the public) and commercialization of ideas
  - Commercialization is necessary
  - Job creation is good
  - What advantage should a tax-exempt entity have in its competition with the tax-paying private sector?

Institutional COI

- An ICOI exists when either the institution or an individual who can act for the institution has a COI
  - For institutions, most often potential royalties or licensure fees
  - For individuals, just like personal COI, but look more broadly at roles

UNC example

- In his book "Engines of Innovation: The Entrepeneurial University in the Twenty-First Century", Holden Thorp describes as an ideal model a lab at UNC where the inventor is essentially allowed to use his UNC lab as the lab for his private company
  - Inventor benefits
  - University benefits (financially)
  - Company generates jobs
  - Students benefit from the environment
  - Public getting new technologies

UNC Example 2

- Do we really want our tax dollars going to support giving the faculty inventor a cheap lab?
  - They are profiting well from this arrangement
  - So is the public….
- Ambivalence….

Innovation & Incentives

- 1980 Bayh-Dole legislation incentivized academic medical centers
  - Requires that AMCs and universities commercialize ideas developed using federal grants
  - Preference for partnering with small businesses
  - Requires that the inventor receives some portion of the revenue

Pathway under Bayh-Dole

- Invention Disclosure (IDF)
- Provisional application for a patent (12 month "hold" on the IP at a reduced cost)
- Full patent application (non-provisional)
- As of "Leahy-Smith America Invents Act", IP granted to first to file instead of first to invent
  - Incentivizes earlier filing (& less complete data)
  - Probably favors organizations with deep pockets

Licensing the IP

- Expectation is that the IP will be licensed
  - For B-D, most frequent model is a start-up company
  - Could be any small business
  - Most start-ups are owned by the faculty-inventors
  - Typically the institution receives equity in trade for the IP
- It is thus the case that the inventor and the institution have financial incentives regarding the new idea

What does it mean?

- Without some form of economic incentives, companies will not commercialize the idea
  - Altruism may drive some inventors, but history shows that financial incentives can focus research
  - Institutions must provide an infrastructure to support the tech transfer process
  - A few home-runs, lots of bunts and strikeouts
  - Most institutions lose money on tech transfer

A model success story

- Duke: Dr. Y.T. Chen, MD, PhD, and Glycogen Storage Disease Type II [Pompe Disease]
  - Lethal autosomal recessive caused by a deficiency in acid alpha-glucosidase
  - Develop myopathy, neuropathy
  - Infantile and late-onset forms
- Duke had a large clinic providing care to Pompe patients

Pompe Disease Pt. II

- Dr. Chen inserted the gene for acid alpha-glucosidase into CHO cells and began to produce the enzyme
- Clinical trials at Duke demonstrated safety and efficacy
  - Required hiring new faculty who did not report to Dr. Chen (to department chair)
- Drug (alglucosidase alfa) licensed to Genzyme; FDA approved April 2006

Myozyme Issues

- Cost: $300,000 per year per patient
- Some patients develop antibodies to the protein
- Further research should be done
  - Duke stood to benefit economically
  - Research team wanted to collaborate with the manufacturer, including some research that might be proprietary, but limited pool of experts

Management for the Institution

- Monetize the royalty stream
  - Basically sell the future Duke royalties to an investor
  - Duke no longer stands to gain from drug sales fully realized
- Will discuss investigator & more institutional management models later

The Good from Bayh-Dole

- Bayh-Dole provides financial incentives that may keep inventive faculty focused on advancing public benefits
- Inventors, small companies, and universities have the potential for financial gain
- Small business innovation using B-D model has provided R&D eventually bought by larger corporations
- Public benefits from novel therapies

The Bad

- Incentivizes novelty over what may be more rapidly useful
- Makes research proprietary – opposed to core academic values
- May place students in a difficult bind
- Perhaps encourages research misconduct?

“The Rebuttable Presumption”

- “The Rebuttable Presumption” refers to an important concept: An institution has a rebuttable presumption that it should NOT do human subjects research related to its own intellectual property
- The allowed exception is if “compelling circumstances are present” that justify doing the research at the institution

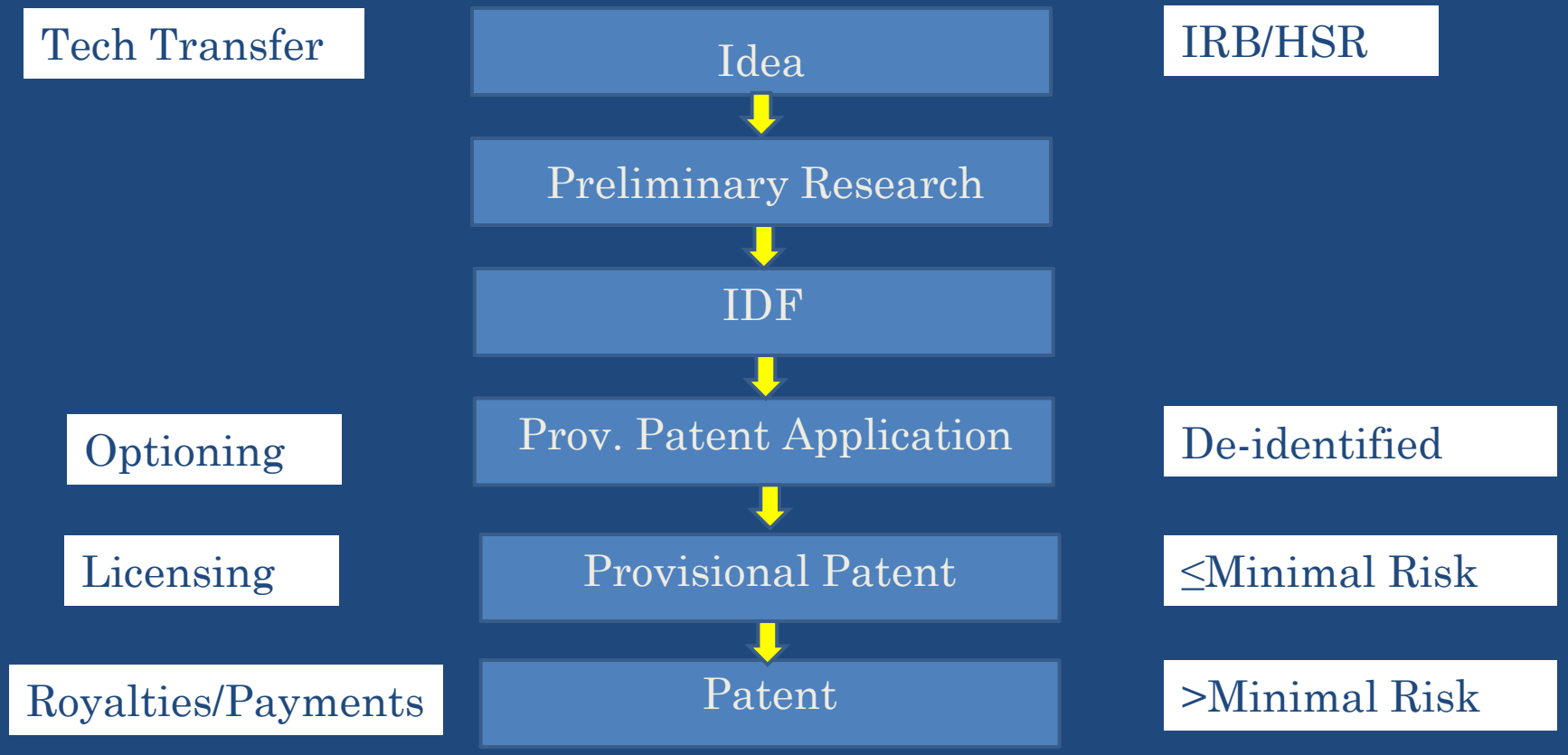
Practical Application

- The rebuttable presumption makes the research
  - Slower
  - More expensive
  - Distances the most motivated people
  - Puts barriers to the people with the greatest expertise
- Can be hard to execute
  - Often the other sites that could do the work are rivals
  - Clinical research is expensive – there are often hidden subsidies when done locally (that make it possible)

Management Strategies

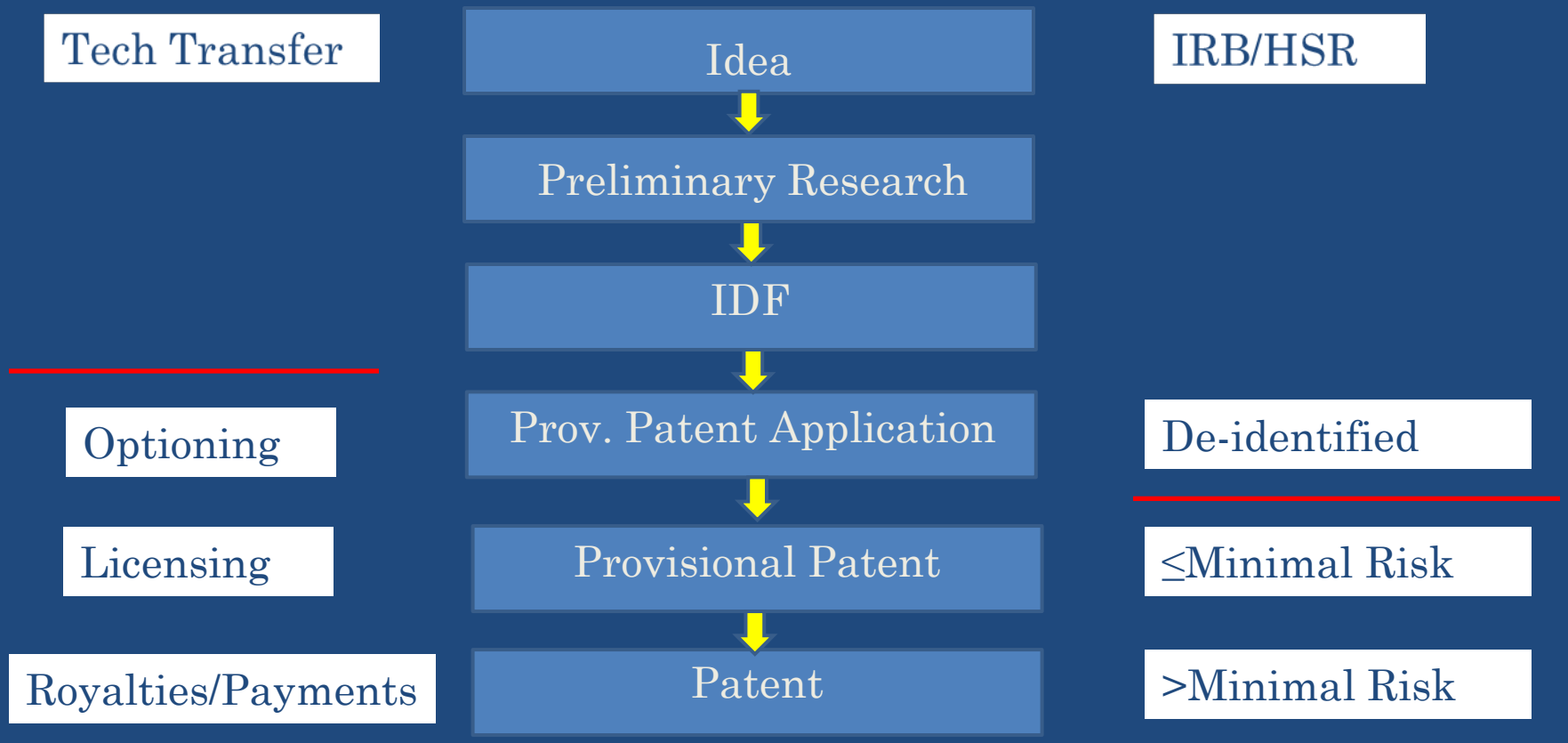
- Institutional
  - Replace/supplement institutional oversight
    - DSMB-plus (may be all external or mixed)
    - External monitoring
    - External IRB
    - Disclosure (esp. in informed consent documents)
  - Remove conflict (divest, monetize)

Pathway of an Idea



Design credit to Susan Aldridge

Pathway of an Idea



Where are we now?

- Manage individuals
- Manage institutional COI
  - Rebuttable presumption is the rule
  - Compelling circumstances reviewed by the COI Committee and Institutional COI Committee
- The big question remains: what is the right balance between the university as an engine of innovation for commercial purposes and as the home for research for knowledge's sake?