The Future of Clinical Research in Private Practice

Alive or Dead?

Larry Karsh MD FACS
Certified Principal Investigator
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International Prostate Cancer Update
Cascade Conference Center
Vail, CO
January 23, 2016

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Clinical Research TUCC

Mission Statement

Conduct clinical research with the utmost integrity and honesty while offering our patient subjects the most advanced therapies in addition to educating them about their disease. In so doing, we will protect their health, safety, and confidentiality.

ARS Question #1

Phase I and II trials are prohibited in private practice according to the Code of Federal Regulations(CFR)

A. True

B. False

ARS Question #2

In general, the pharma industry preferentially selects academic sites over private practice sites because their IRBs "fast track" pharma trials.

A. True

B. False

OCTOBER 5, 1987 A McGRAW-HILL PUBLICATION $2.00

BusinessWeek

Research & Development

America's Most Competitive Companies

PAGE 78

Why become an Investigator?

- Intellectual challenge
- Remain on the cutting edge of technology
- Offer new choices to patients who have no other alternative treatments
- Strengthen stature among peers and community
- Serve on advisory boards, speaking engagements, consultant to industry
- Pathway to publication
- Promote research as a new service of the practice
- Additional revenue stream to the practice
- Prevent “burnout”

#1 with Readers Since 2001

Urology Times

January 2016 VOL. 44, NO. 1 | UrologyTimes.com

Expert clinical analysis. Practice advice. Policy perspectives.

UROLOGIST BURNOUT

Exhaustion jumps, satisfaction slumps

Ripple effect includes early retirement, reduced work hours, medical errors

Lisette Hilton | UT CORRESPONDENT

National Report—A new study suggests physician burnout is increasing among doctors in many specialties, and the statistics for urology are troubling. Solutions need to go beyond what individual physicians do for themselves to prevent and address burnout. This is a system-wide issue that needs to be addressed, according to the study's authors, from Mayo Clinic in Rochester, MN and the American Medical Association.

INSIDE

6 TIPS FOR PREVENTING BURNOUT

PAGE 20

Researchers published an update (*Mayo Clin Proc* 2015; 90:1600-13) from a 3-year study looking at burnout and work-life balance among U.S. physicians. The study compares data from 2011 to that collected in 2014. The latest survey is based on 6,880 physician responders; just under 2% were urologists.

While the sample of urologists is relatively small, findings about the specialty are notable, according to Tait Shanafelt, MD, a Mayo Clinic [illegible] and the study's first author.

"At the time of our 2011 study, urologists had a below-average rate of burnout among physician specialty disciplines. Between 2011 and 2014, urologists had one of the largest increases in burnout of all specialties [increasing from 41% to 64%]," Dr. Shanafelt said. "In 2014, urology ranked second highest of 24 specialties evaluated [vs. 15th out of 24 in 2011]. Urologists also had a decline in satisfaction with work-life balance, moving from the 15th most favorable score out of 24 specialties to the 23rd most favorable score."

Overall, 54.4% of the physicians surveyed had at least one professional burnout symptom, compared to 45.5% in 2011. Satisfaction with work-life balance declined, too, going from 48.5% in 2011 to 40.9% in 2014, according to the study.

More than frustrated

Psychiatrist H. Steven Moffic, MD, said burnout has many definitions, including the simple: "Burnout is emotional exhaustion from undue stress."

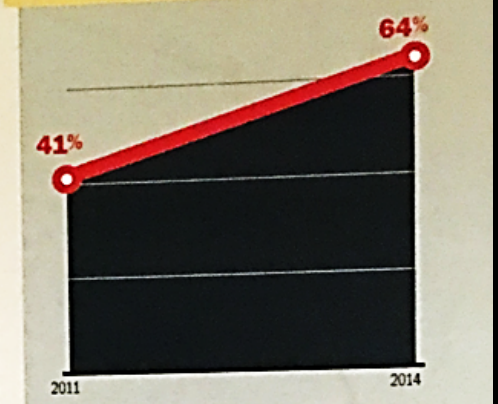
The current study authors describe burnout as a syndrome of emotional exhaustion, loss of meaning in work, feelings of ineffectiveness, and a tendency to view people as objects instead of human beings.

Based on the definition, researchers categorized burnout drivers into five dimensions:

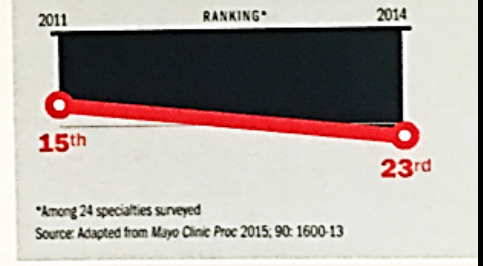
Please see **BURNOUT**, on page 18

AMONG UROLOGISTS...

Prevalence of burnout is up



And satisfaction is down



*Among 24 specialties surveyed

Source: Adapted from *Mayo Clinic Proc* 2015; 90: 1600-13

Key Players in Clinical Trials

- Institutional Review Board/Independent Ethics Committee (IRB/IEC)
- Sponsor
- Investigator
- Subject

IRB/IEC

Independent body composed of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial

Sponsor

The company or organization taking responsibility for initiation, management, and financing of trial

Contract Research Organization (CRO)

Hired by sponsors to carry out some of their tasks

Sponsor may allocate tasks but never allocate responsibility

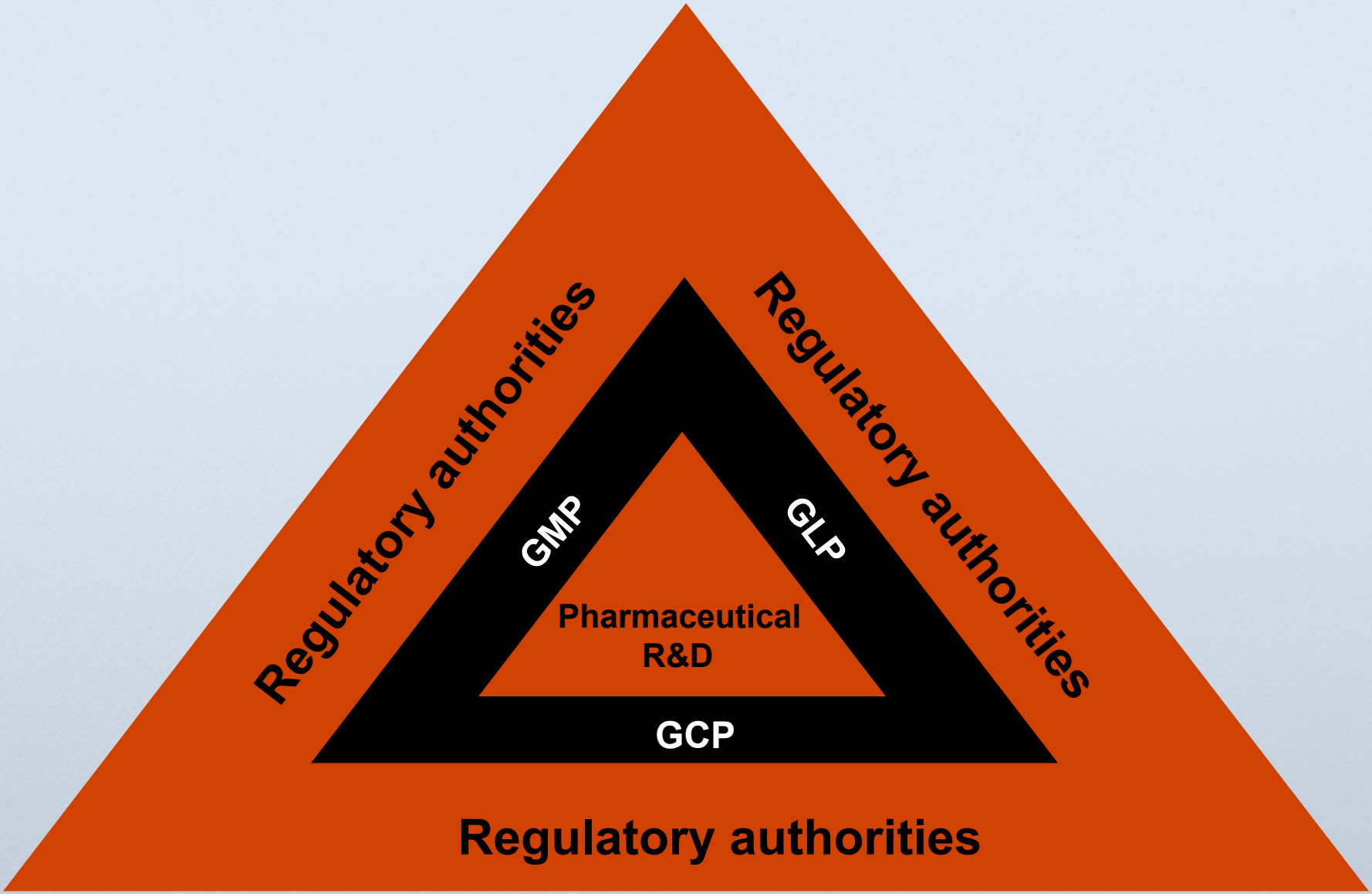
Investigator

Person responsible for the conduct of the clinical trial at trial site.

Subject

Individual who participates in a clinical trial

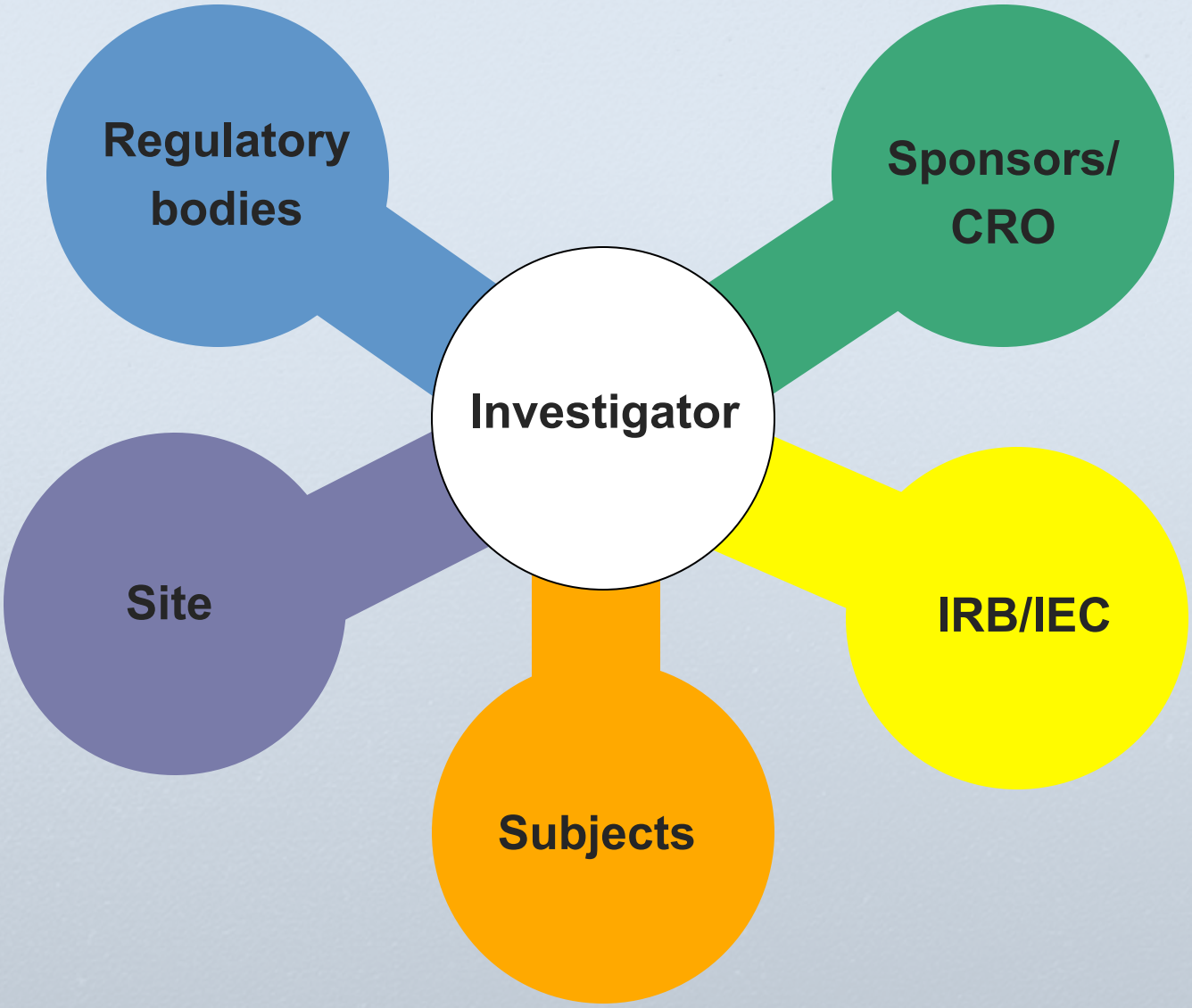
Regulations



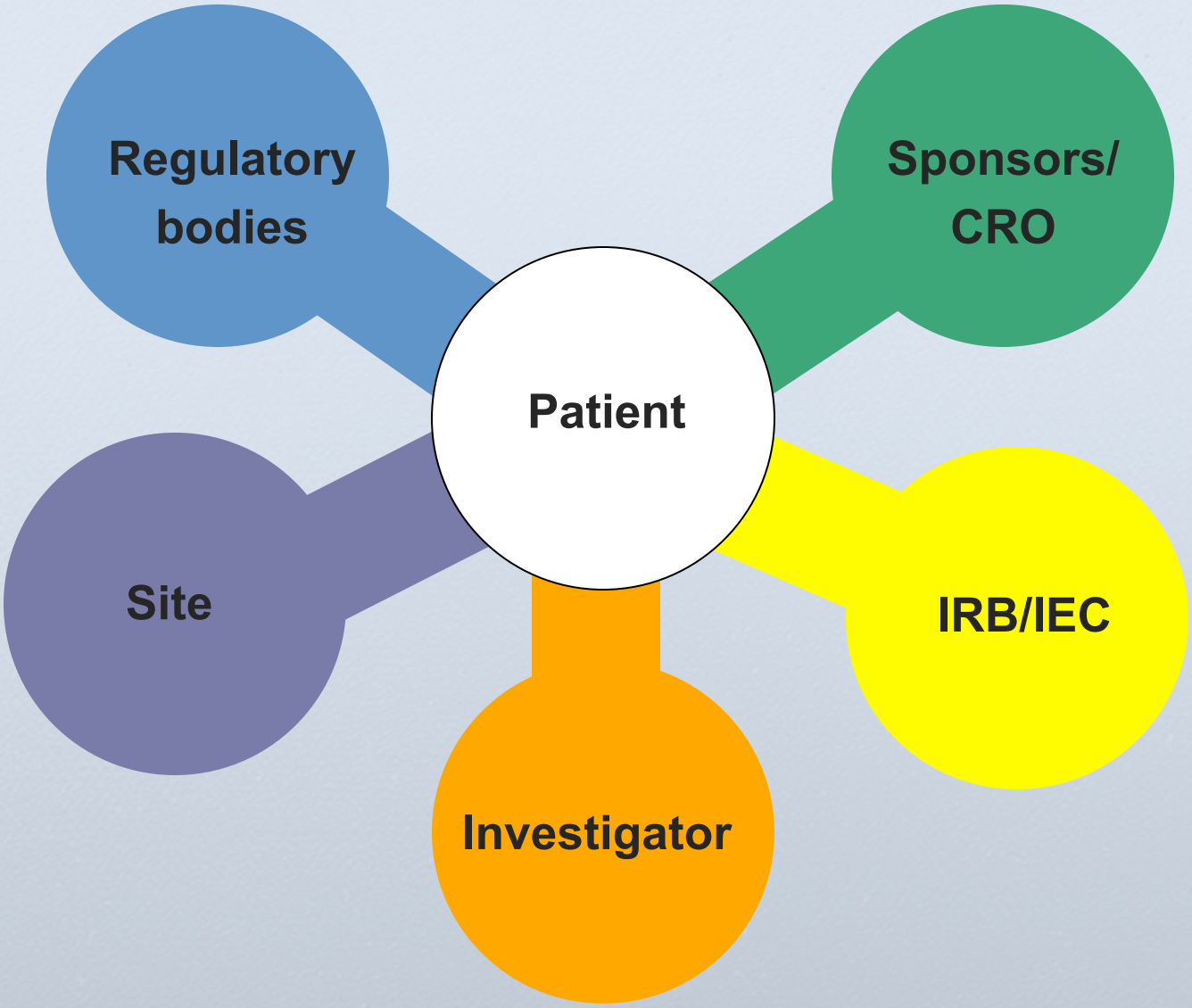
FDA's ROLE

- Assure safety and the rights of subjects/patients
- Input on design of protocols and overall clinical program
- Assure quality and integrity of data
- Assure quality of clinical trial materials
- Issue regulations and guidelines

The investigator: The heart of the clinical trial



The patient: The soul of the clinical trial



Keys for Success

- Business acumen
- Scientific curiosity
- The right staff
- Infrastructure
- Motivation/Dedication
- Portfolio of clinical trials

Successful Investigator Profile

- Requires a solid understanding of what regulators, sponsors, monitors, the Institutional Review Board (IRB) and FDA expect of an investigator.

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 30 (2012) S28–S32

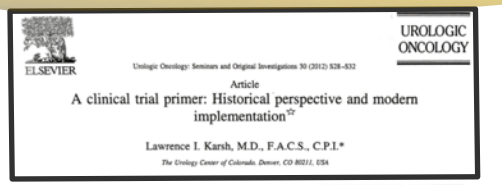
UROLOGIC ONCOLOGY

Article

A clinical trial primer: Historical perspective and modern implementation☆

Lawrence I. Karsh, M.D., F.A.C.S., C.P.I.*

The Urology Center of Colorado, Denver, CO 80211, USA



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A clinical trial primer: Historical perspective and modern implementation☆

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Abstract

The structure of modern clinical trials is designed to protect patient safety while generating safety and efficacy data. Safety is the primary concern, and United States regulations are shaped by a series of responses to incidents, including notable safety lapses and unethical trials. These regulations focus on 3 essential components, defined by the 1979 Belmont Report: respect for persons, beneficence, and justice. Further, the international community has formally outlined good clinical practice (GCP), which mandates that trials are designed to produce meaningful data, conform to international ethics regulations, and provide assurances that data are reported in a credible and reliable manner. The Food and Drug Administration (FDA) and federal government have outlined the necessary components of clinical trials in the Code of Federal Regulations (CFR). These include institutional review boards (IRBs), standard operating procedures (SOPs), sites, sponsors, investigators, and patients. The investigator is the center of the trial and is required to sign an agreement with the federal government to uphold the CFR. Investigator duties include making sure that investigator and support staff having appropriate qualifications, delegating duties, monitoring the study for compliance and record keeping, providing care, and accepting accountability for the trial, among other duties. Physicians, who already have significant time demands, need a well-trained staff, including clinical coordinators, to adequately meet these duties. Despite these requirements, trials can have significant benefits for investigators, practices, and patients, foremost of which is the ability to provide cutting edge care. However, the clinical trial process requires routine evaluation and continual performance improvement in order to ensure that patients not only receive excellent care, but also do so in the safest possible manner.

Keywords: Clinical trials; Compliance; FDA; GCP

How we got here: The evolution of United States regulations

The structure of modern clinical trials began after World War II, but was shaped by several notable events prior to this. In 1937, 107 people, many children, died as a result of the Elixir Sulfanilidamide tragedy [1,2]. In order to increase the popularity of sulfanilidamide, a Tennessee company created a liquid formulation in which the sulfapilidamide had been diluted with diethylene glycol—the main component of antifreeze—that caused vascular nephropathy [2]. The toxicity of the inactive ingredients was not tested, as it was not required by existing regulations. As a direct result of the event, the FDA established the 1938 Federal Food, Drug, and Cosmetic Act, which required drug manufacturers to send new drug application (NDA) reports to the FDA, showing drug safety. It also banned false labeling and dangerous ingredients, requiring manufacturers to disclose all active ingredients [3]. Prescriptions were required for certain medications, although it would take the 1951 Durham-Humphrey Amendment to create the category of prescription drugs. Most importantly, the 1938 act was the first to require scientific tests when manufacturing a drug.

This was not the first drug regulatory act on the books. Previously, the 1906 Pure Food and Drug Act was designed to eliminate adulterated and misbranded food and drugs [3]. While the legislation had been under consideration for some time, the 1906 publication of Upton Sinclair's *The Jungle*, an exposé of the Chicago meatpacking industry, generated

Disclosure/Conflict of Interest Statement: L.I. Karsh is a consultant for Amgen, Dendreon, Bayer, Allergan, Spectrum, Janssen and Astellas/Medivation.

* LIK serves on advisory boards for Amgen, Johnson and Johnson, Pfizer, Sanofi Aventis, and Spectrum, and as a speaker for Allergan, Amgen, Dendreon, Ferring, GlaxoSmithKline, and Pfizer.

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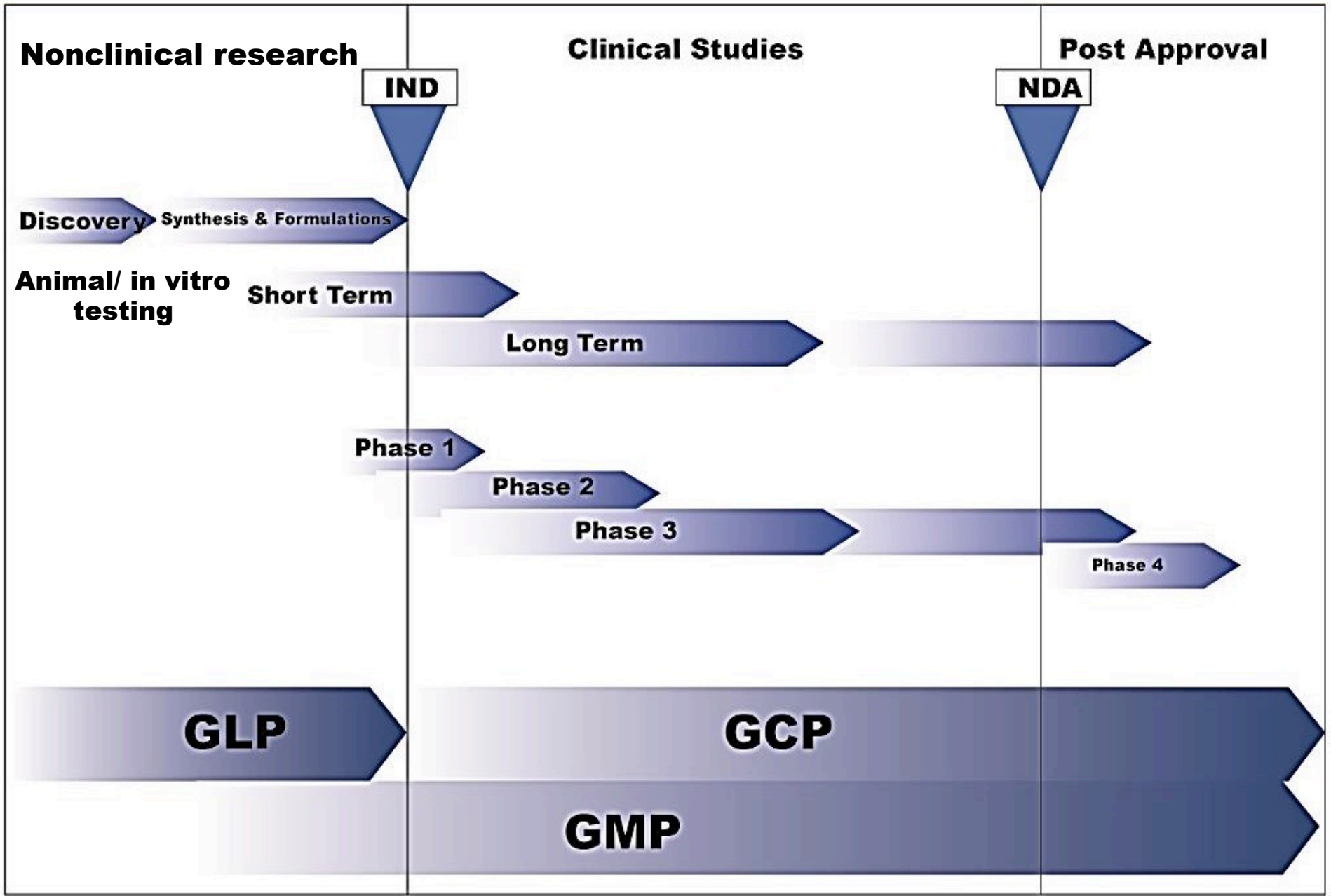
Clinical Development: The Fundamentals

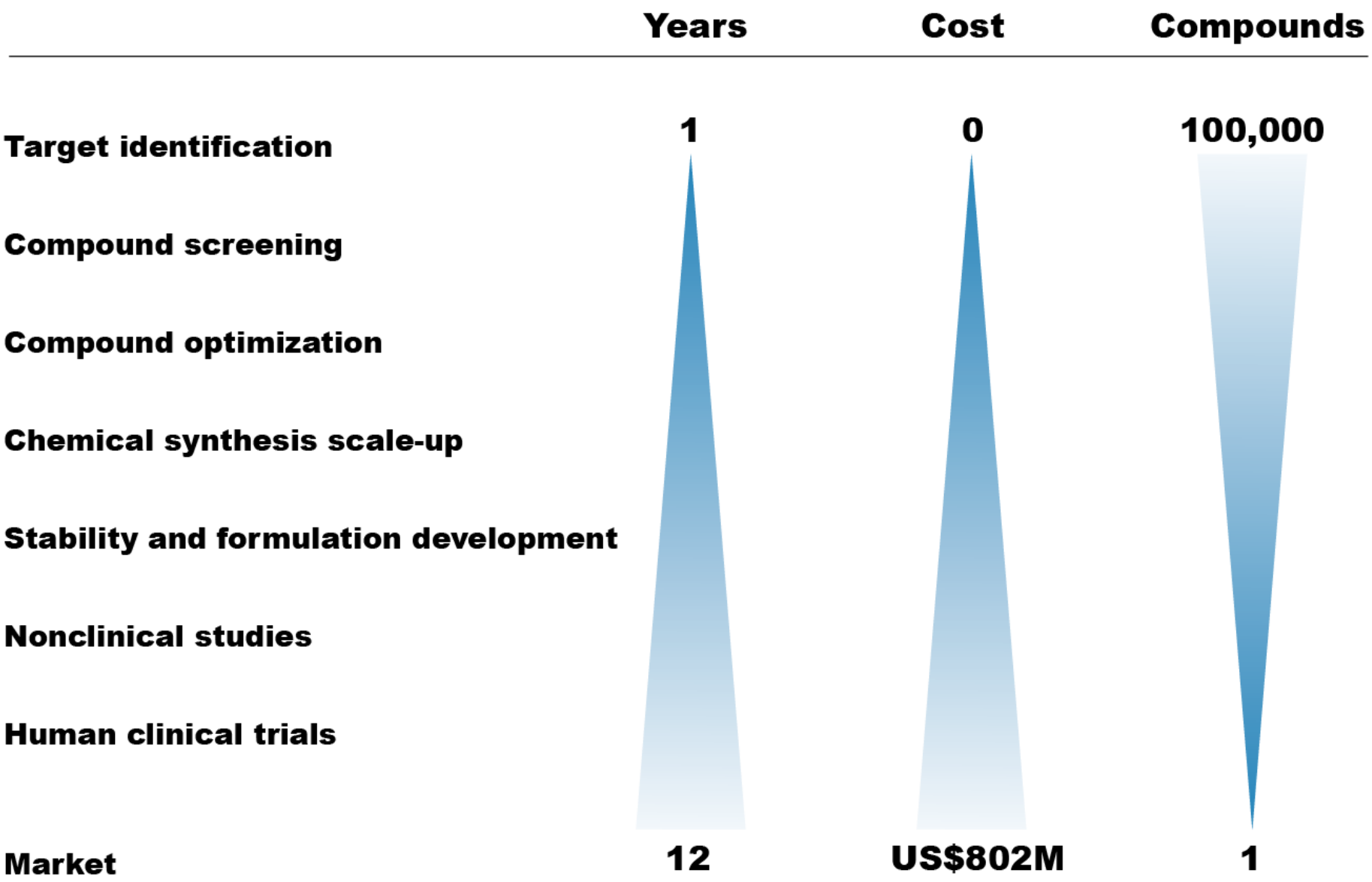
Table 1
The fundamentals of clinical development

Phase I	Evaluation of safety, determination of a safe dosage range, and identification of side effects in a small group of subjects (20–80).
Phase II	Larger trials (100–300 subjects) to determine whether a treatment is effective and further evaluate safety.
Phase III	Larger studies (1000–3000 subjects) to confirm safety and efficacy and compare the investigational treatment with other options.
Phase IV	Post-marketing trials comparing different approved treatments or side effects. Phase IV trials are designed to help optimize already available treatments.

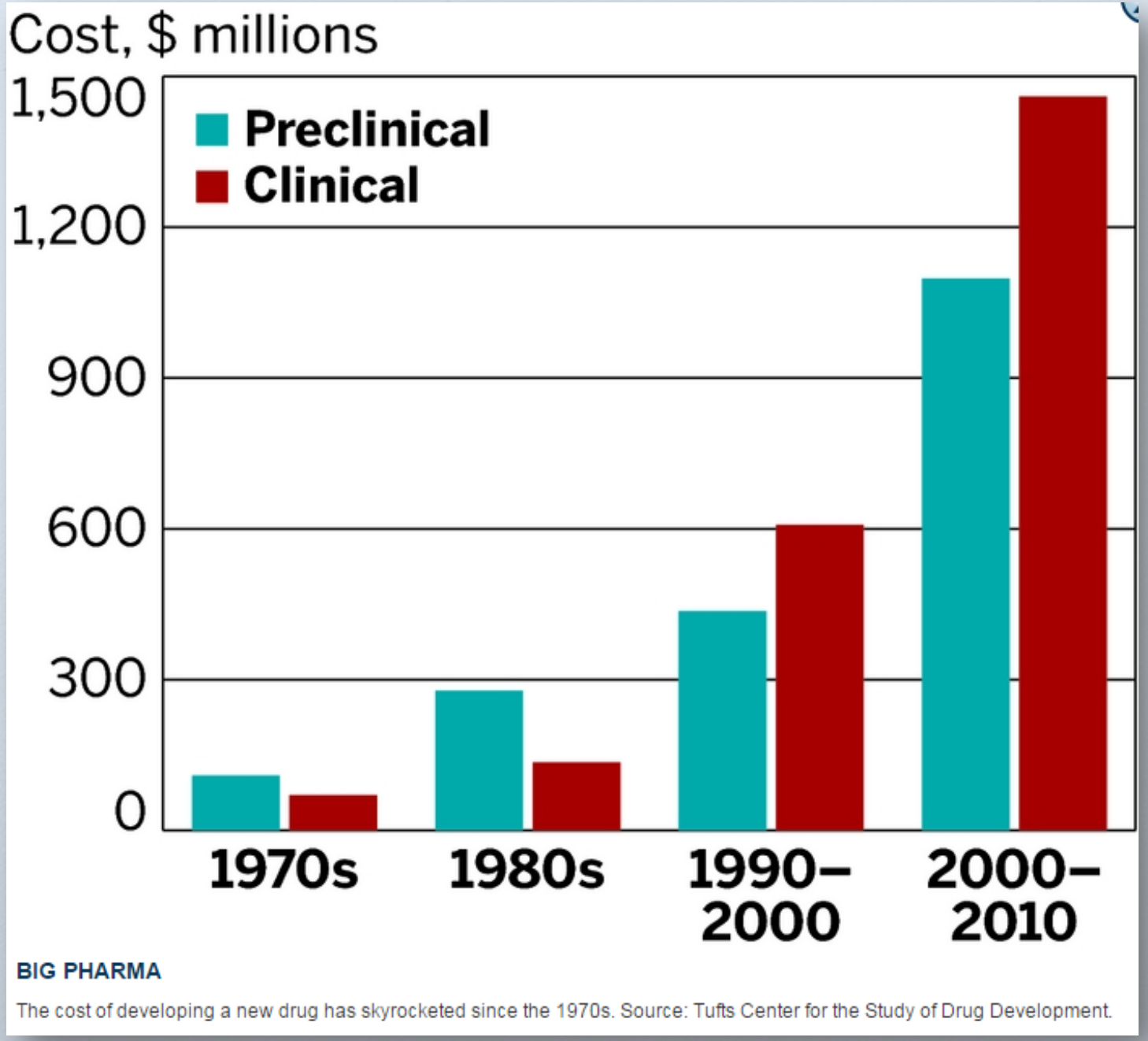
The Drug Development Process



Product Development Timeline



2003



BIG PHARMA

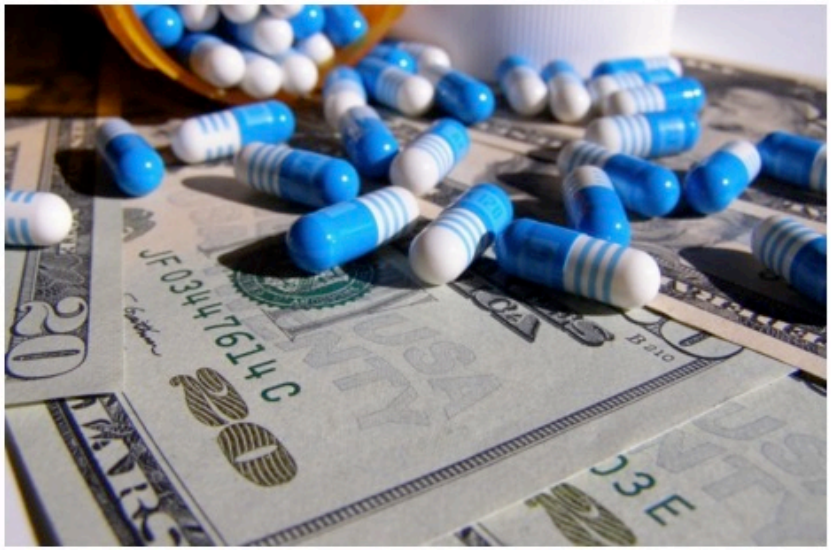
The cost of developing a new drug has skyrocketed since the 1970s. Source: Tufts Center for the Study of Drug Development.

The Washington Post

Wonkblog

Does it really cost $2.6 billion to develop a new drug?

By Jason Millman November 18, 2014 Follow @jasonmillman



(Image from StockMonkeys.com)

The never-ending debate about what drugs should cost is in part driven by the fact that no one seems to know what it actually costs to develop one. And now we have a new analysis from an influential think tank for what it believes to be the cost of getting a drug approved: $2.6 billion.

UACT
UNION FOR AFFORDABLE CANCER TREATMENT

February 3, 2015

Joseph DiMasi
Center for the Study of Drug Development
Tufts University
75 Kneeland Street
Suite 1100
Boston, MA 02111
Tel.: 1.617.636.2170

cc: Anthony Monaco, President, Tufts University; Kenneth Kaitin, Director of CSDD; Henry Grabowksi, Duke University; Ronald Hansen, University of Rochester

Dear Dr. DiMasi:

At the suggestion of Tufts University President Anthony Monaco, the Union for Affordable Cancer Treatment (UACT)[1] would like to obtain from you some clarifications regarding the recent "Tufts Drug Development Cost Study" and the November 18, 2014 press conference during which the conclusions of that study were presented.[2]

We wrote to Dr. Monaco to ask who funded the study and the press conference that announced the results of a study, without providing the public the study itself, nor many of the details used to justify the new result.

Many observers will undoubtedly read the new study as a justification of high drug prices, including the very high prices for new drugs to treat cancer, an outcome that occurred following the release of the previous two iterations of the study. Indeed, the $2.6 billion study number was cited by John Castellani, the CEO of PhRMA, in a January 26, 2015 letter to the New York Times where he specifically defended high prices for cancer drugs.

[1] More information about UACT is available on our web site at http://cancerunion.org
[2] http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

Public and Private Sector Contributions to the Research & Development of the Most Transformational Drugs of the Last 25 Years

A Tufts Center for the Study of Drug Development White Paper

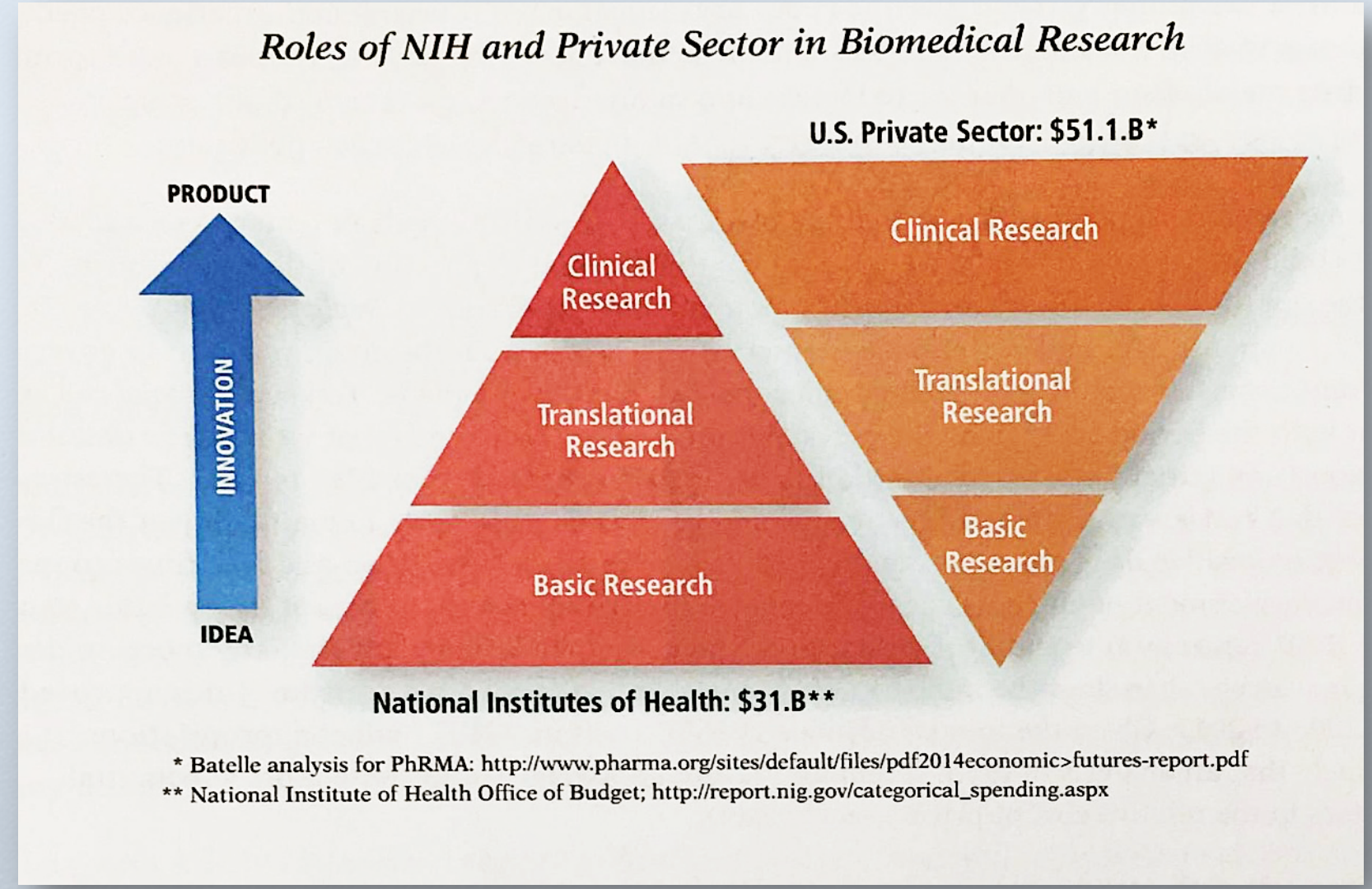
Tufts University School of Medicine • Boston, Massachusetts, USA

JANUARY 2015

AUTHORS:
Ranjana Chakravarthy
Kristina Cotter
Joseph DiMasi
Christopher-Paul Milne
Nils Wendel

Sponsored in part by a grant from Pfizer Inc.

Government and BioPharma Industry Investments Are Highly Complementary



Development Costs

R&D by Public and Private Sectors

	Public	Private
Basic and applied science	54%	44%
Discovery and technologies	42%	58%
Chemistry, manufacturing and formulation (CMC)	19%	81%
Phase I-III development	22%	73%

Additional Costs

- Capital costs of money invested in research
- Drug failures **only 11.8% succeed**
- Comparators for newer drugs are standard of care therapies and are costly

A Tufts center for the Study of Drug Development White Paper
Tufts University School of Medicine, Boston, Massachusetts
January 2015

Industry Challenges

Why the frustration with academic medical centers?

- Slow review of proposals due to red tape
- Delays in start date and enrollment
- Competing priorities
- No sense of urgency

Why the shift to community physicians?

- Review proposals and contracts faster
- Recruit patients more rapidly
- Overall lower trial cost
- Diversity of patient base

Time is money-patents are expiring !!!!

Regardless of these challenges, industry,investigators,and patients can benefit through more collaboration between the academic and private sectors

Clinical Drug Development for mCRPC

Where have we been and how did we get to where we are today?

Evolution of Clinical Trial Design for Prostate Cancer

End points and outcomes in CRPC

- **PSAWG** **March, 1999**
- **PCWG2** **August, 2008**
- **PCWG3** **May, 2015**

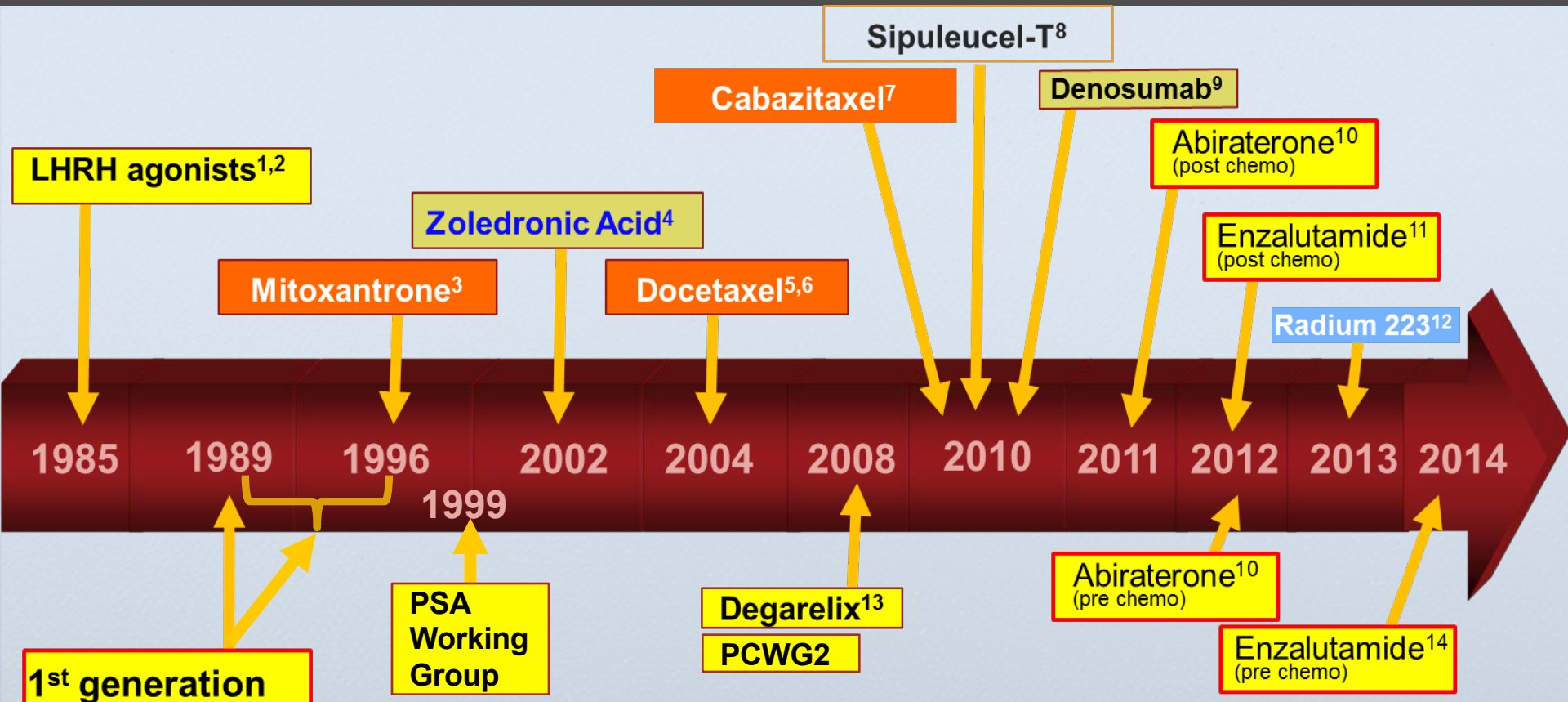
PSA as an Intermediate EP

Because PSA is elevated in the majority of patients with advanced prostate cancer and anecdotal evidence suggested that changes in PSA often antedated changes on bone scan, several groups proposed the use of posttreatment changes in PSA to rapidly screen the activity of novel agents for the treatment of advanced prostate.

PSAWG March 1999

- Formed by a panel of experts to standardize phase 2 trials of novel therapies in CRPC and formulate recommendations to allow clinical investigators to “speak the same language”.
- Posttreatment PSA decline did not meet the criteria for a true surrogate endpoint but changes in PSA were considered a valuable aid in screening therapies to move forward to phase 3 testing.
- PSAWG recommendations set the stage for the development of a new generation of clinical trials in advanced prostate cancer

Drug Development Since 1985



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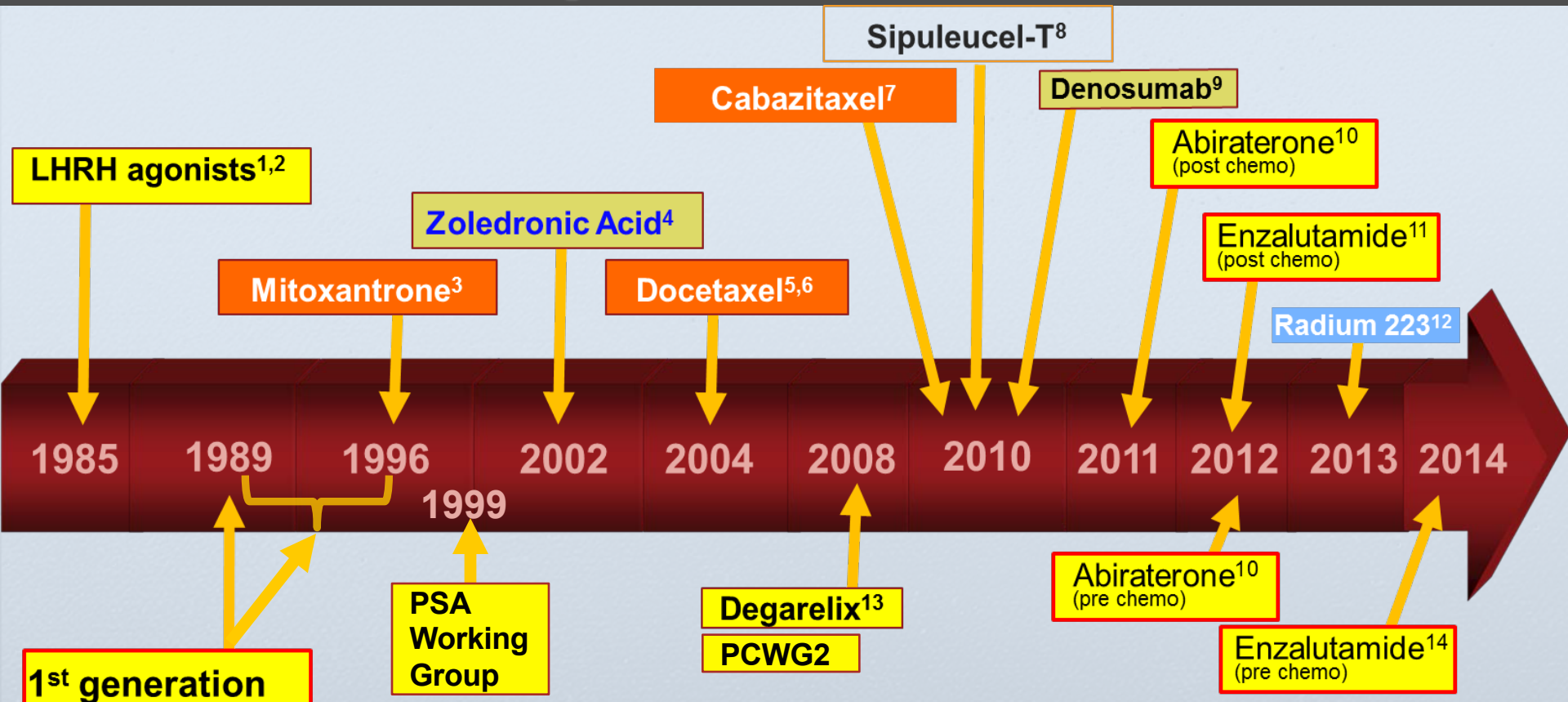
PCWG2 August 2008

- Shift in emphasis from reliance on posttreatment changes in PSA to time-to-event endpoints.
- Proposal for 12 weeks of treatment with IP to ensure adequate exposure to a novel therapy.
- Requirement for 2 new bone lesions to qualify for disease progression.
- Confirmation of bone scan progression on subsequent bone scan to rule out tumor “flare” and nonspecific scan changes.

Renaissance Era of Drug Development Since 2010



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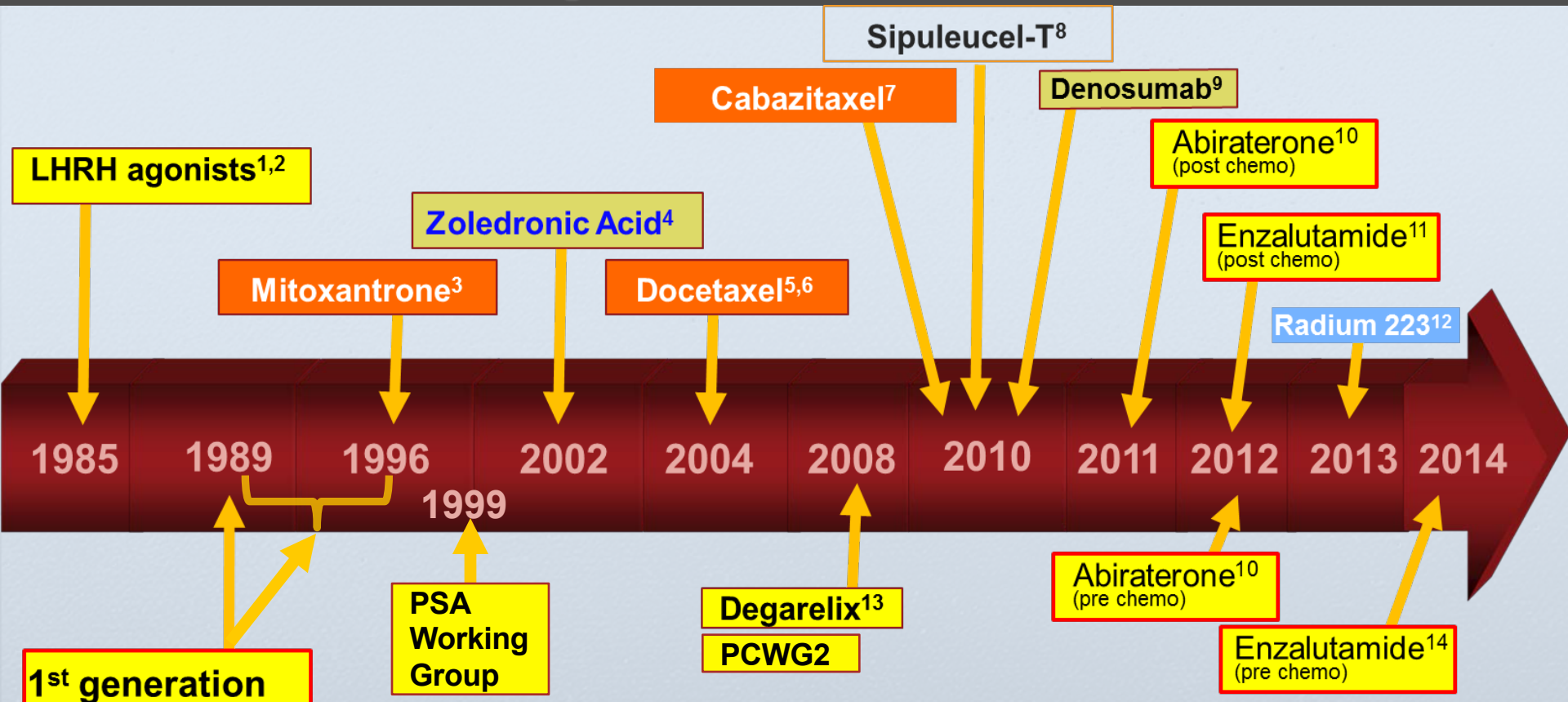
PCWG3 May 2015

- PCWG3 updates the PCWG2 consensus criteria based on available new treatments and disease manifestations as well as data validating biomarkers proposed in PCWG2.
- The revised criteria define the endpoints for the M0 to M1 transition.
- These recommendations will guide clinical trial design and conduct for therapeutics being tested in both M0 and M1 patient populations.

Renaissance Era of Drug Development Since 2010



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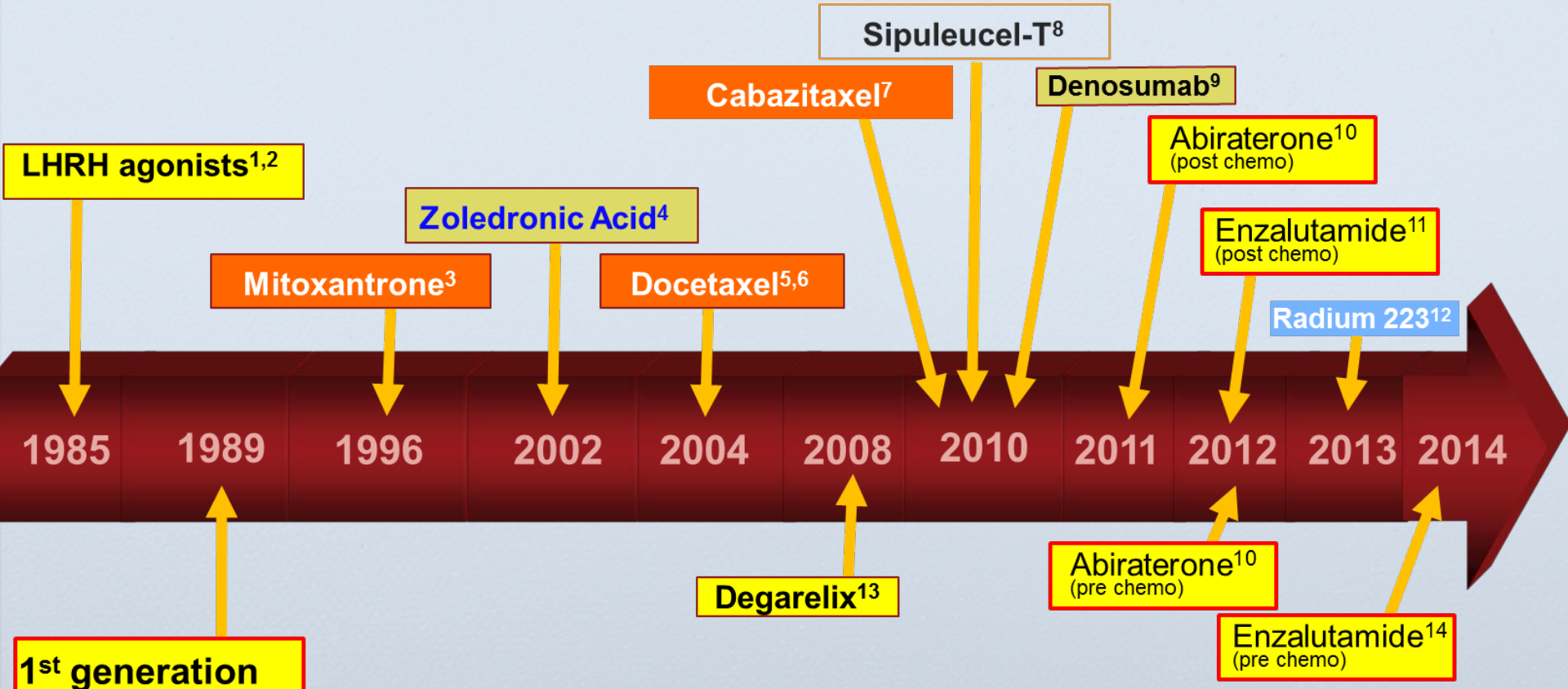
An so it continues …



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An so it continues …

In Development

2015

PCWG3

ARA M0
- JNJ-56021927/ARN-509 (SPARTAN)
- ODM-201 (ARAMIS)
- MDV3100/Enza (PROSPER)

ARA & ABI M1
- TOK-001 (ARMOR 3)
- JNJPCR3001 (ACIS)
- Enza +/- Abi (ALLIANCE)

Immunotherapy
- BNIT-PRV-301 (PROSPECT)
- Prostvac

2016 and beyond

Immunotherapy

Serial biologic profiling tissue/ blood

Predictive biomarkers

Sequencing

Is the Future of Clinical Research in Private Practice alive or dead?

Summary

- The future of clinical research in private practice is alive and thriving.
- Collaboration between community and academic sites will move us closer to our goal of finding the safest, most effective therapies for our patients.
- Community practitioners should consider clinical research as an opportunity to expand their careers and benefit their patients with the caveat that you must have a solid understanding of what regulators, sponsors, monitors, the International Review Board (IRB) and FDA expect of an investigator.

ARS Question #1

Phase I and II trials are prohibited in private practice according to the Code of Federal Regulations(CFR)

A. True

B. False

ARS Question #2

In general, the pharma industry preferentially selects academic sites over private practice sites because their IRBs "fast track" pharma trials.

A. True

B. False

ARS Question #3

As a result of this lecture:

A. I have not yet done clinical trials but am encouraged to start a program

B. I have been doing clinical trials and will expand our program

C. I have been doing clinical trials but have decided to quit

D. I will never do clinical trials

THANK YOU

IPCU

INTERNATIONAL PROSTATE CANCER UPDATE

January 20–23
2016

Vail Cascade

Vail, Colorado

The Future of Clinical Research in Private Practice

Alive or Dead?

TUCC
THE UROLOGY CENTER OF COLORADO

Results PCWG3

- Distinguish prostate adeno from non adenoca.
- Considers sequence and # of prior therapies in lieu of pre- and post- taxane distinctions.
- Defines endpoints for transitioning from **M0** to **M1**.
- Focus outcomes on proof of mechanism and optimal biologic dose for non-cytotoxic therapies.
- Emphasize pt. reported outcomes,fPFS,CTC enumeration,and time to clinical events rather than alterations in individual biomarkers.
- Distinction between 1st evidence of progression based on one disease manifestation in contrast to terminating Rxment due to lack of benefit.

Results PCWG3 (cont.)

- Document progression in existing lesions as distinct from new lesions.
- Serial biologic profiling of disease from tissue and/or blood to understand treatment resistance and identify predictive biomarkers for prospective trials.

Summary PSAWG

- Recommendations for trial design to allow clinical investigators developing novel agents to "speak the same language".
- PSA was used as an intermediate endpoint but other important parameters such as OS,rPFS,symptoms, and mechanism of action as it relates to a clinically relevant composite endpoint(i.e bisphosphonates).
- 1st trials for CRPC to integrate posttreatment changes in PSA were hampered by different posttreatment PSA parameters that limited cross-trial comparisons and created confusion with regard to prioritization of agents for further development.