FDA-Arthritis Foundation
OA Drug Development Workshop

'*Statistical Considerations on the Use of Surrogate Endpoints*'

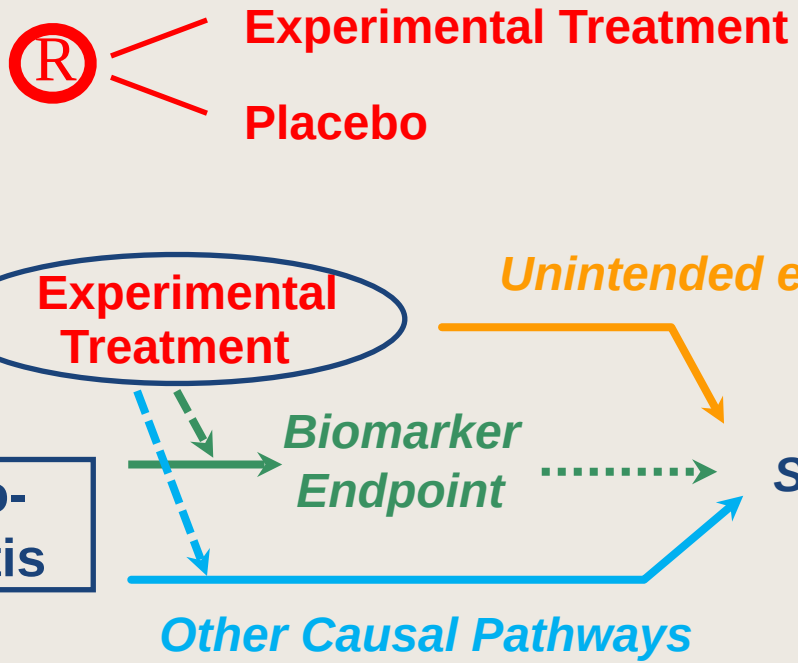
Thomas R. Fleming
Professor of Biostatistics
Univ of Washington, Seattle

Some Key Principles

~ Strong individual-level correlation between a biomarker and a direct measure of how an individual 'feels, functions or survives' doesn't justify that a treatment effect on the biomarker reliably predicts the treatment's effects on how an individual feels, functions or survives.

~ Validation of a biomarker as a replacement endpoint, requires:

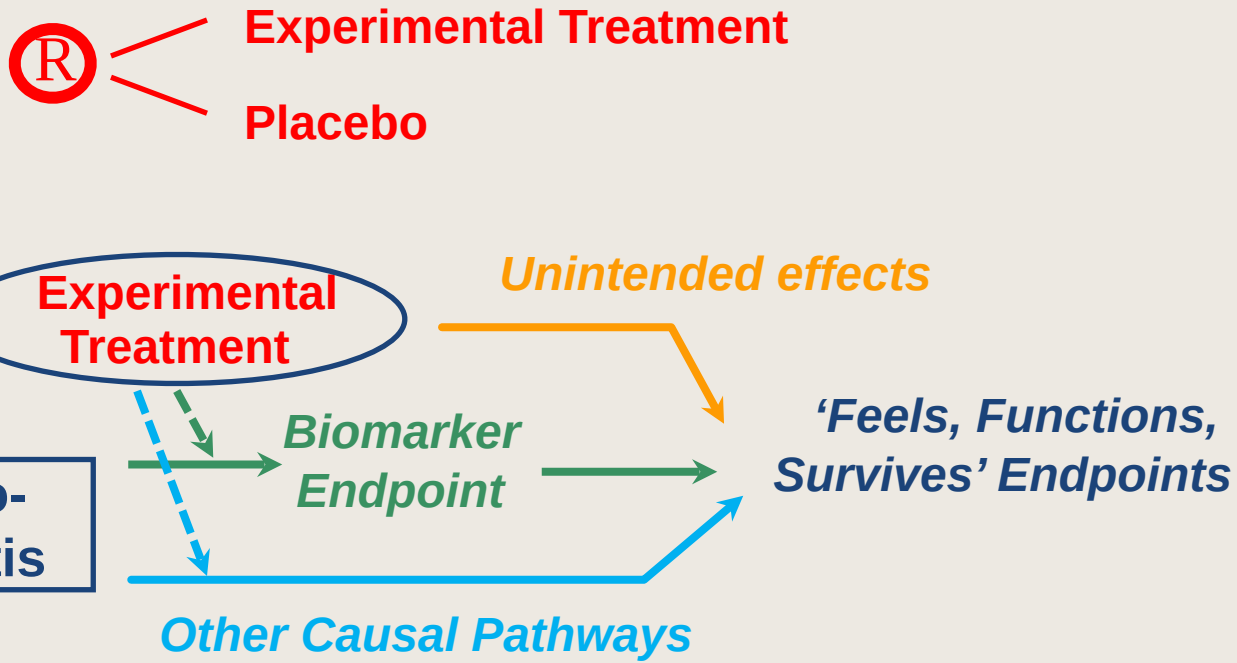
- An in depth clinical understanding of
  - ✓ the causal pathways of the disease process; and
  - ✓ the treatment's intended & *unintended* mechanisms of action;
- Meta-analyses of clinical trials showing the relationship between:
  - ✓ the ***net*** effect of the treatment on the biomarker, and
  - ✓ the ***net*** effect of the treatment on direct measures of how an individual feels, functions and survives



E.g., Kim, Levin, Nikolov et al, 2020

- *Total Knee Replacement*
- *Severe Pain**
- *Severely impaired functioning**

* Using Patient Reported Outcomes such as WOMAC index subscales: pain, stiffness, functional disability



*Treatments' relative effects on on a **Biomarker Endpoint** could be misleading regarding their true relative clinical efficacy*

Immunologic Biomarkers in **Acellular Pertussis Vaccines**

(3-arm Sweden I Trial with DT control: 10,000 subjects)

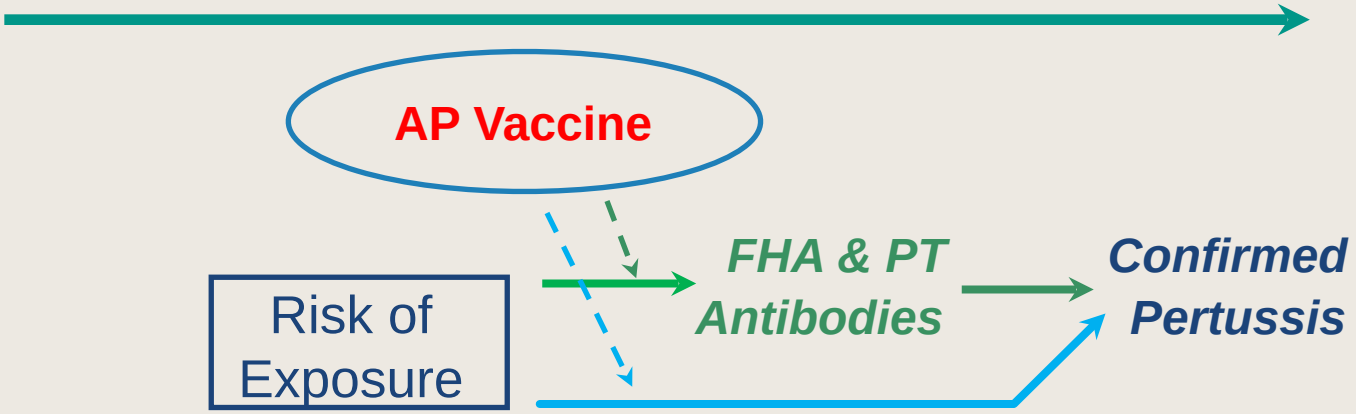
- **Vaccine Efficacy**

	VE	95% CI
SKB	58%	(51%, 66%)
Aventis Pasteur	85%	(81%, 89%)

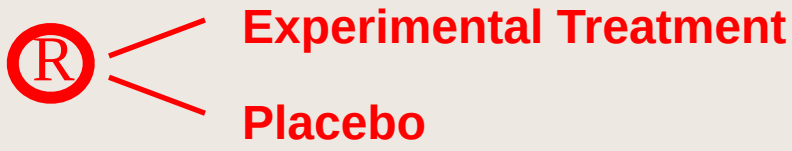
- **Immunologic Biomarkers**

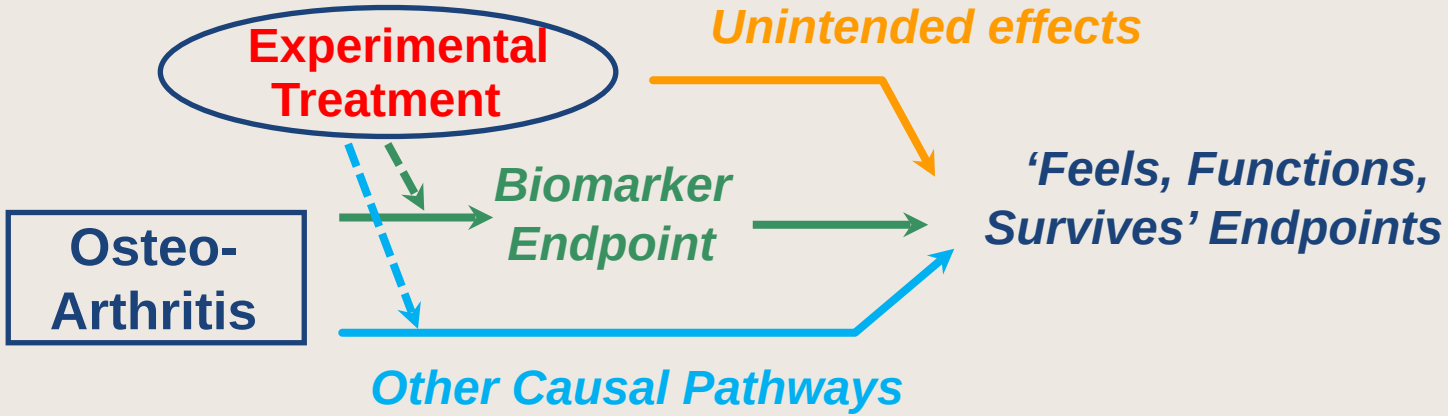
Filamentous Haemagglutinin (FHA) and Pertussis Toxoid (PT) antibody responses were superior with the SKB vaccine

Multiple Causal Pathways



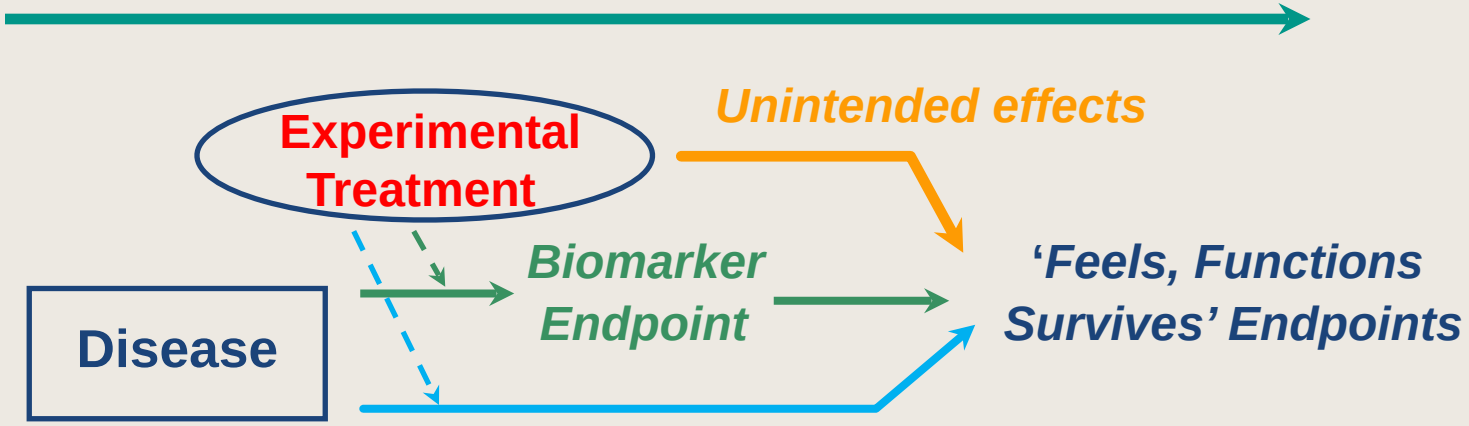
- Other Immune Responses, including those resulting from **additional** antigens in the vaccines:
  - ~ Pertactin
  - ~ Fimbriae (types 2 and 3)
- Durability of effect



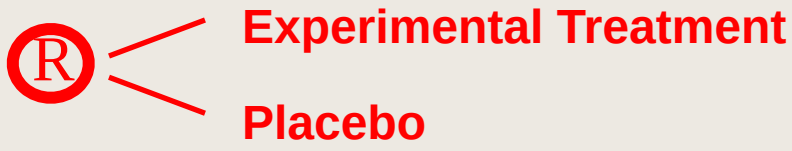


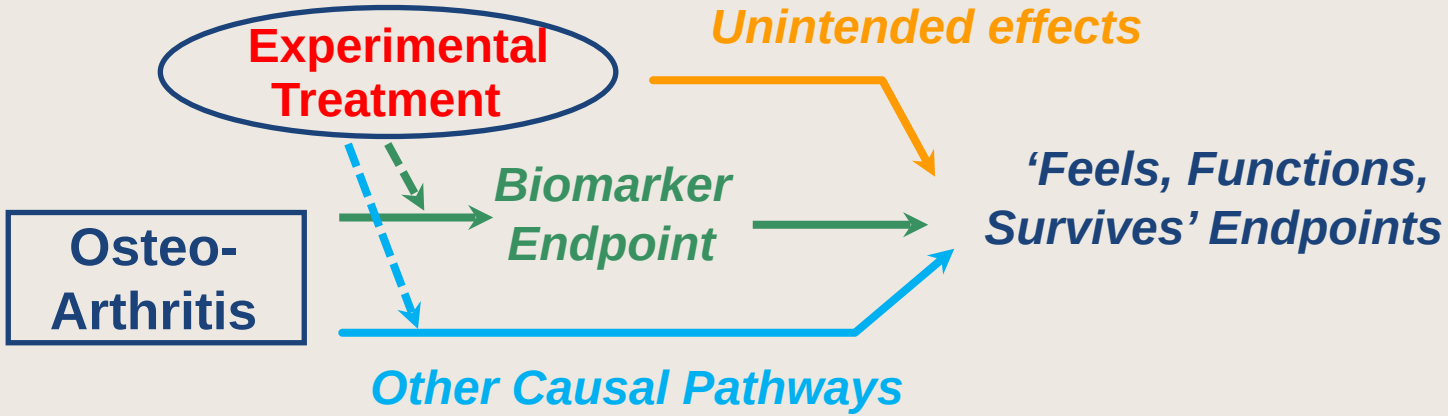
*The treatment's effect on the **Biomarker Endpoint** could **overestimate** or underestimate the treatment's true clinical efficacy*

Interventions having Mechanisms of Action Independent of the Disease Process

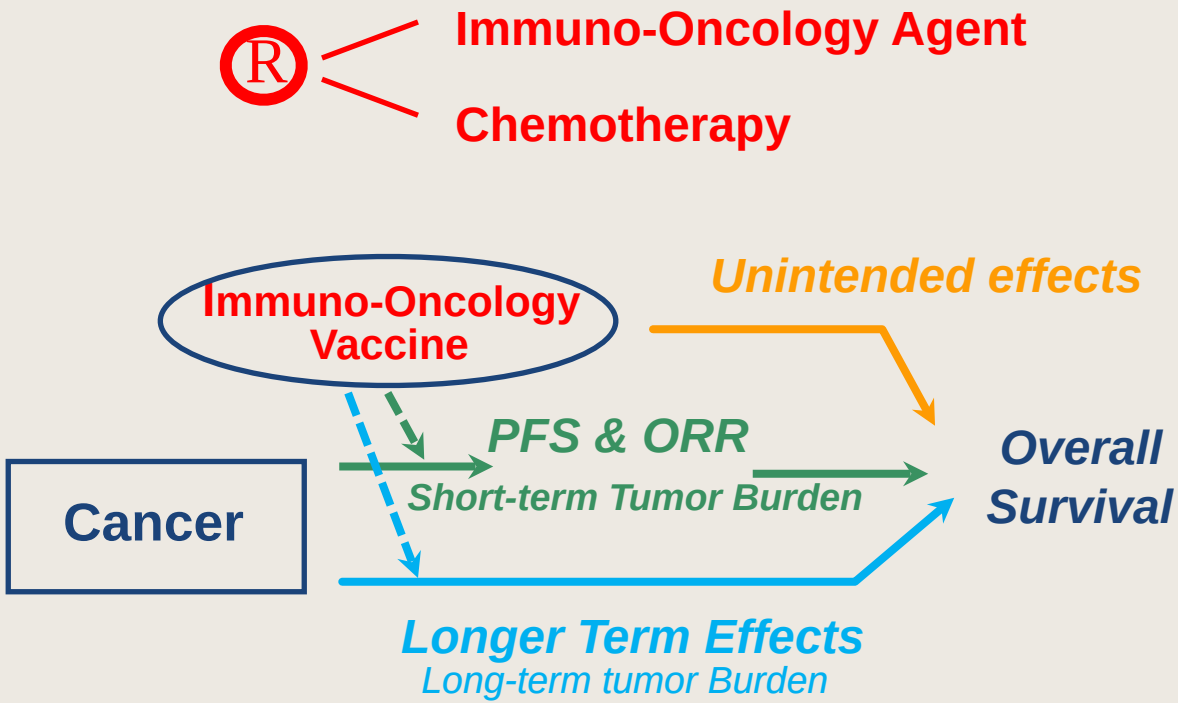


ESAs: ↑ **Thrombosis** ⇒ ↑ Mortality
Cox-2s, Muraglitazar, Rosiglitazone: ↑ **CV Risk Factors** ⇒ ↑ CV Death/ MI /Stroke
Troglitazone: ↑ **Serious Hepatic Risks** ⇒ ↑ Morbidity
Natalizumab: ↑ **Prog. Multifocal Leukoencephalopathy** ⇒ ↑ Morbidity / Mortality
Ezetimibe/Simvastatin: **Block pathways linked to CA prot.** ⇒ ↑ Cancer Mortality?
Long Acting *β*-Agonists: ↑ Asthma-related deaths
Torcetrapib: **Activates renin angiotensin system** ⇒ ↑ **BP** ⇒ ↑ Mortality
Revatio in Pediatric PAH: ↑ doses ⇒ Improved hemodynamics yet ⇒ ↑ Mortality



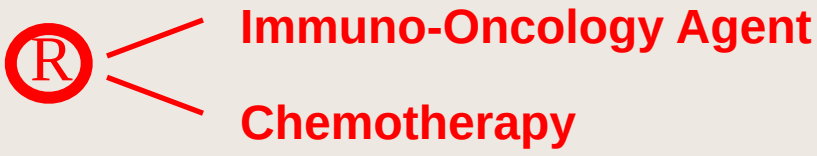


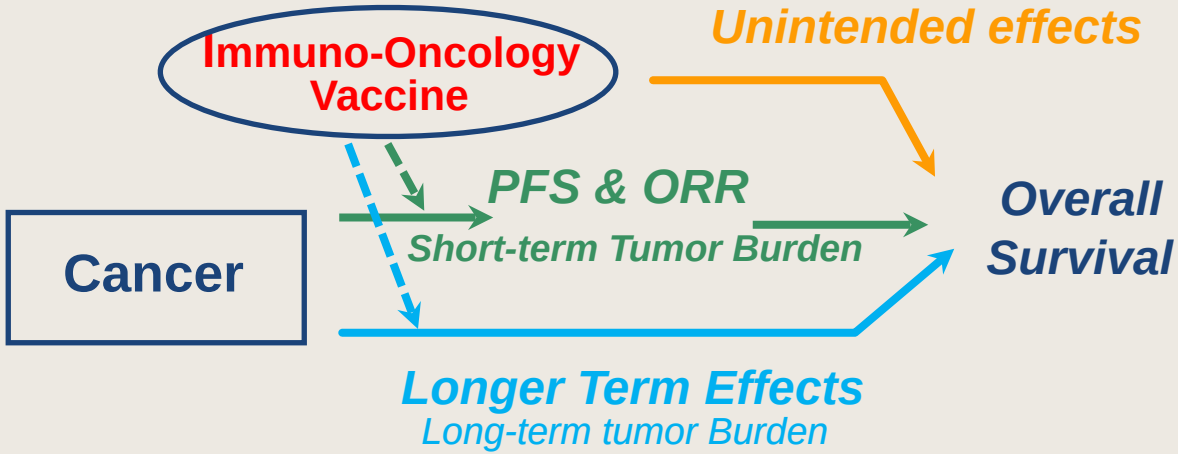
*The treatment's effect on the **Biomarker Endpoint** could overestimate or **underestimate** the treatment's true clinical efficacy*



DeMets DL, Psaty BM, Fleming TR. When can intermediate outcomes be used as surrogate outcomes? *JAMA* February 27, 2020

Different Classes of Agents





DeMets DL, Psaty BM, Fleming TR. When can intermediate outcomes be used as surrogate outcomes? *JAMA* February 27, 2020

Establishing Validity of a Replacement Endpoint

How does one establish a biomarker endpoint to be valid as a replacement endpoint for direct measures about how an individual 'feels, functions or survives'

Key Evidence:

The **net** effect of the treatrment
on the '*Replacement*' Endpoint
reliably predicts
the **net** effect of the treatment
on the *'Feels, functions, survives'* Endpoint

Illustration: Validating a Biomarker Surrogate

➢ **Anti-Hypertensives**

(> 500,000 patients from randomized trials)

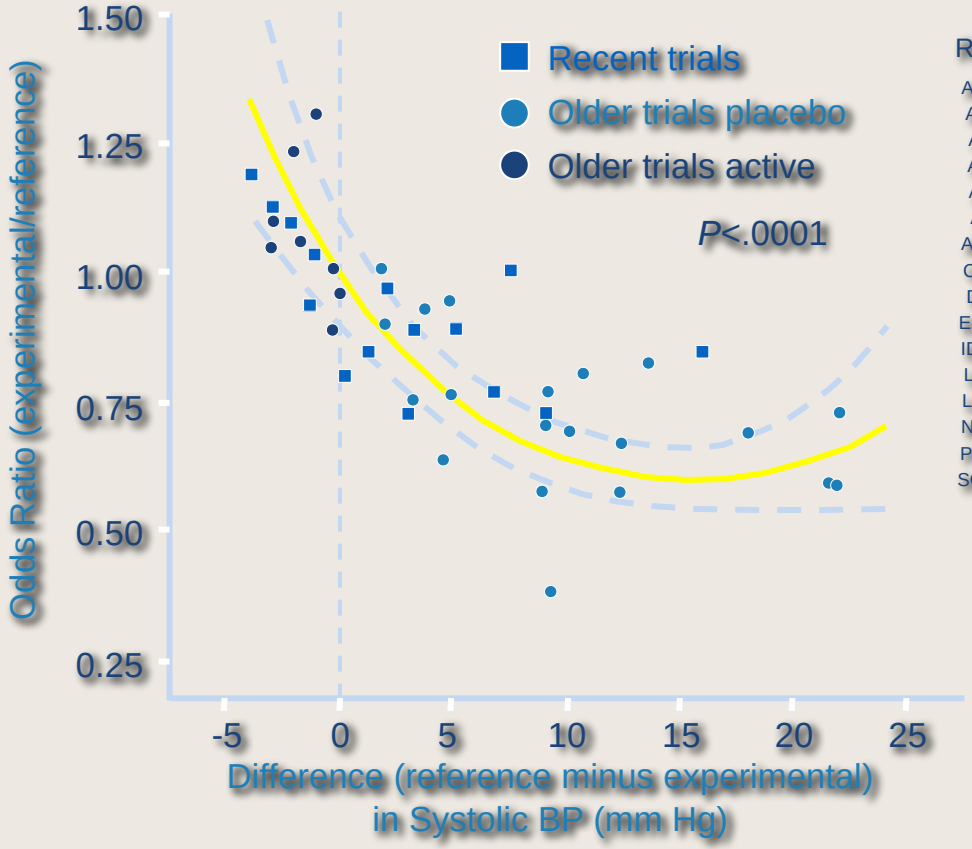
…β-blockers, low dose diuretics, ACE-I, CCBs, ARBs…

FDA Cardio-Renal Advisory Committee: **6/15/2005**

Effects on ***Blood Pressure*** predicting effects on each of the following, considered individually:

✓ *Stroke, MI, CVD, Mortality, Heart Failure*

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials



Recent

AASK L vs. H
ABCD/NT L vs. H
ALLHAT/Aml
ALLHAT/Lis
ALLHAT/Lis ≥65
ALLHAT/Lis Blacks
ANBP2
CONVINCE
DIABHYCAR
ELSA
IDNT2
LIFE/ALL
LIFE/DM
NICOLE
PREVENT
SCOPE

Older

ALLHAT/Dox
ATMH
EWPHE
HEP
HOPE
HO
HOT M vs. H
INSIGHT
MIDAS/NICS/VHAS
L vs. H
MRC
MRC2
PART2/SCAT
PATS
PROGRESS/Per
PROGRESSION/Com
RCT70-80
RENAAL
SHEP
STONE
STOP 1
STOP2/CCBs
STOP2/ACEIs
Syst-China
Syst-Eur
UKPDS C vs. A
UKPDS L vs. H

43 clinical trials

Staessen et al. *J Hypertens*. 2003;21:1055-1076.

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Institute of Medicine, 2010
"Evaluation of Biomarkers & Surrogate Endpoints"

- ***Addressing Assay Performance***

  …analysis of analytical performance of an assay…
  e.g., limit of quantitation, across lab reproducibility, etc

- ***Evidentiary Assessment***

  …relationship between biomarker & disease state
  …data regarding **effects of interventions on both biomarker and clinically meaningful outcomes…**

- ***Justifying the Proposed Use***

  …determining whether available evidence provides sufficient justification for the **context of use** proposed…

Replacement Endpoints

➢ A replacement endpoint **cannot** be assumed to be a generic surrogate endpoint for a particular disease

Reasons why use needs setting-specific justification:

— Multiple causal mechanisms of action
— *Breadth*, *Magnitude* and *duration* of effect matters
— Intended and *unintended* effects of intervention

➢ How does evaluating replacement endpoints impact the public?

Response: Need "*reliable*" as well as "*timely*" evaluation
…not simply *"a choice"*; rather, "*an informed choice*"

Some Uses of Biomarkers/Replacement Endpoints

- As Measures of **Biologic Activity** of Experimental Treatments
  - ✓ In Proof-of-Mechanism or Proof-of-Concept Trials
  - ✓ In Registrational Trials
- As **Replacement Endpoints** for Registrational Evaluations, in studies specifically intended to evaluate:
  - ✓ Refining dosing/schedules to address safety risks
  - ✓ Generalizing results to broader categories of patients
  - ✓ New treatments in the class of established effective treatments
  - ✓ New treatments that are in new classes

Straightforward justification

Very Challenging

Validation of Biomarker Endpoints: **Future Steps**

- Continued evaluation of aggregate data from clinical trials designed to **reliably** evaluate efficacy of OA treatments,
  - ✓ With inclusion being independent of level of trial positivity
  - ✓ With reliable estimation of each treatment's effect on:
    - Various biomarker endpoints (need standardized assays)
    - Direct measures of how patients 'feel, function, or survive'
- Increasing the number of properly controlled studies of treatments:
  - ✓ Ideally randomized
  - ✓ Ideally having standard-of-care controls
  - ✓ Ideally evaluating effects on **both** Biomarker & Clinical Endpoints

…**of particular importance for evaluation of new classes of treatments**…

Principles & Insights

"A Correlate does not A Surrogate Make"

* Fleming TR, DeMets DL: Surrogate endpoints in clinical trials: Are we being misled? *Annals of Internal Med* 1996; 125:605-613.

* IOM, 2010. *"Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease:*. Washington DC. National Academies Press

* Fleming TR, Powers JH: Biomarkers and Surrogate Endpoints in Clinical Trials *Statistics in Medicine* 2012; 31: 2973-2984