FDA-Arthritis Foundation
OA Drug Development Workshop

‘Statistical Considerations on the Use of Surrogate Endpoints’

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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 \textit{net} effect of the treatment on the biomarker, and
    ✓ the \textit{net} effect of the treatment on direct measures of how an individual feels, functions and survives
Osteo-Arthritis

Experimental Treatment

Placebo

Experimental Treatment

Unintended effects

‘Feels, Functions, Survives’ Endpoints

Biomarker Endpoint

Other Causal Pathways

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
Experimental Treatment
Placebo

Osteo-Arthritis

Experimental Treatment

Biomarker Endpoint

‘Feels, Functions, Survives’ Endpoints

Unintended effects

Other Causal Pathways

Treatments’ relative effects 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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKB</td>
<td>58%</td>
<td>(51%, 66%)</td>
</tr>
<tr>
<td>Aventis Pasteur</td>
<td>85%</td>
<td>(81%, 89%)</td>
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</tbody>
</table>

• Immunologic Biomarkers

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

**Experimental Treatment**

- 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

**Biomarker Endpoint**

‘Feels, Functions Survives’ Endpoints

**Unintended effects**
The treatment’s effect on the **Biomarker Endpoint** could overestimate or **underestimate** the treatment’s true clinical efficacy.

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**Osteo-Arthritis**

**Experimental Treatment**

**Placebo**

**Experimental Treatment**

**Biomarker Endpoint**

**‘Feels, Functions, Survives’ Endpoints**

**Other Causal Pathways**

**Unintended effects**
DeMets DL, Psaty BM, Fleming TR. When can intermediate outcomes be used as surrogate outcomes? *JAMA* February 27, 2020
Different Classes of Agents

Immuno-Oncology Agent
Chemotherapy

Cancer

Immuno-Oncology Vaccine

PFS & ORR
Short-term Tumor Burden

Long-term tumor Burden

Longer Term Effects

Unintended effects

Overall Survival

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

Illustration: Validating a Biomarker Surrogate

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✓ *Stroke, MI, CVD, Mortality, Heart Failure*
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...
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...
“A Correlate does not Make a Surrogate”

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