Traditional and Surrogate Endpoints: Principles and Examples

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Traditional & Surrogate Endpoints

**Traditional Endpoints**

- Patient Survival; Graft Survival; Acute Rejection

**Goal:** Discern the efficacy differences between different immunosuppressive regimens within the course of a 1-2 year clinical study with a feasible sample size

**Potential Replacement Endpoints**

- Histology: Subclinical Injury/Inflammation on Kidney Biopsy
- Donor Specific HLA Antibodies
- Composite Endpoint of Allograft Function (GFR, Histology, DSA) and Long Term Graft Function
Issues in Replacement (Surrogate) Endpoints

~ Criteria for Choosing Endpoints

~ “A Correlate does not a Surrogate Make”

~ Validation of Replacement (Surrogate) Endpoints
Some Characteristics for Primary Endpoints in Phase 3 Clinical Trials

- Consistently & readily measurable
- Sensitive
- Well defined & reliable
- Clinically meaningful

A “Clinically Meaningful Endpoint”: …a direct measure of how a patient “feels, functions or survives”…

… Robert Temple, FDA
Biomarkers & ‘Feels, Functions, Survives’ Endpoints

- **Biological Activity:** Hemodynamic Measures in PAH: $PVRI, \ mPAP, \ CO$
  $SBP, \ DBP, \ NT-proBNP$

- **Feels, Functions, or Survives**

  ~ **Functions:** Ability to conduct normal activities
    - Ability to walk, Ability to engage in recreational activities,
      Ability for self care, Risk of syncope
    - Time in hospital or missing school (overall, or cause specific)

  ~ **Feels:**
    - Chest pain, breathlessness, fatigue, dizziness

  ~ **Survives**
    - Physician or Observer administered & PROs...
Potential ‘Feels, Functions, Survives’ Endpoints

Patient Reported Outcomes (PROs):

“Any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else”.

Biomarkers & ‘Feels, Functions, Survives’ Endpoints

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“Biomarkers are measurements of biological processes. Biomarkers include physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images.

Cholesterol and blood sugar levels are biomarkers, as are blood pressure, enzyme levels, measurements of tumor size from MRI or CT, and the biochemical and genetic variations observed in age-related macular degeneration…”

Histology on Kidney Biopsy; Donor Specific HLA Antibodies; GFR

Categorization of Nomenclature
Outcome Assessments

Direct Measures of Patient “Functions, Feels, Survives”

- Patient (symptoms: chest pain, dyspnea, fatigue, dizziness)
- Clinician (PANNS for schizophrenia syndrome, Clinician Global Measures)
- Observer (seizures, infant behavior, stroke, death)

Indirect Measures

- Measures depending on patient motivation or clinician judgment to perform the test

Indirect Measures

- Biomarkers (e.g. HbA1c, CD-4, PSA, PVRI, NT-proBNP, CO HR, Blood Pressure, Pulm Arterial Pressure, TIMI-III flow, HDL, LDL, body temperature, urine GAG, urine KS cardiac rhythm, blood cultures, PCR, quantitative measures from radiology imaging)

# John Powers, Dave DeMets, Marc Walton, Laurie Burke, Bob Temple...
Biomarkers (as Replacement Endpoints)

...“Post hoc, ergo, Propter hoc”...

Treatment effects on Biomarkers:

• Establish *Biological Activity*

• But not necessarily the net effects on
  ~ How a patient feels
  ~ The ability to conduct normal activities
  ~ Overall Survival
Issues in Replacement (Surrogate) Endpoints

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The Biomarker Endpoint is not in the Causal Pathway of Disease Process
The Biomarker Endpoint is not in the Causal Pathway of the Disease Process.

- **Disease**: e.g., CD4 Trans of HIV
- **Biomarker**
- **Mother-to-Child**
- **HIV Viral Load**

- **Disease**: e.g., CEA, PSA
- **Biomarker**
- **Ca. Symptoms & Death**

- **Tumor Burden**
- **NT-proBNP in PAH**

- “Correlates”: Useful for Disease Diagnosis, or Assessing Prognosis
- “Valid Surrogates”: Replacement Endpoints
Multiple Pathways of the Disease Process

Intervention

Disease

Biomarker Endpoint

Feels, Functions or Survives Endpoint

Intervention

Disease

Biomarker Endpoint

Feels, Functions or Survives Endpoint
Biomarker (as a Surrogate) in Chronic Granulomatous Disease

- CGD $\rightarrow$ Recurrent Serious Infections
- Interferon $\gamma$ …Increase Bacterial Killing and Superoxide Production?

- International CGD Study Group Trial
  Interferon $\gamma$:
  - 70% Reduction in Recurrent Serious Infections
  - Essentially No Effect on Biological Markers
Multiple Pathways of the Disease Process

Disease

Intervention

Surrogate Endpoint

Feels, Functions or Survives Endpoint

Interferon $\gamma$

CGD

Bacterial Killing

Recurrent Serious Infections
Biomarker (as a Surrogate) in Acellular Pertussis Vaccines

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

- **VE**
  - SKB: 58% (51%, 66%)
  - Aventis Pasteur: 85% (81%, 89%)

- **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
Multiple Pathways of the Disease Process

Thrombolytic

M.I.

TIMI III
(Rapid II / Gusto III)

30-Day Mortality

What magnitude and what duration is needed?

Intervention

CGD

Biomarker Endpoint

Recurrent Serious Infections
Interventions having Mechanisms of Action Independent of the Disease Process

Disease

Intervention

Biomarker Endpoint

Feels, Functions or Survives Endpoint
Illustration:
Ventricular Arrhythmia after M.I.

- Arrhythmia:
  - Risk factor for Sudden Death
- Antiarrhythmic Drugs:
  - Class IC antiarrhythmic agents
    ...Strong Sodium-Channel Blockade

Cardiac Arrhythmia Suppression Trial:
The drugs, relative to placebo, TRIPLE the death rate.
Interventions having Mechanisms of Action Independent of the Disease Process

Intervention

Disease

Arrhythmia Suppression

Overall Survival
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
Issues in Replacement (Surrogate) Endpoints

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Validation of Replacement (Surrogate) Endpoints

Property of a Valid Replacement (Surrogate) Endpoint:

- **Net effect of the Intervention on the Replacement (Surrogate) Endpoint** reliably predicts the **Net effect of the Intervention on the ‘Feels, Functions, or Survives’ Endpoint**
Using Replacement (Surrogate) Endpoints for Direct Measures of ‘Feels, Functions, Survives’

Clinical
- Comprehensive understanding of the
  ~ Causal pathways of the disease process
  ~ Intervention’s intended and unintended mechanisms of action

Statistical
- Meta-analyses of clinical trials data
Mechanisms of Action of the Intervention & Causal Pathways of the Disease Process

Torcetrapib

CHD

HDL Cholesterol

LDL Cholesterol

SBP / DBP

CV Morbidity & Mortality
Using Replacement (Surrogate) Endpoints for Direct Measures of ‘Feels, Functions, Survives’

Clinical
- Comprehensive understanding of the
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- Meta-analyses of clinical trials data
Illustration of Validating a Surrogate

- Anti-Hypertensives
  (>500,000 patients from rand 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 and Older Trials


Odds Ratio (experimental/reference)

1.50
1.25
1.00
0.75
0.50
0.25

Difference (reference minus experimental) in Systolic BP (mm Hg)

Recent trials
Older trials placebo
Older trials active

P < .0001

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
- HOT
- 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

Slide: Henry Black’s lecture
Illustration of Validating a Surrogate

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

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

  ✓ Stroke, MI, CVD, Mortality, Heart Failure
Colon Adjuvant: Hazard Ratios for DFS vs. Overall Survival
• **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 deemed to be a generic surrogate endpoint for a particular disease.

**Reasons why use needs setting-specific justification:**

- Multiple causal pathways of the disease process
- *Magnitude* and *duration* of effect matters
- Intended and *unintended* effects of interventions

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

As “Correlates”…

• Disease Diagnosis

• Assessing Prognosis

• In Patient-specific Therapeutic Strategies

• Primary Endpoints
  in Screening or Proof of Concept Trials

• Measures of Biologic Activity
  in Confirmatory (registrational) trials
Uses of Biological Markers: High Clinical Utility

• As Replacement or “Surrogate” Endpoints…
  ...When one can fully capture effects on the principle causal mechanism of disease process (w treatment lacking key unintended mech)

• In Identifying Enriched Populations…
  …When the key mechanism(s) of Rx effect on the causal factor(s) of the disease process are specific to a targeted population (eg, gene) (w treatment possibly having unintended mech)
  ...EGFR Inhibitors: KRAS Wild Type vs. Mutation
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  ...Physician or Observer administered & PROs...
Direct Measures of ‘Feels, Functions, Survives’ in PAH

~ Overall survival ~ 6MWD @ 48 wks ~ Syncope (freq. & severity)
~ NYHA Functional Class (1-2 vs. 3-4) ~ Clinician Global Measures
~ Level of successful social interaction with peers (mod. CAMPHOR)
~ Days school missed for health-related reasons; Everyday living skills
~ Symptoms: SF-36, Borg Dyspnea Score, Pain Measures

Composites of measures of ‘Feels, Functions and Survives’:

~ (E.g. Acute Coronary Syndrome: CV Death, Stroke, MI)
  ✓ PAH: Death, L.T., PAH Hosp, (NYHA↑ & 6MWT↓)

~ (E.g. CABP: Cough, Pleuritic chest pain, Dyspnea, Sputum Prod)
  ✓ PAH: Chest pain, Dyspnea, Fatigue, Dizziness/Syncope

…..scored as Absent, Mild, Moderate, and Severe…..

The endpoint: a) one-point improvement in at least two symptoms
& b) no worsening of any other symptoms, at day TBD
“A Correlate does not A Surrogate Make”


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