Lankenau Medical Center
Main Line Health
Well ahead.®

The Role of Outcome Trials in Pulmonary Drug Development

Peter R. Kowey, MD, FACC, FAHA, FHRS
Lankenau Medical Center
Jefferson Medical College
Philadelphia

Disclosure: Kowey's Attitude

I have consulted for dozens of drug and device companies over the last 33 years. I have regularly counseled them to do whatever possible during pre-clinical and clinical development to avoid the need for an outcomes trial, which I regard as generally over-priced and over-rated.

However, when such a trial is absolutely needed, I have further advised them to plan wisely and spend liberally to get as close as possible to the truth since the results will be held as incontrovertible

Alternatively, no matter what you find, your results may be nitpicked to death by people with initials like SN or CF

Lankenau Medical Center
Main Line Health
Well ahead.®

Erich Fromm

"The task we must set for ourselves is not to feel secure, but to be able to tolerate insecurity."

Objective

The goal of an excellent development program is not to be arrive at absolute certainty regarding cardiac safety, but to be able to describe the nature and relative extent of the hazard for doctors and patients so they can decide if the benefit of therapy justifies the putative risk.

Priority Continuum

Are there factors that increase the probability of needing a robust outcome assessment?

- Target population (asthma vs COPD)
- Biological plausibility (HR/BP changes)
- Biomarker/surrogate evidence (ECG data)
- Event signal

TIOSPIR Precedent

- UPLIFT was a winner
- Residual question of a liability of a particular delivery system led to TIOSPIR
- Results recently brought into question in a letter to the NEJM because of an imbalance of one component of the composite primary endpoint (MI)

Lankenau Medical Center
Main Line Health
Well ahead.®

COPD: Why is it Unique?

- Patients have a high CV disease burden
- Hypoxia and metabolic disturbances can amplify cardiac harm
- Mostly elderly patients with multiple co-morbidities
- Routinely subjected to polypharmacy with endless potential for DDIs

Lankenau Medical Center
Main Line Health
Well ahead.®

OPEN HEART (Inaugural Issue)

"One year mortality in MI patients is significantly higher in those with COPD…"

"This increased risk falls substantially in analyses that controlled for both comorbidities and treatment patterns, pointing to a significant undertreatment of CV disease in this group."

Lankenau Medical Center
Main Line Health
Well ahead.®

Is an Outcomes Trial Ever an Imperative?

After all the we have heard today, is an outcome trial the default position?

Or is it a “preferred” alternative when other CV data are unclear?

Or are outcome trials mandated or suggested in specific target populations or disease states?

Lankenau Medical Center
Main Line Health
Well ahead.®

Reality-ville

We hope that careful consideration of the “nitty gritty” will increase the likelihood of ascertaining enough information to obviate a formal outcomes trial

However, in the end, how will regulators view a program that has few hard outcome events in treatment an placebo arms or (even worse) minor imbalances?

Sir Winston Churchill

"Success if the ability to go from one failure to another with no loss of enthusiasm."

Lankenau Medical Center
Main Line Health
Well ahead.®

Operational Issues

Population

- Selection
- Characterization of CV risk (by risk scores)
- Enrichment

Lankenau Medical Center
Main Line Health
Well ahead.®

Operational Issues

Endpoints (obscured in COPD patients)

- MACE
- Heart Failure exacerbations
- Arrhythmic events
- Hospitalizations
- Revascularizations
- Deaths (overall and CV)

Lankenau Medical Center
Main Line Health
Well ahead.®

Operational Issues

Dose and drug delivery

- Intermittent or continuous
- Ordinary duration
- Controls (active versus placebo)

Other Operational Issues

Missingness (drug versus study withdrawal)

Study duration

Event versus enrollment driven

Adequacy of information regarding background Rx

Adequacy of CV Rx

Lankenau Medical Center
Main Line Health
Well ahead.®

Outcomes Trial: How to Avoid Them

- Start out with the assumption that cardiac safety will be a priority review item
- Define the patient population well, enriching some studies
- Provide adequate control groups with well understood background therapy
- SOP for collection and definition of cardiac AEs
- Adjudication of pooled safety data set

Outcome Study Deferred

Outcomes trials may be preferred but not necessarily before approval

Consider ways to stage the analysis to maximize information available for regulatory review

Define dose and details about drug administration to maximize the chances for a successful trial

Risk/Benefit

A higher priority should be placed on issues of cardiac safety for drugs for which the incremental benefit beyond what is otherwise available has not been well established.

Oscar Wilde

"If one tells the truth, one is sure, sooner or later, to be found out."

Lankenau Medical Center
Main Line Health
Well ahead.®