Estimands: Clinical Perspective

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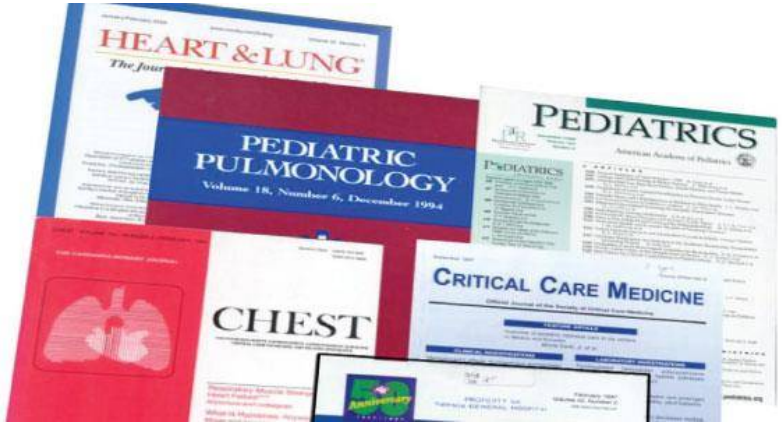
Objectives

The discuss the clinical implications of using the treatment policy estimand:

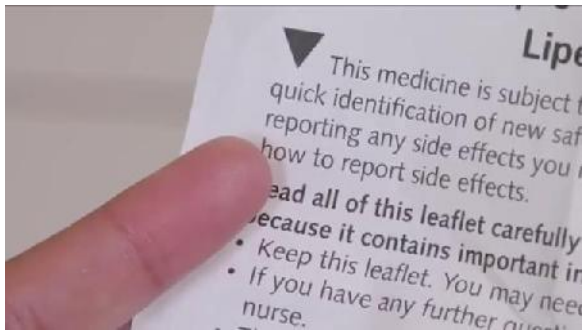
- Design of clinical trials to minimize missing data for patients on treatment
- Data to be collected post study drug discontinuation
- Clinical interpretation of the treatment effect
- Analyses needed to understand the magnitude of the treatment effect



New drug recently approved based on positive Benefit/Risk assessment

Understanding the Clinical benefit:

- Disease/endpoints knowledge
- How Clinical benefit compares with the effect of already approved drugs



Definition of the Benefits I want to observe for a new drug

Discovery new drug

Preclinical development

Clinical development

Registration

New drug marketed and prescribed

Design of the studies to be included in the Clinical program to Support the approval of product

Results

Clinical Trial Design: planing phase

Trial objective(s)

Estimand(s)

Target Product Profile:

- Usually defined in relation to competitors profile
- Superiority, comparable effect (BE, non-inferiority, etc)

Regulatory guidelines

Comprehensive review of Clinical development plans of previously approved drugs in the same indication

- Which were the main concerns during regulatory evaluation?

Validated tools and Minimal Clinical Important Difference (MCID)

= specification of the effect to be estimated in a Clinical trial

The description of an estimand includes 4 attributes:

Population	• Based on Inclusion/Exclusion criteria
Variable or outcome measure	• Assessments of interest based on study objective
Intercurrent events (confounding factors)	• Early discontinuation • Intake prohibited medication, rescue medication • Non-compliance • Death, etc
Population-level summary measure	• Summary measure for the variable (i.e. mean change, % patients, time to event)

Intercurrent events: "Traditional" analysis approach

No data collected post-IP discontinuation

Protocol defines washout periods for the assessment of a variable since last intake of rescue medication

- Example: washout of 6h after salbutamol intake before an FEV1 assessment of a long-acting bronchodilator

Handling of missing data post-IP outcomes using pre-discontinuation information Efficacy ("on-treatment") Estimand

Imputation:

- LOCF
- WOCF
- BOCF
- Multiple imputation..etc

No-imputation: direct-likelihood approach (MMRM)

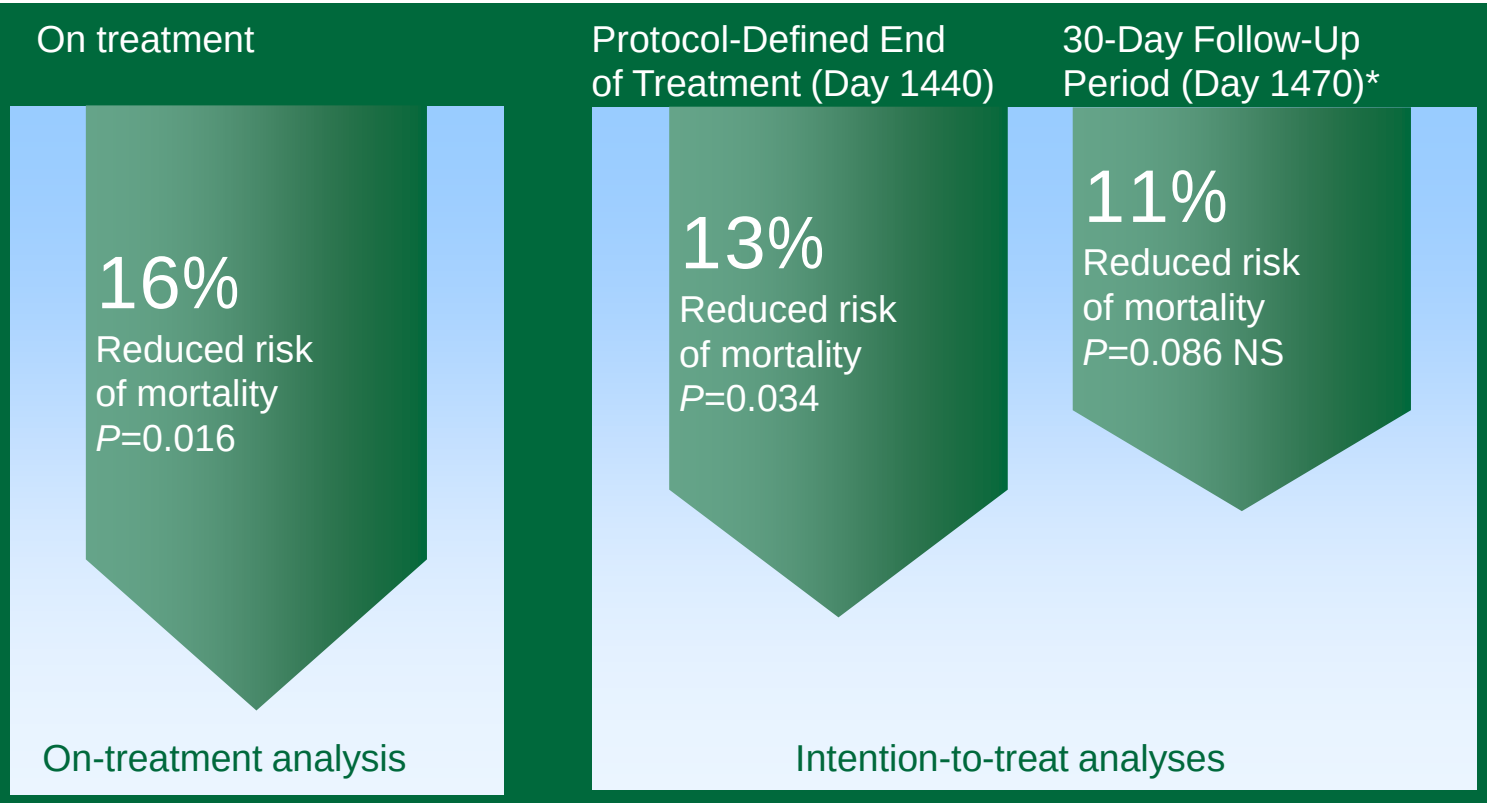
We (clinicians) tend to simplify things…..

Statistician		Clinician
Treatment Policy estimand (or de facto)	→	"on study" analysis
While on treatment estimand (or efficacy or de jure)	→	"on treatment" analysis

How things are evolving?

- Precedent for anti-diabetic drugs (dapagliflozin)
  - Initially the “on treatment” estimand (excluding post-rescue treatment) was accepted
  - However, during evaluation period “treatment policy” estimand utilizing all data, including data collected after rescue medication was also requested
- Respiratory drugs:
  - Precedents: use of “on treatment” estimand to evaluate the treatment effect of bronchodilators in lung function, symptoms and exacerbations
  - Mortality or CV outcome studies “on-study” analysis (instead of the “on-treatment” analysis) have been used and consequently patients who discontinued treatment were followed up until study completion
  - Recently, “treatment policy” estimand has been also requested by regulators for other endpoints such as exacerbations

UPLIFT study: Reduced Risk of Mortality



- 16% lower mortality risk with tiotropium while patients received study medication
- Effect extended to end of treatment period (day 1440), as defined by protocol
- Effect became non-significant within the 30-day follow-up period (day 1470), when according to protocol, patients were discontinued from their study medication

Example:
Lung function of dual bronchodilators in COPD

Umeclidinium/vilanterol: Trough FEV1 at 6 m

Treatment	n	Trough FEV_1 (mL) at Day 169 — Difference From: Placebo (95% CI) n = 280	Umeclidinium 62.5 mcg[a] (95% CI) n = 418	Vilanterol 25 mcg[a] (95% CI) n = 421
ANORO ELLIPTA	413	167 (128, 207)	52 (17, 87)	95 (60, 130)

n = Number in intent-to-treat population

Tiotropium/olodaterol: Trough FEV1 at 6 m.

	Trial 1			Trial 2		
	n	Mean (L)	Difference(L) (95% CI)	n	Mean (L)	Difference(L) (95% CI)
Trough FEV_1 response						
STIOLTO RESPIMAT	521	0.134	-	497	0.145	-
Tiotropium 5 mcg	520	0.065	0.071 (0.047, 0.094)	498	0.096	0.050 (0.024, 0.075)
Olodaterol 5 mcg	519	0.054	0.082 (0.059, 0.106)	503	0.057	0.088 (0.063, 0.113)

Glycopyrrolate/formoterol: Trough FEV1 at 6 m.

Treatment	N	Trough FEV_1 (mL) at Week 24 — Difference from: Placebo* LS Mean (95% CI)	Glycopyrrolate 18mcg BID* LS Mean (95% CI)	Formoterol Fumarate 9.6 mcg BID* LS Mean (95% CI)
Trial 1				
BEVESPI AEROSPHERE	429	N=161 150 mL (114, 186)	N=344 59 mL (31, 88)	N=367 64 mL (36, 92)
Trial 2				
BEVESPI AEROSPHERE	433	N=170 103 mL (67, 140)	N=367 54 mL (25, 83)	N=350 56 mL (27, 85)

N = Number in the intent-to-treat population

Description of the treatment effect of these combination of long acting bronchodilators vs each monotherapy (and placebo) in the label is based on the “on treatment” estimand

Treatment Policy Estimand
Applicability to Lung Function studies

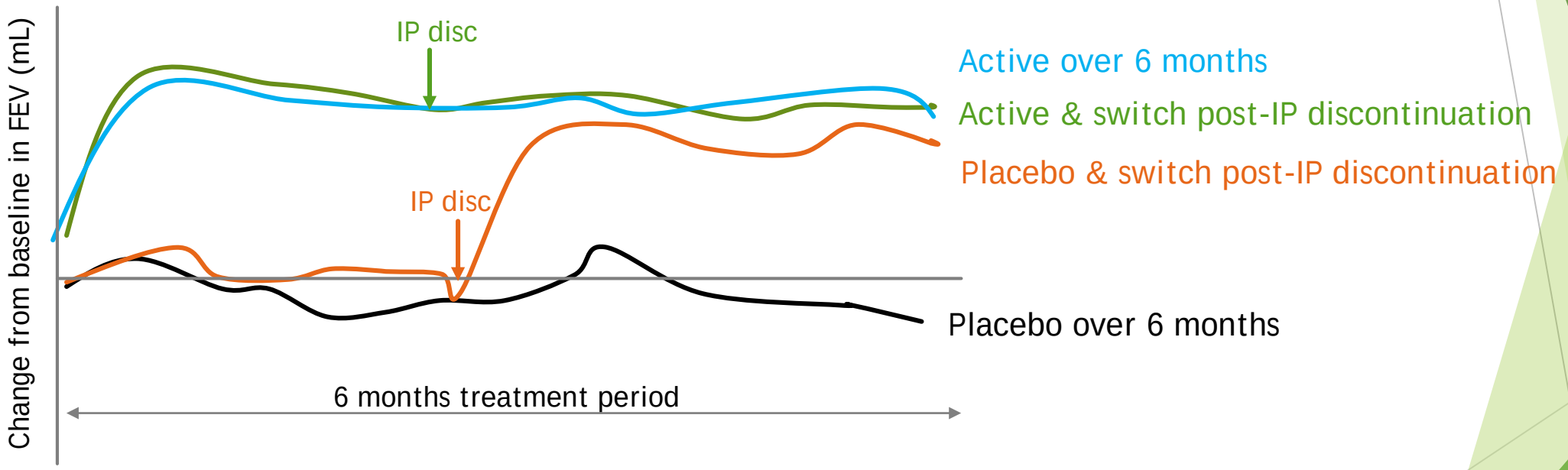
Treatment Policy: The occurrence of the intercurrent event is irrelevant the value for the variable of interest is used regardless of whether ot not the intercurrent event occurs

- All patients and all data on these patients are included until the end of the study
- Includes data on patients who switch to alternative treatments

Which is the problem?:

- Lung function outcomes measure is relatively short term, so the outcome is a mixture of the effect of randomized drug and rescue medication
- May be difficult to interpret unless rescue medication is carefully controlled or few discontinuations
- This approach has been requested by some regulators for this type of outcome

Implications of changing the estimand as compared to what has been used in previous approved drug: treatment effect of a new bronchodilator



More discontinuations are expected in placebo than active Treatment policy estimand is anticipated to reduce the treatment effect vs placebo

Different approaches with estimands depending on the endpoint and drug?

Bronchodilator

Main characteristics of drug A:

- Fast onset of BD effect (miniutes), short half life (5-8h) complete washout 2 days after interruption

Lung function:

Treatment effect for most bronchodilators have been established vs placebo (no background medication except rescue medication) using "on treatment" estimand

Drug A vs placebo or drug B (which is less effective) reduced effect using treatment poligy if higher drop-outs

Exacerbations:

Study vs placebo (on top of background medication to reduce risk), however still limited treatment effect (20%)

FDA requests to use treatment policy, however no precedents of approved indications using that estimand and sponsors feel more comfortable using "on-treatment" estimand

Monoclonal antibody

Main characteristics of drug A:

- Onset of effect after 4 weeks, long half life (25 d) complete washout 4 months after interruption
- To be used as adjuntive therapy to other active drugs

Lung function:

Limited effect as it acts binding anti-inflammatory citokines

FEV1 effect will remain after early discontinuation

Exacerbations:

Magnitude of improvements in exacerbation reduction are greater than with bronchodilators

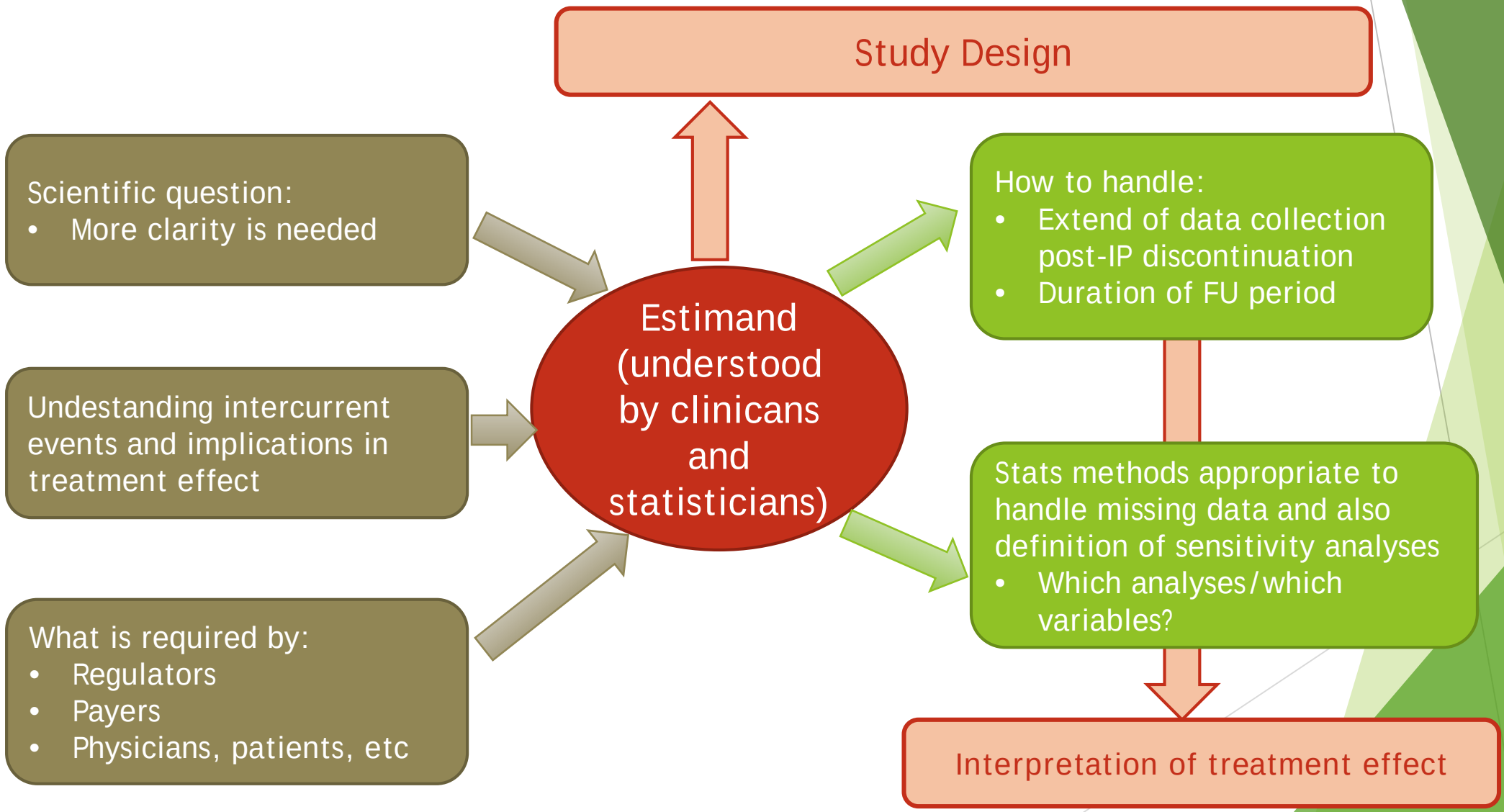
"Treatment policy" estimand has been accepted by sponsors

However clinicians are concerns on impact on results depending on the extend of study drug discontinuation and relation to total study duration

Questions from a Clinical perspective

- Threshold (i.e. MCID) for Clinical relevance used by regulators for new drugs after ICH E9 Addendum on estimands?
- Which results will be reflected in the label?
- How physicians will assess treatment effect vs previously approved products?
  - Physicians are not familiar with these methodological problems with missing data
- Is sensitivity analysis using “on treatment” estimand needed?
- Is the “treatment policy” applicable to all study designs/endpoints or is there room for discussion with regulators?
  - Superiority, therapeutic equivalence, non-inferiority
  - Clinicians vs statisticians approach may be different
  - What about payers?

Considerations to define the estimand for a study



What clinicians should consider

- To understand implications when using a different estimand from the one we have been “traditionally” used at disease, endpoint and type of drug level
  - Agreement between regulatory agencies (FDA, CHMP, PMDA, etc) and its members (clinicians, statisticians, etc)
- Multidisciplinary approach when defining estimands for each study involving clinicians, statisticians, regulatory, comercial, etc
  - Study designs will need to be adapted based on the estimand selected
  - Cost increase due to data collection after early discontinuation
  - Sample size adjusted based on the assumptions for the estimand

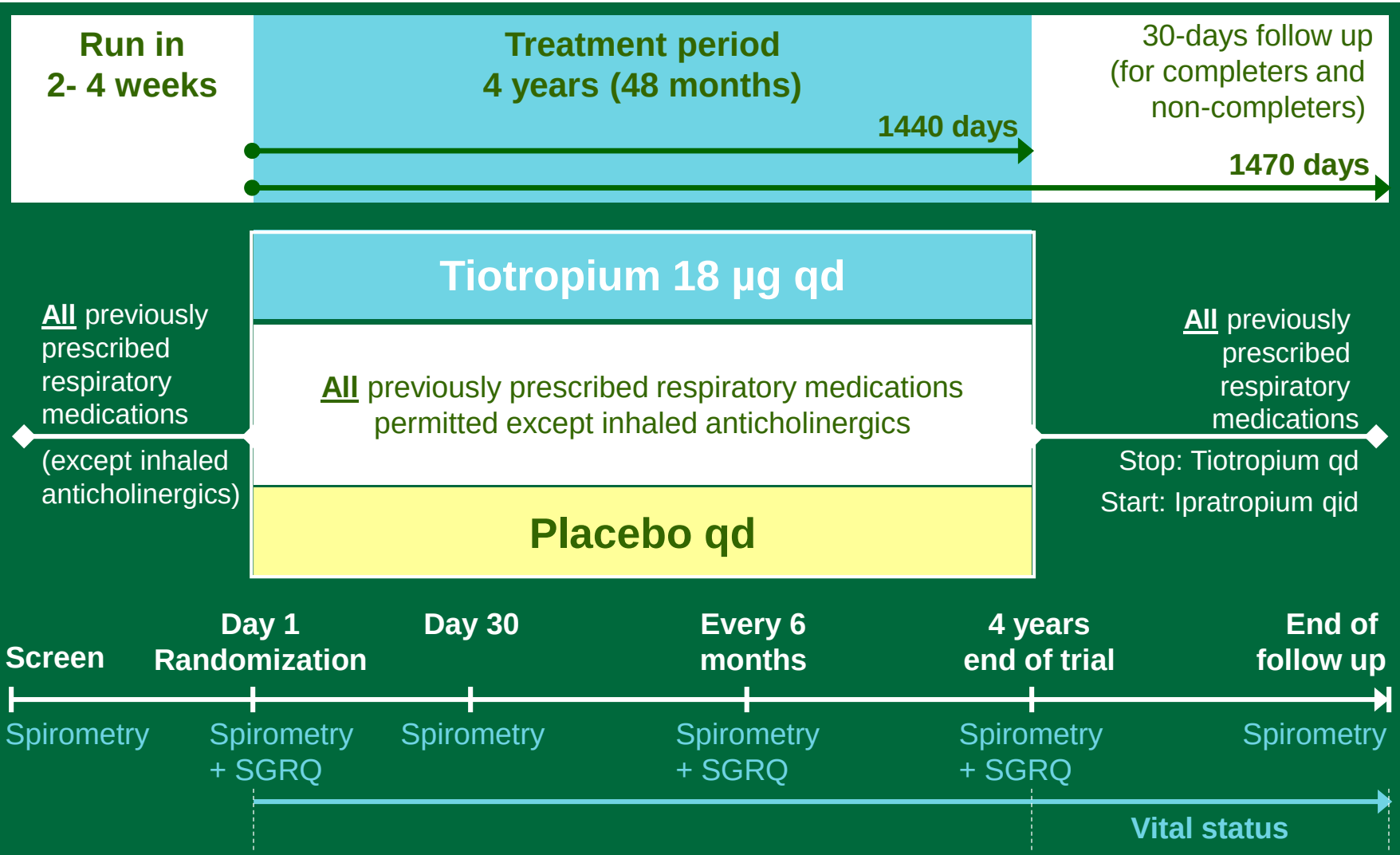
Conclusions

1. During the development of new compounds regulatory agencies are already requesting sponsors to use treatment policy estimand
2. Treatment policy estimand definition requires a multidisciplinary discussion
3. Collection of data after early discontinuation should be defined in the protocol (which endpoints, duration FU period, etc?)
4. To anticipate implications in the analysis and interpretation of results
5. Further clarity is still required, specially to better understand how regulators and physicians would evalute the treatment effect of a new compound in comparison with previously approved ones

MOITAS GRAZAS

Thanks!!

UPLIFT® Design and Method



SAAC = short-acting anticholinergic; SGRQ = St George's Respiratory Questionnaire

Fatal Events in UPLIFT®: Definitions

On-treatment

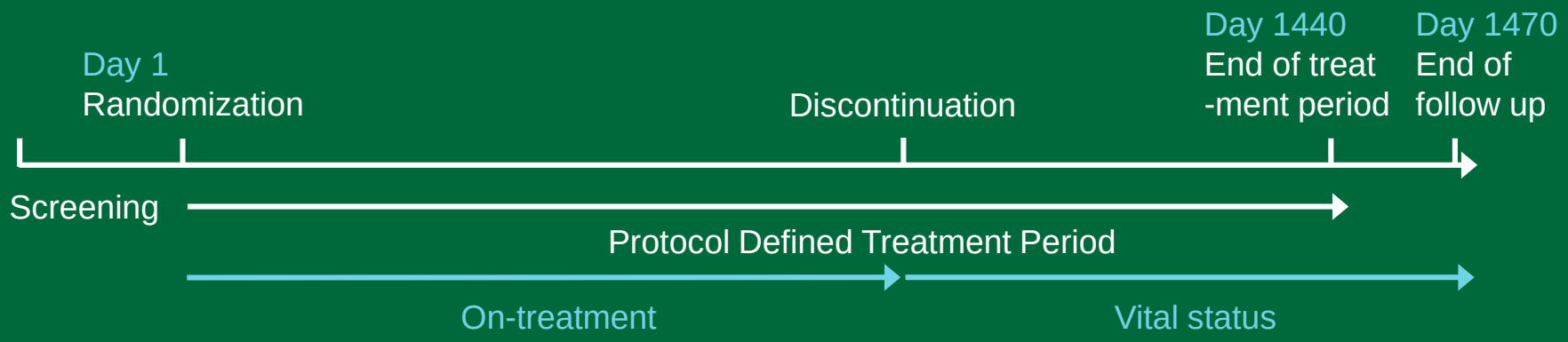
- First to last day of treatment + 30 days

Vital status (intention to treat)

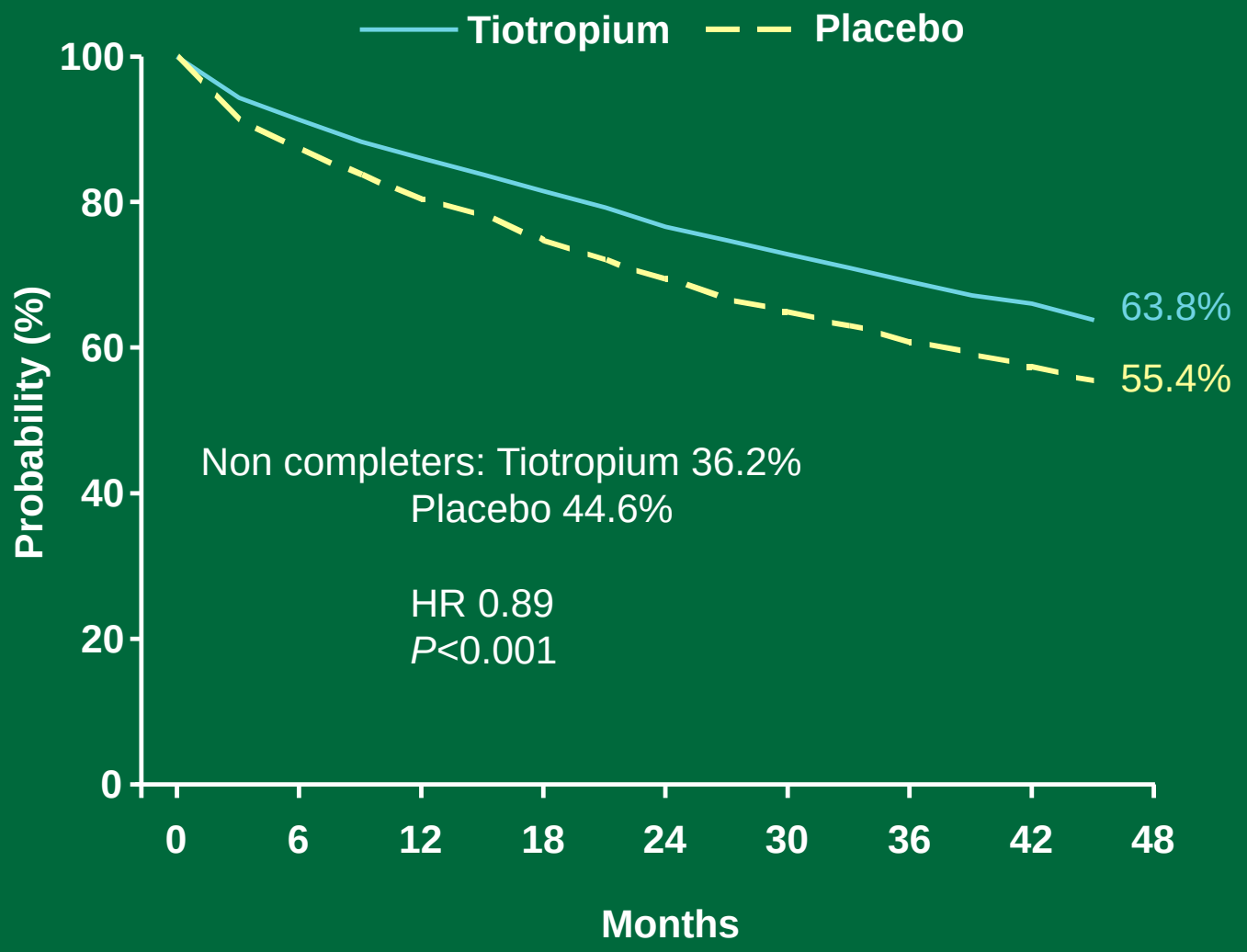
- 4 years (Day 1440)
- 4 years + 30 days follow-up (Day 1470)

Cause of death

- Investigator
- Mortality adjudication committee



Probability of Completion Is Higher with Tiotropium than with Control



UPLIFT® Study data on file, Boehringer Ingelheim/Pfizer

Conclusions

1. During the development of new compounds regulatory agencies are already requesting sponsors to use treatment policy estimand
2. Use of treatment policy estimand requires a multidisciplinary discussion to define the optimal study design
3. Collection of data after early discontinuation should be defined in the protocol (which endpoints, duration FU period, etc)
4. Important to anticipate the implications in the analysis and interpretation of results
5. Further clarity is still required, specially to better understand how regulators and physicians would evalute the treatment effect of a new compound in comparison with previously approved ones