Where we are with Estimands?

IBIG forum 2019

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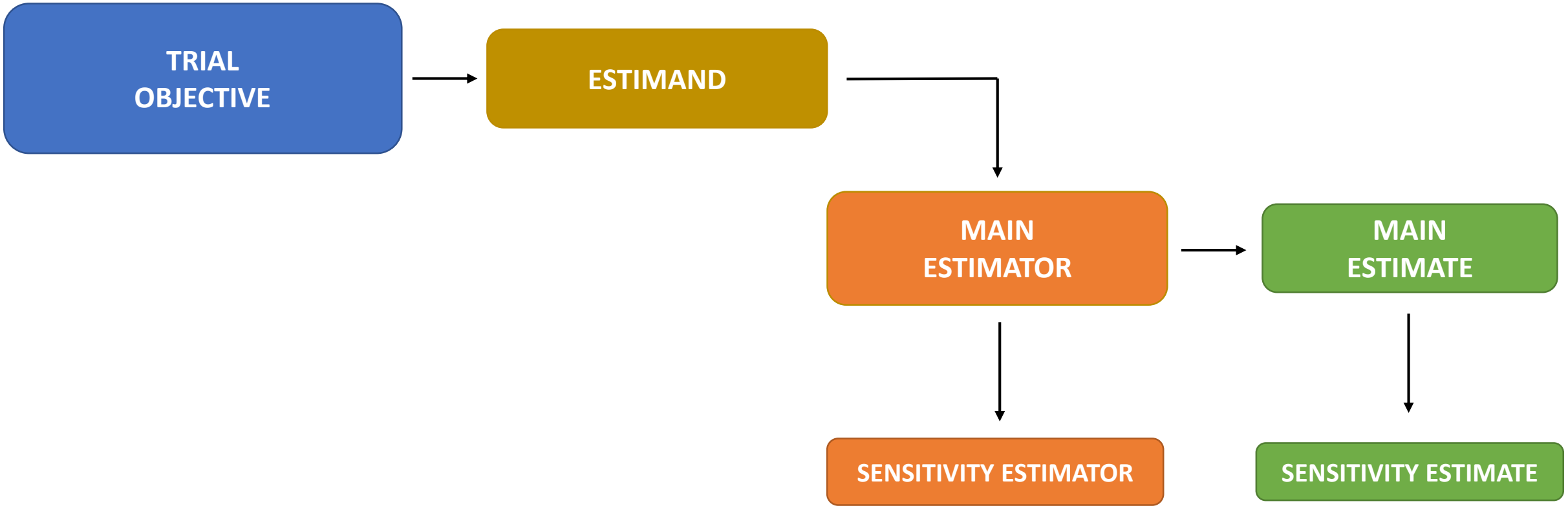
GUIDANCE DOCUMENT ON ESTIMANDS

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- E9 (R1) addendum on Estimands and Sensitivity Analysis in Clinical Trials
- Guideline on statistical principles for clinical trials
- Current thinking of the Food and Drug Administration (FDA) on the topic

PROPOSED WORKFLOW

UNIVERSITÀ DEGLI STUDI DI PADOVA



TRIAL OBJECTIVE

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- What is the scientific question that must be addressed?
- Quantify treatment effects
- Device or medication vs. placebo or control

DEFINITION OF ESTIMAND

ESTIMAND

Definition of 4 attributes:

1) The **population**, i.e. patients targeted by the scientific question
2) The **variable** to be obtained to address the scientific question
3) How to account for **intercurrent events**
4) The **summary statistics** that quantifies the treatment effect

INTERCURRENT EVENTS

- ***Treatment policy strategy***: occurrence of the intercurrent events is ignored
- ***Composite strategy***: the intercurrent event is integrated with the measures of clinical outcome as the variable of interest
- ***Hypothetical strategy***: definition of a scenario in which the intercurrent event would not occur
- ***Principal stratum strategy***: target population as the subjects that would not experience the intercurrent event
- ***While on treatment strategy***: consider the value of a variable prior to the occurrence of the intercurrent event

TRIAL DESIGN AND CONDUCT

- The choice of the estimand must be reflected in the design of the trial
  - Example: if the occurrence of an intercurrent event is not of interest, the values of the variable are collected regardless of the occurrence of the intercurrent event

- Sample size calculation should be implemented accounting for the strategies adopted to handle intercurrent events

- Multiple objectives with multiple estimands ⟶ Multiplicity issues

TRIAL ANALYSIS: MAIN ESTIMATION

MAIN ESTIMATION

- Estimands expressed through analytic approaches
- Provide an interpretable estimation
- Clearly definition of the assumptions, which should be justifiable

TRIAL ANALYSIS: SENSITIVITY ANALYSIS

SENSITIVITY ANALYSIS

- Evaluate the robustness of the estimand
  - How results change when different imputation strategies are considered for missing data
- Investigate how the estimates change if departures from the assumptions are encountered
- Change one assumption at a time

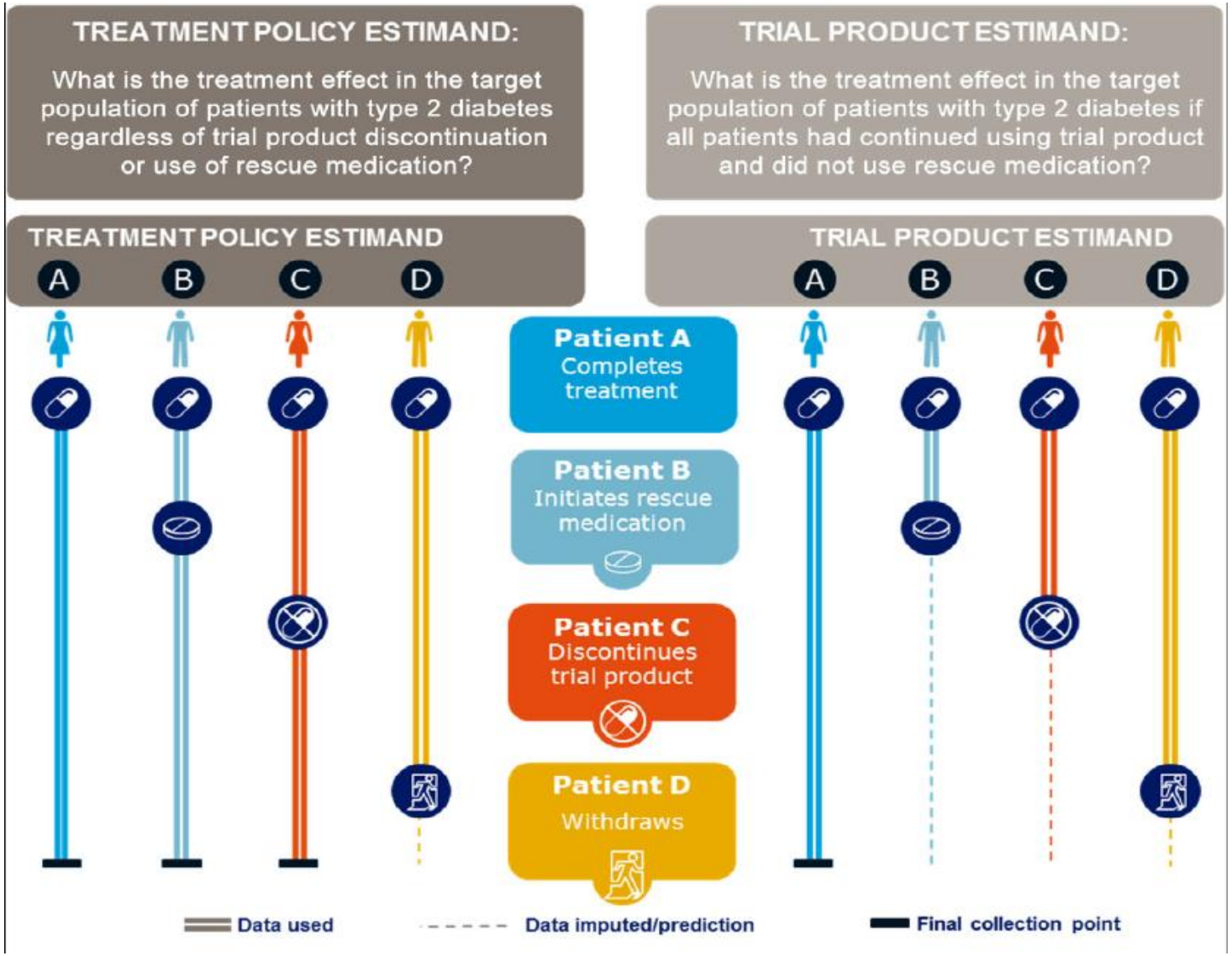
PIONEER 1 RCT

PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes

*Vanita R. Aroda,[1,2] Julio Rosenstock,[3] Yasuo Terauchi,[4] Yuksel Altuntas,[5] Nebojsa M. Lalic,[6] Enrique C. Morales Villegas,[7] Ole K. Jeppesen,[8] Erik Christiansen,[8] Christin L. Hertz,[8] and Martin Haluzík,[9] for the PIONEER 1 Investigators**

Diabetes Care 2019;42:1724–1732 | https://doi.org/10.2337/dc19-0749

PIONEER 1 RCT: DEFINITION OF ESTIMANDS



PIONEER RCT 1: MAIN ESTIMATION

- **Treatment policy estimand:** *mean difference between oral semaglutide and placebo in change from baseline to Week 26 in HbA1c and body weight in patients with type 2 diabetes, regardless of trial product discontinuation and/or addition of rescue medication.*

- **Trial product estimand:** *mean difference between oral semaglutide and placebo in change from baseline to Week 26 in HbA1c and body weights in subjects with type 2 diabetes if all patients had continued to use trial product for the entire planned duration and did not use rescue medication.*

PIONEER RCT 1: STATISTICAL METHODS

Treatment policy estimand:

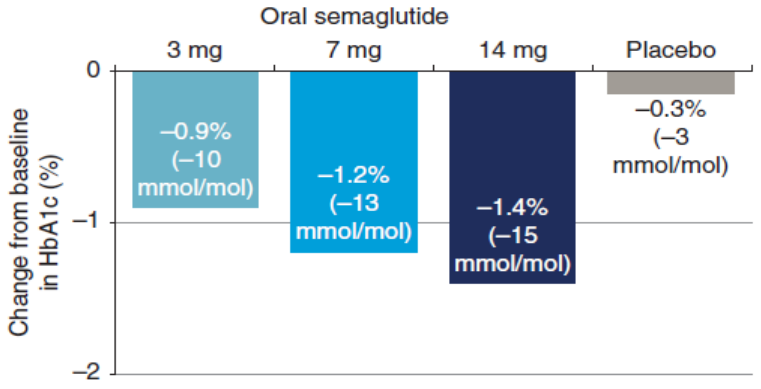
- *Pattern mixture model, using multiple imputation to handle missing data from Week 26 for both endpoints (imputation undertaken within groups)*
- *The aim is to assess the efficacy of the product*

Trial product estimand:

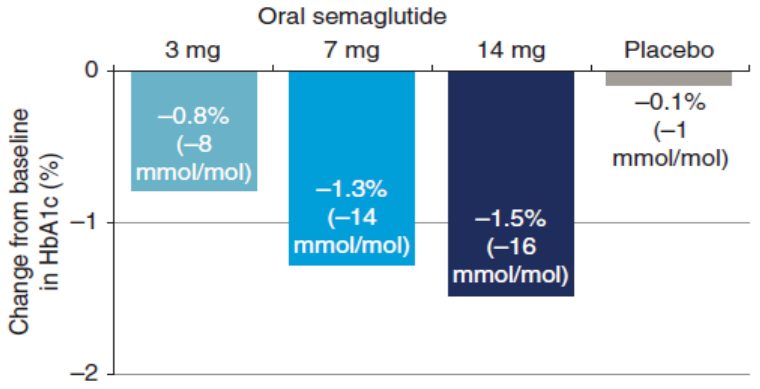
- *Mixed model for repeated measures with treatment, region and baseline value as fixed effects and visit as random effects, using multiple imputation to handle missing data (imputation undertaken within groups)*
- *The aim is to assess the anticipated effect of the trial product*

PIONEER RCT 1: RESULTS

(A) HbA1c

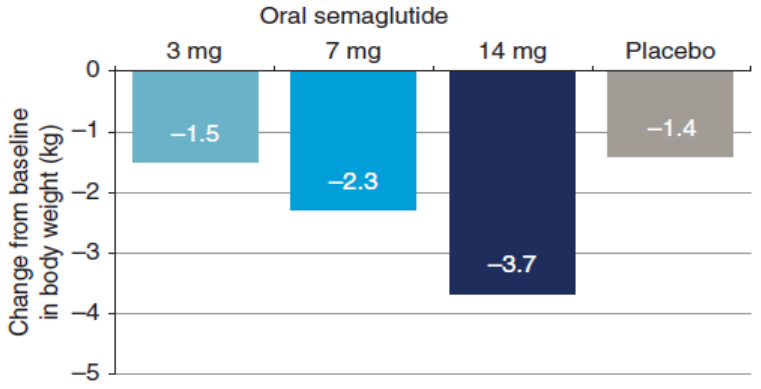


ETD [95%CI]: %; mmol/mol; *P* value
Oral semaglutide 3 mg vs placebo:
−0.6 [−0.8 to −0.4]%; −6 [−9 to −4] mmol/mol; *P*<0.001
Oral semaglutide 7 mg vs placebo:
−0.9 [−1.1 to −0.6]%; −9 [−12 to −7] mmol/mol; *P*<0.001
Oral semaglutide 14 mg vs placebo:
−1.1 [−1.3 to −0.9]%; −12 [−15 to −9] mmol/mol; *P*<0.001

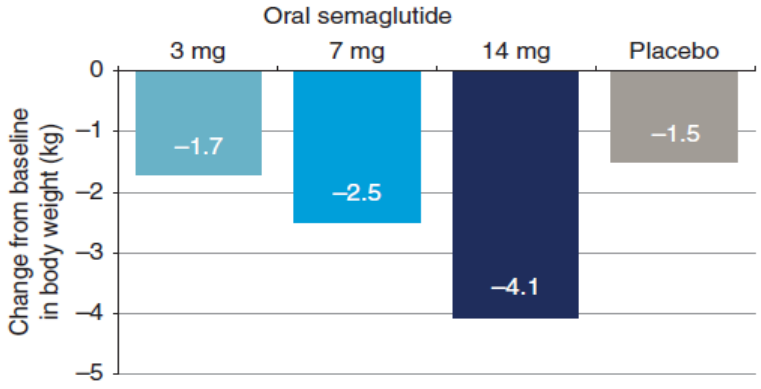


ETD [95%CI]: %; mmol/mol; *P* value
Oral semaglutide 3 mg vs placebo:
−0.7 [−0.9 to −0.5]%; −7 [−10 to −5] mmol/mol; *P*<0.001
Oral semaglutide 7 mg vs placebo:
−1.2 [−1.5 to −1.0]%; −14 [−16 to −11] mmol/mol; *P*<0.001
Oral semaglutide 14 mg vs placebo:
−1.4 [−1.7 to −1.2]%; −16 [−18 to −13] mmol/mol; *P*<0.001

(B) Body weight



ETD [95%CI]: kg; *P* value
Oral semaglutide 3 mg vs placebo: −0.1 [−0.9 to 0.8] kg; *P*=0.87
Oral semaglutide 7 mg vs placebo: −0.9 [−1.9 to 0.1] kg; *P*=0.09
Oral semaglutide 14 mg vs placebo: −2.3 [−3.1 to −1.5] kg; *P*<0.001



ETD [95%CI]: kg; *P* value
Oral semaglutide 3 mg vs placebo: −0.2 [−1.0 to 0.6] kg; *P*=0.71
Oral semaglutide 7 mg vs placebo: −1.0 [−1.8 to −0.2] kg; *P*=0.01
Oral semaglutide 14 mg vs placebo: −2.6 [−3.4 to −1.8] kg; *P*<0.001

FINAL REMARKS

- ICH E9 (R1) addendum describes a general framework and a concept of estimand
- More estimands allow the evaluation of treatment effect from different perspectives
- Intercurrent events should always be clearly included in the estimands of interest
- Sensitivity analyses are fundamental to test the robustness of the estimates

Thank you!