The Estimands Academy for Trial Teams

"Bringing estimands to *life* through real case studies"

Webinar 1: PIONEERing estimands in Clinical Development

US/EU webinar: 12th January 2021 3-4:30 pm UK /4-5:30 pm CET/10-11:30 am EST/7-8:30 am Pacific time

EU/ASIA webinar: 19th January 2011 9-10:30 am UK/10-11:30 am CET/4-5:30 pm Shanghai

EFSPI
European Federation of Statisticians in the Pharmaceutical Industry
Representing Statistical Associations in Europe

efpia
European Federation of Pharmaceutical Industries and Associations

EFPIA / EFSPI Estimand Implementation Working Group (EIWG)

EIWG brings together statisticians and clinicians to support the estimand journey

Estimand Implementation Working Group (EIWG) Members

Institution	Member
AMGEN	Mary Elliott-Davey
AstraZeneca	David Wright
BAYER	Vivian Lanius
Boehringer Ingelheim	James Bell
CONSILIUM Salmonson & Hemmings	Rob Hemmings*
PT Stat Consulting	Paul Terrill
gsk	**Chrissie Fletcher**+
	Oliver Keene
	Jatin Patel (C)
	Millie Wang (C)

Institution	Member
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LEO	Christian Pipper
Lilly	Pepa Polavieja
Lundbeck	**Nanco Hefting**+ (C)
	Mette Josiassen
medac	Michael Tribanek
MERCK	Armin Schueler
mundipharma	Nick Manamley
NOVARTIS	Melanie Wright
novo nordisk®	Helle Lynggaard
	Rikke Mette Agesen (C)

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Pfizer	Maria Dilleen
	Rod Junor (C)
PPD®	Sue McKendrick
	Nikolay Stoyanov (C)
Roche	Judith Anzures-Cabrera
SERVIER	Estelle Lambert
ucb	Christian Loesch
	Katsumi Yoshida
	Amel Besseghir

+Co-Lead *Adhoc member C = Clinician

Disclaimer

- Opinions are those of the presenters and are not necessarily the views of all our respective companies.

Introductions

	**Nanco Hefting** is Chief Scientific Specialist in the Clinical Research – Psychiatry department at H. Lundbeck A/S and is the **Co-Chair of the EIWG**. **Moderator of this session.**	
	**Sue McKendrick** is an Associate Statistical Science Director **leading the cross-functional Estimand Working Group at PPD** and is also a member of the EIWG training team. **Co-Presenter.**	
	**Melanie Wright** is a Biostatistics Global Group Head and has **led the development and roll-out of a cross-functional training on estimands at Novartis**. Mel is also a member of the EIWG training team. **Co-Presenter.**	
	**Rikke Mette Agesen** is a **Senior International Medical Manager at Novo Nordisk**. Rikke holds a PhD in Type 1 diabetes and hypoglycaemia. Rikke helps to provide the physician's perspective at the EIWG.	
	**Helle Lynggaard** is a Principal Statistician and is a **key driver in implementing estimands in Novo Nordisk studies**. Helle **provided support to the clinical trial team working on PIONEER 1** (our case study today) and she is also a member of EIWG.	

Acknowledgements

Our sincere thanks to:

- Novo Nordisk for their PIONEERing work and allowing us to use their case study.
- To EFPIA/EFSPI for sponsoring and promoting the webinar.
- To EIWG members for the lively discussion and comments on the slides.
- To Sue McKendrick for the “souper“ analogy

Agenda

Introductions and Acknowledgements	Nanco Hefting (Lundbeck)
Learning Outcomes	Melanie Wright (Novartis)
Introduction to the Estimand Framework	Sue McKendrick (PPD)
The Story of PIONEER 1 (Novo Nordisk Diabetes Study) • Discussion: Rationale for Choice of Estimands	Mel and Sue + Helle Lynggaard, Rikke Mette Agesen (Novo Nordisk)
Are Different Stakeholders Interested in Different Questions? • Discussion: Considering Different Points of View	Sue + Helle, Rikke
Conclusions and Recap Learning Outcomes	Mel and Sue
Q & A	Nanco + All

Learning Outcomes

- To discuss the **definition** of the estimand using **simple language** and to be able to identify **intercurrent events**
- Recognize the **benefits** of following the estimand framework (ICH E9 (R1) addendum) in the context of a clinical trial, in order to:
  - **Gain alignment** on the **question(s) of interest**
  - **Frame questions** which may be of **interest** to **different stakeholders**
  - **Be transparent**

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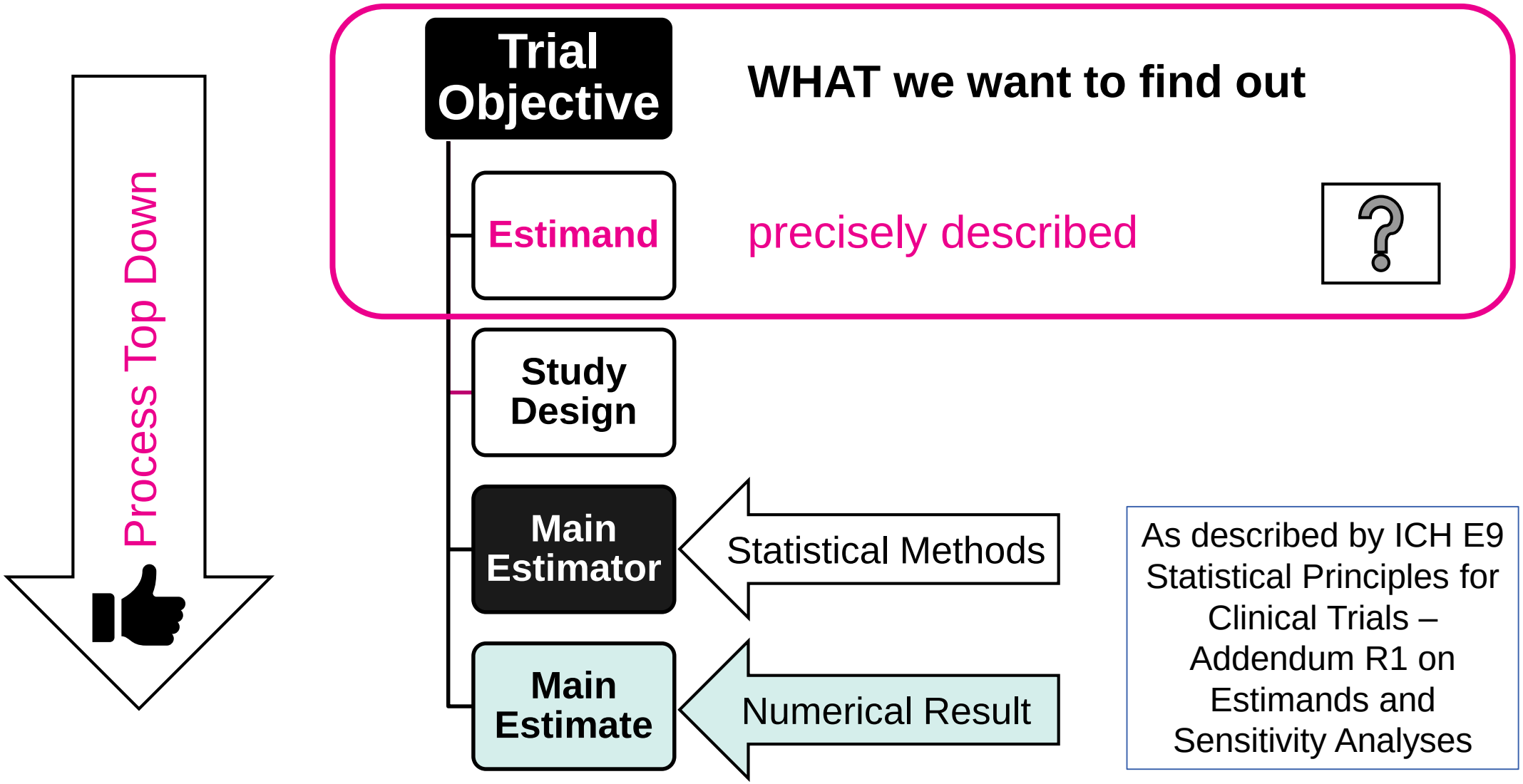
Introduction to the Estimand Framework



As described by ICH E9 Statistical Principles for Clinical Trials – Addendum R1 on Estimands and Sensitivity Analyses

Soup Analogy: It's like Writing a Recipe for Soup...

Sue's Soup

- No clear recipe
- Not reproducible
- All left over veg thrown in

French Onion Soup

- Precise recipe
- Reproducible
- Only include recipe ingredients

Study with Estimands

- Precise description of what we want to estimate
- Transparency
- Clear which data will be needed

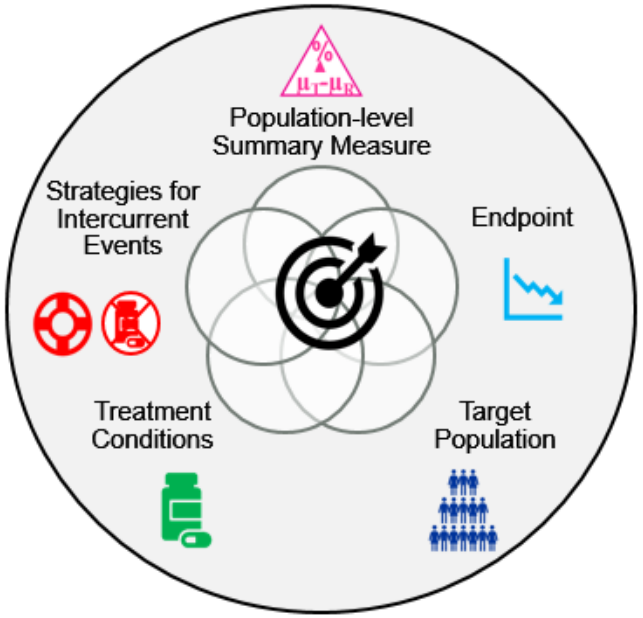
Good Practice or Over Complicating it?

- Recipe with clearly described ingredients
- Estimand documented in clinical research

The Estimand

Precise description of

“WHAT do we want to find out in our clinical study?”



Population-level summary measure

Endpoint

Population

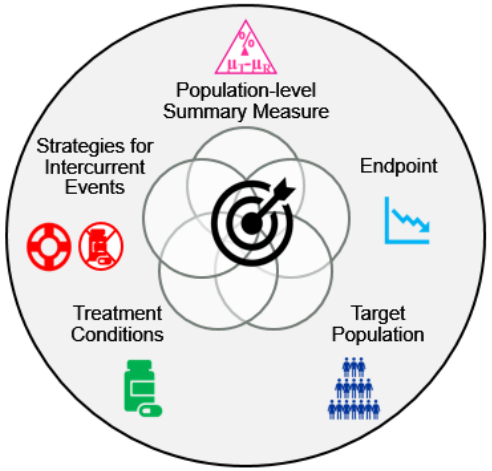
Treatment Conditions

Strategies for Intercurrent Events

Estimand, Estimator and Estimate...

....WHAT, HOW and the NUMERICAL result

The Estimand



WHAT type of soup?

Recipe
Ingredients

The Estimator
(statistical methods)

HOW to cook the soup

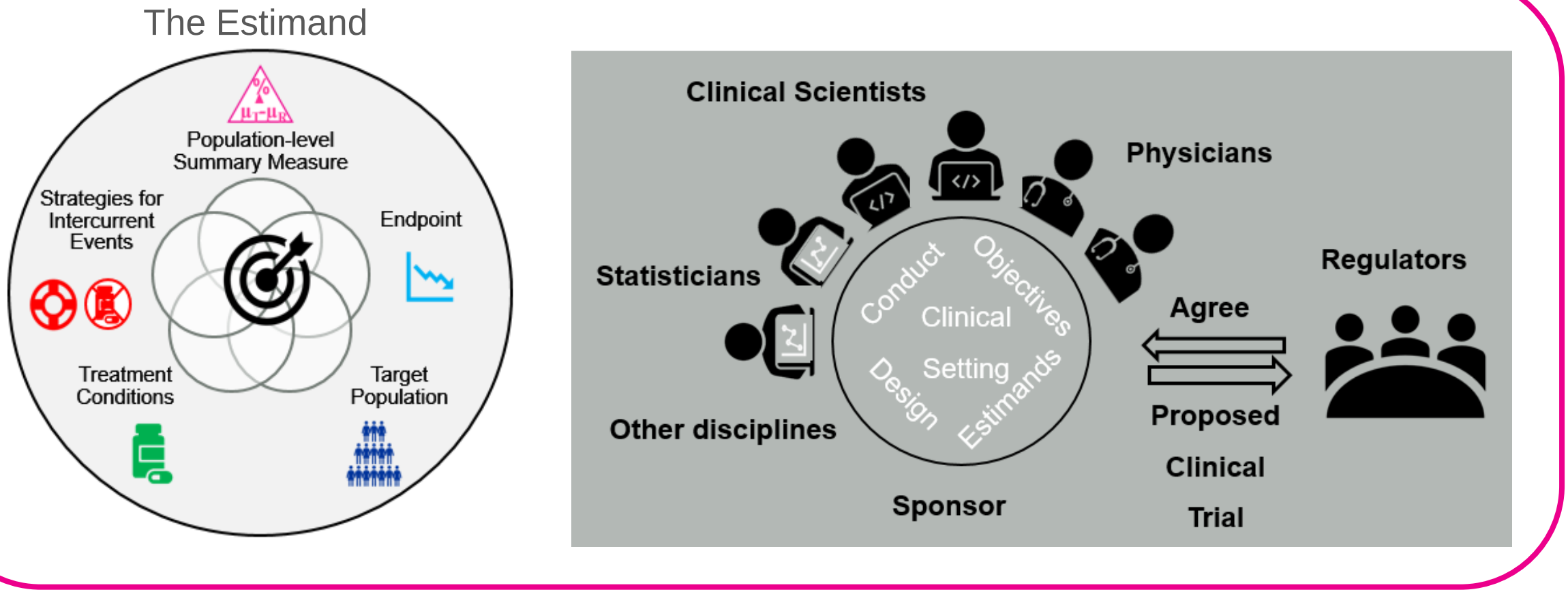
The Estimate of the treatment effect (numerical result)

RESULT!
The tasty soup!

Recipe book = PROTOCOL

Multi-disciplinary Discussions during Protocol Development

…Who Decides what Type of Soup?



ICH E9(R1) advocates a multi-disciplinary undertaking to ensure regulators agree with what we are planning to estimate

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Are Different Stakeholders Interested in Different Questions?	Sue
• Discussion: Considering Different Points of View	+ Helle, Rikke
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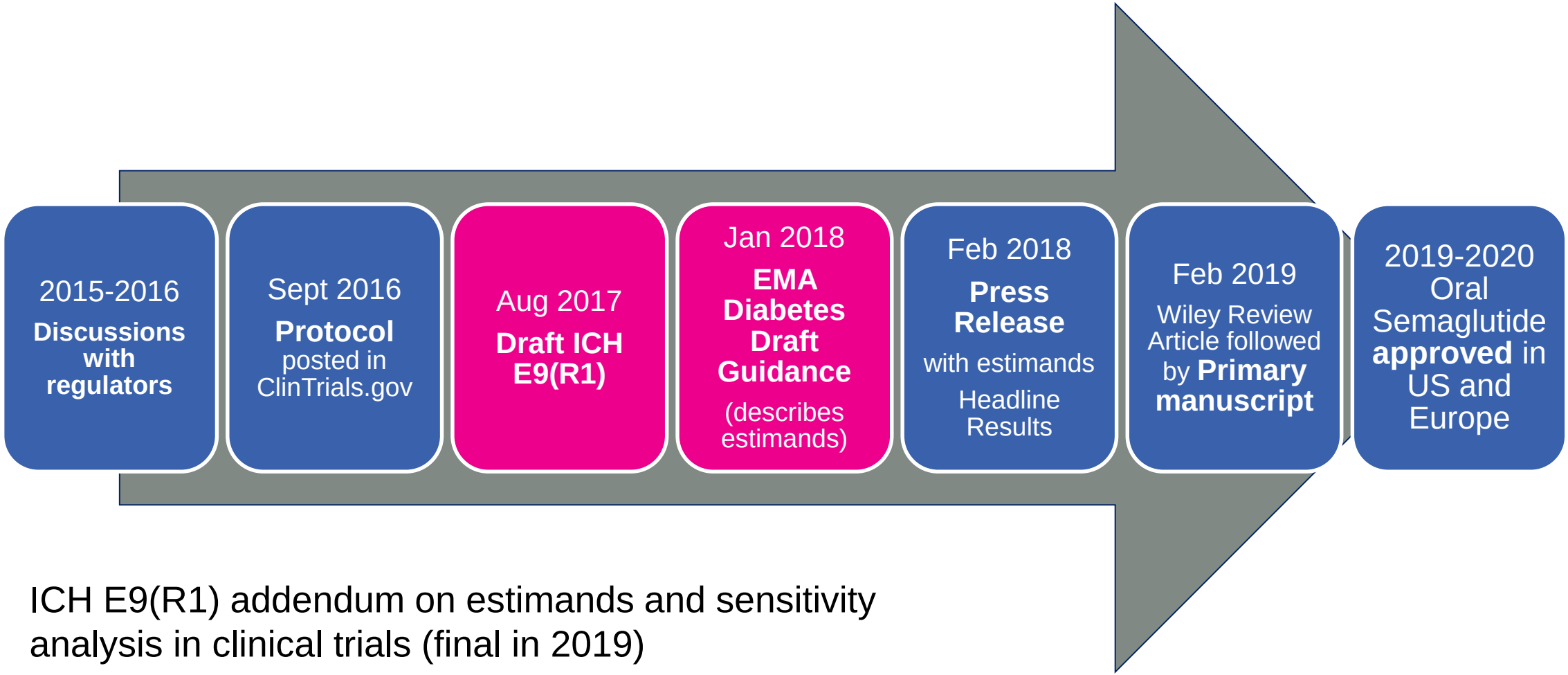
The Journey of PIONEER 1: Phase 3a Clinical Trial with Estimands



ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials (final in 2019)

PIONEER 1 Background: Phase 3a Study

Investigational Medicinal Product (IMP)

- 26 weeks treatment: tablets taken orally, once daily
- Semaglutide (3, 7 and 14 mg) vs placebo (N=703 randomized parallel groups)
- Semaglutide is a novel GLP-1 analogue

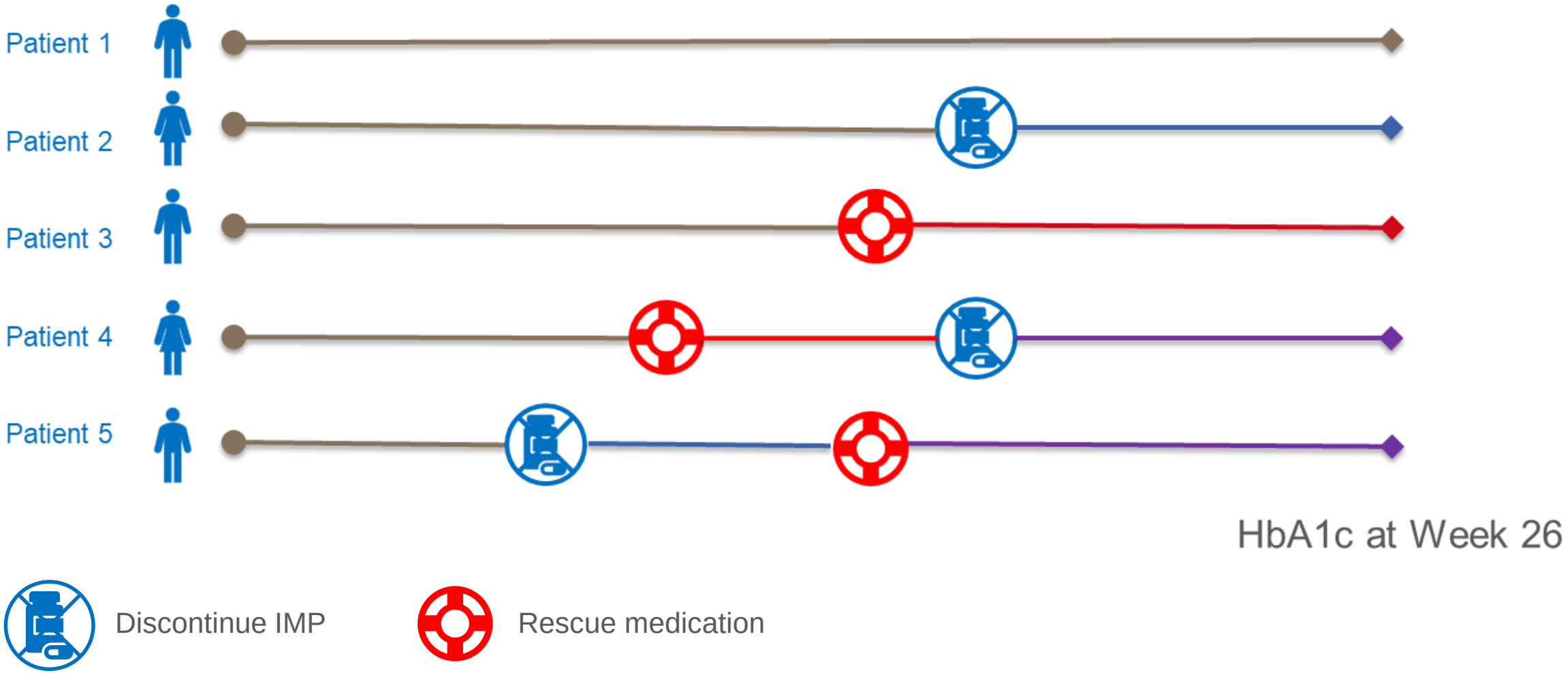
Primary Objective

- To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) versus once-daily placebo on glycaemic control in subjects with type 2 diabetes mellitus treated with diet and exercise only

Primary Endpoint

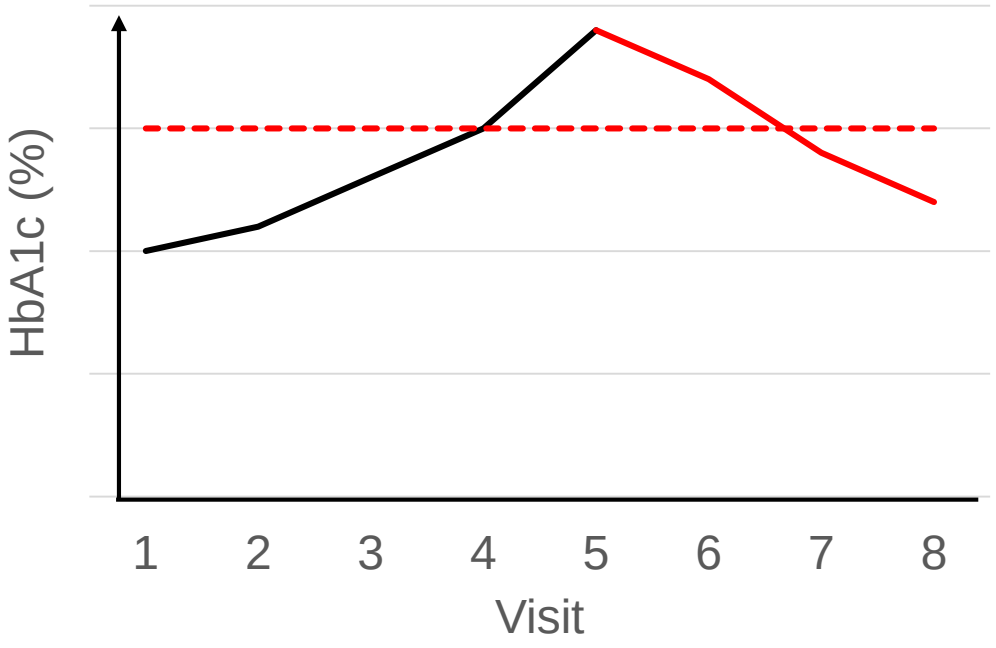
- Week 26 change from baseline in glycated haemoglobin A1c (HbA1c)

PIONEER 1: Patient Journeys

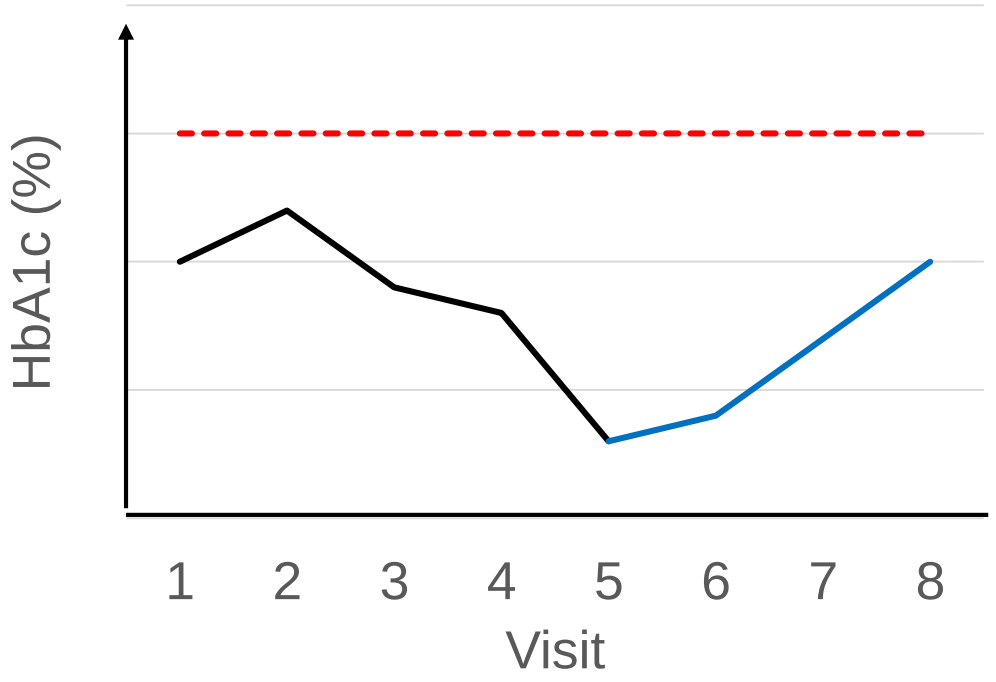


Intercurrent Events Impact the Interpretation of Outcome (HbA1c)

Rescue medication



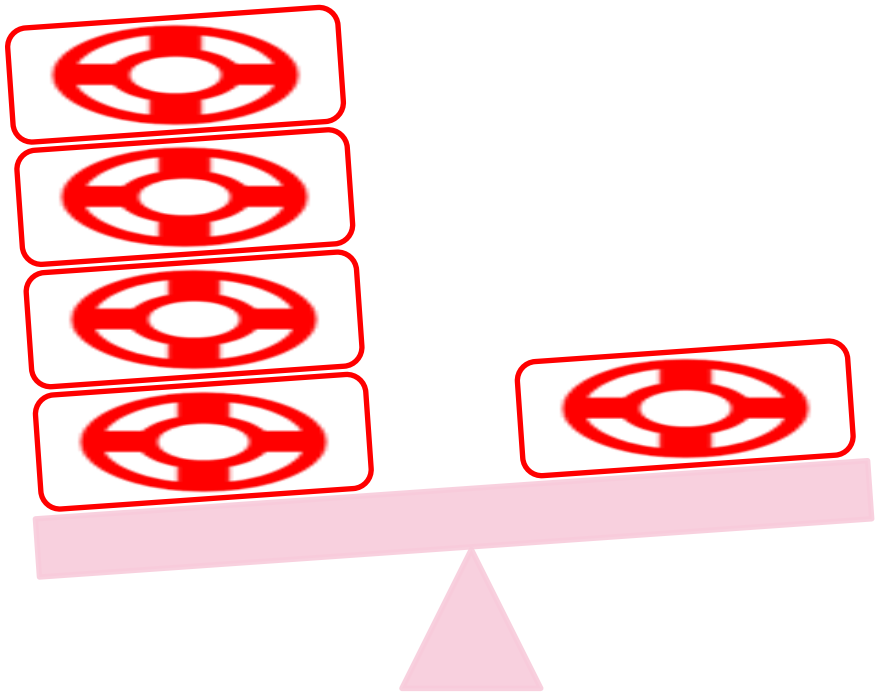
Discontinuation of treatment



Imbalance in Intercurrent Events

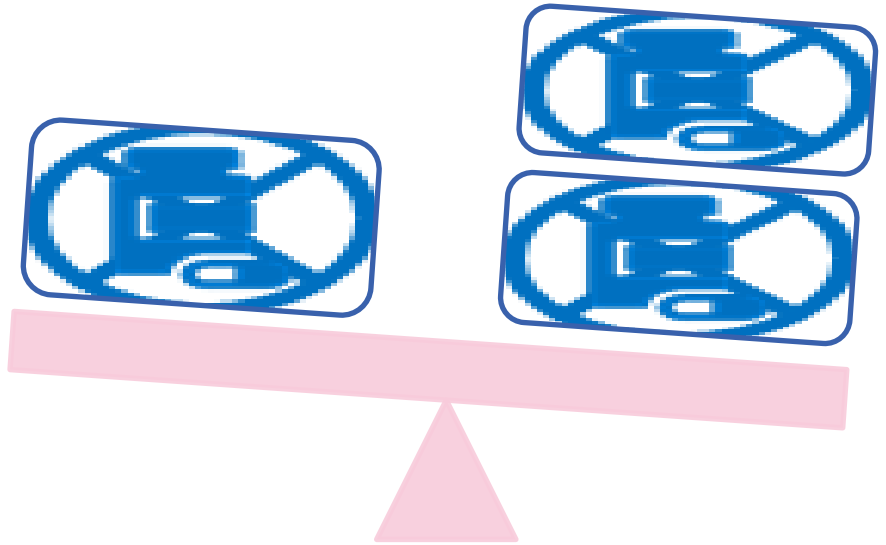
Placebo

14 mg



Placebo

14 mg



Patient Journeys and ICH E9 (R1) Addendum

- The diversity of **patient journeys** can raise fundamental questions regarding the evaluation of **treatment effects** in clinical trials
- The ICH E9 (R1) addendum introduces the concept of an **estimand** to precisely describe the **treatment effect of interest**
- The estimand framework helps to structure discussions about the relationship between **patient journeys** and the treatment effect of interest by considering **strategies for intercurrent events**

Acknowledgement: Degtyarev et al (2019)

ICH E9(R1) Strategies for Intercurrent Events

1. **Treatment Policy –** irrespective of the intercurrent event
2. **Hypothetical** - a scenario is envisaged in which the intercurrent event would not occur
3. **While on Treatment –** the response prior to the occurrence of the intercurrent event is of interest
4. **Composite Variable –** the intercurrent event is incorporated into the variable/endpoint
5. **Principal Stratum –** the population of interest is defined by those in whom the intercurrent event would or would not occur

PIONEER 1

Primary Objective

To compare the effects of three dose levels of once-daily **oral semaglutide** (3, 7 and 14 mg) versus once-daily **placebo** on **glycaemic control** in **subjects with type 2 diabetes mellitus** treated with diet and exercise only

Estimand 1

the "**Confounded**" or "**Reality**" Recipe!

(irrespective of intercurrent events)

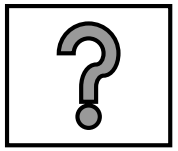
Estimand 2

the "**Pure**" or "**If Only**" Recipe!

(as though intercurrent events did not happen)

Estimand 1 – the Confounded / Reality Recipe!

What is the difference between means in



change from baseline HbA1c after 26 weeks

in patients with Type 2 diabetes,

treated with
oral semaglutide 14 mg versus placebo*,
irrespective of adherence to IMP and with use of rescue medication as required?

*(as an adjunct to diet and exercise);
IMP = investigational medicinal product

Population-level summary measure

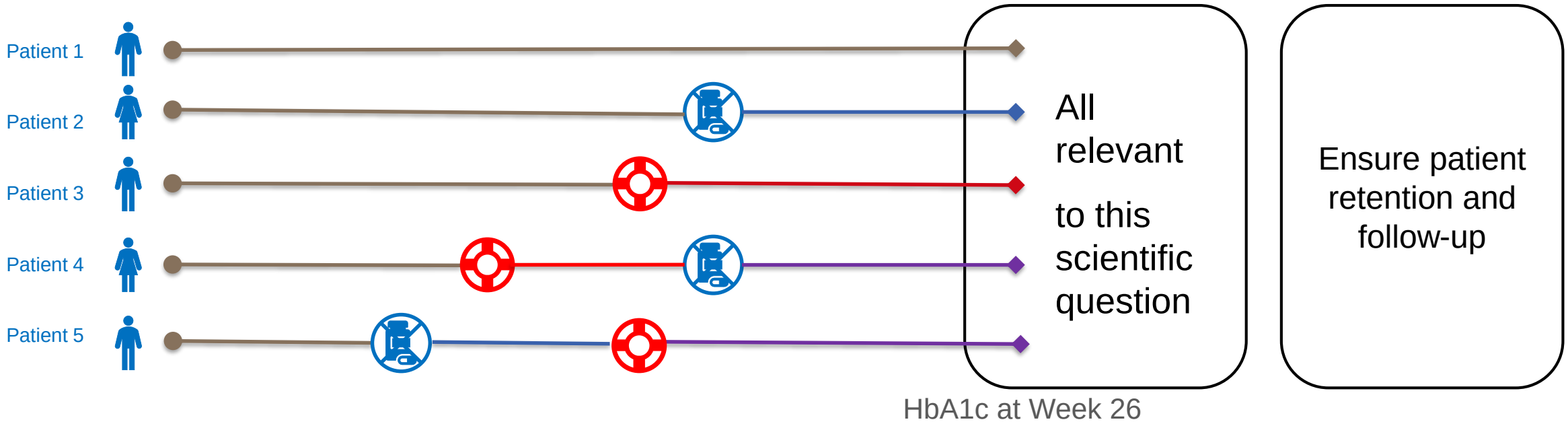
Endpoint

Population

Treatment Conditions

Strategies for Intercurrent Events

Estimand 1 (Confounded / Reality)– Full Patient Journeys



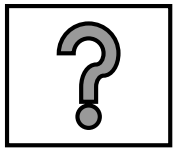
According to the Addendum:

Rescue medication is reflected according to the **treatment policy strategy**

Treatment discontinuation is reflected according to the **treatment policy strategy**

Estimand 2– the Pure / If Only Recipe!

What is the difference between means in



change from baseline HbA1c after 26 weeks,

in patients with Type 2 diabetes,

treated with
oral semaglutide 14 mg versus placebo*,

as though patients always adhered to IMP and
as though rescue medication is unavailable?

*(as an adjunct to diet and exercise)

Population-level summary measure

Endpoint

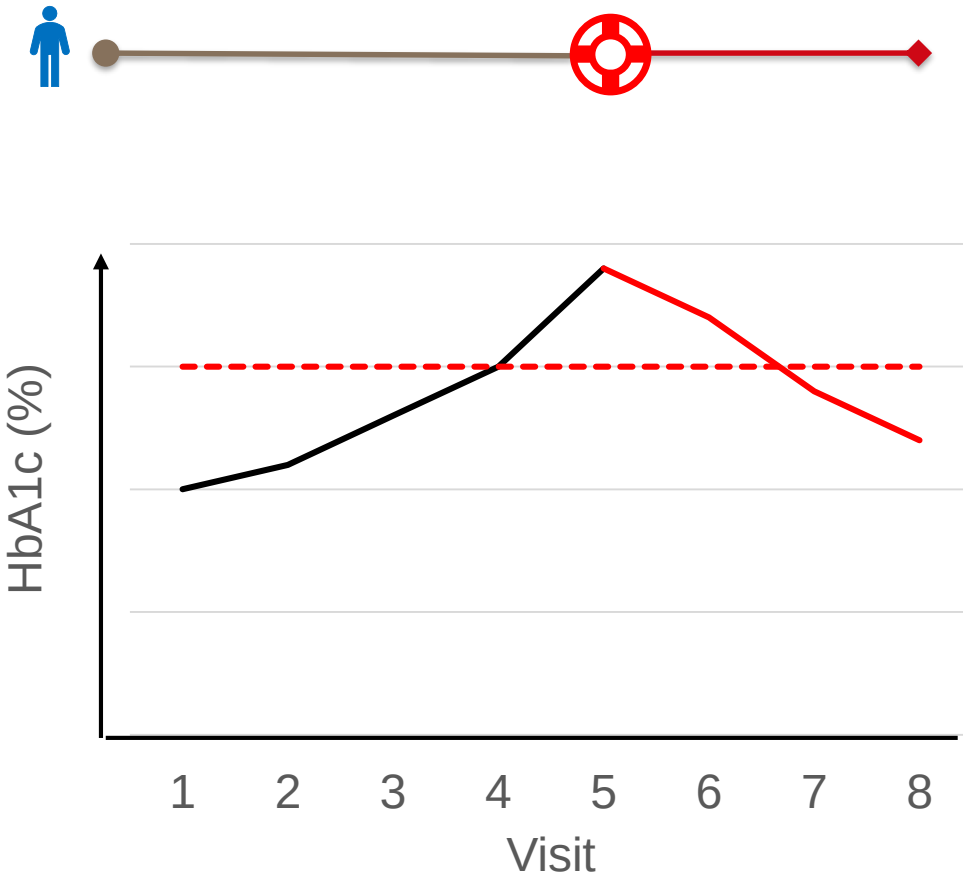
Population

Treatment Conditions

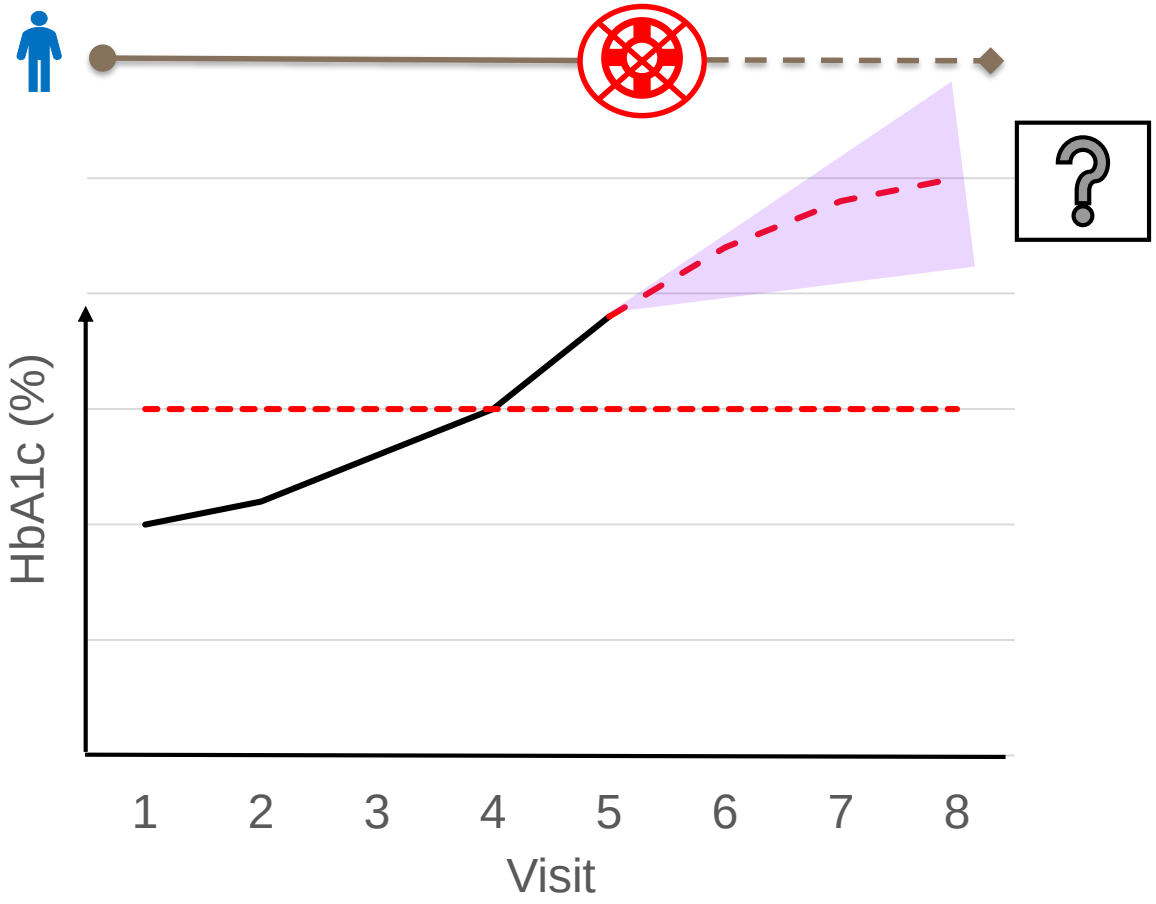
Strategies for Intercurrent Events

What if Rescue Medication Were Unavailable?

Rescue medication

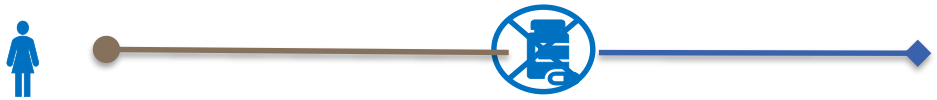


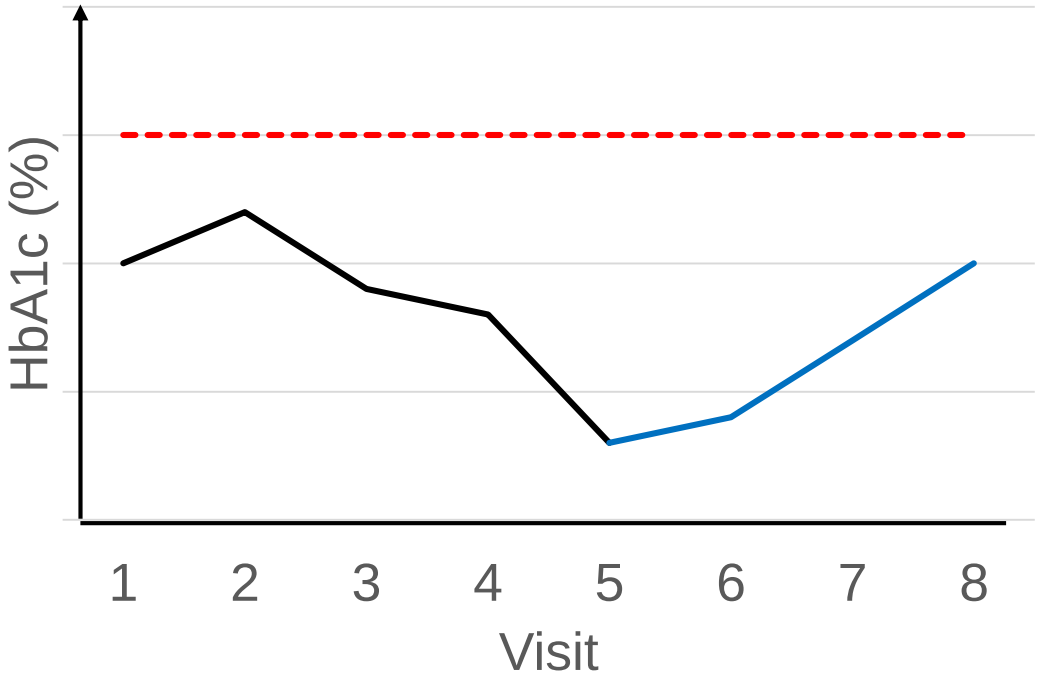
Prediction or imputation as though no rescue



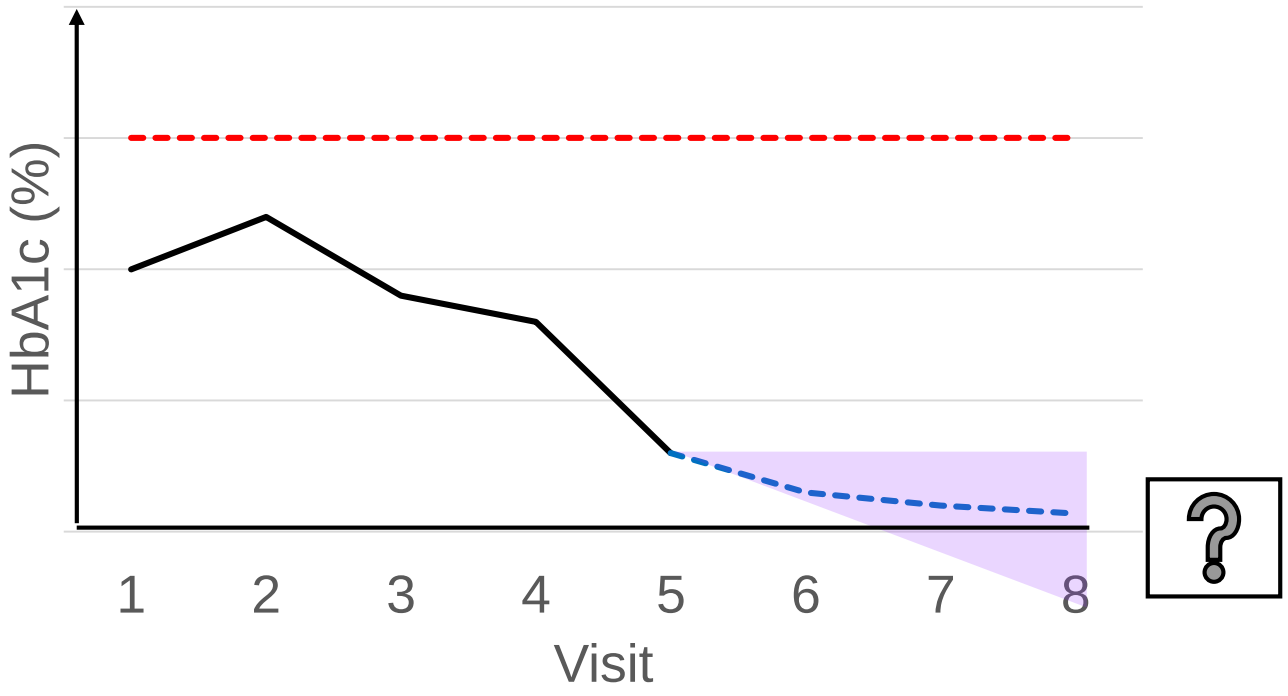
What if this Patient was to Continue Taking Treatment

Discontinuation of IMP

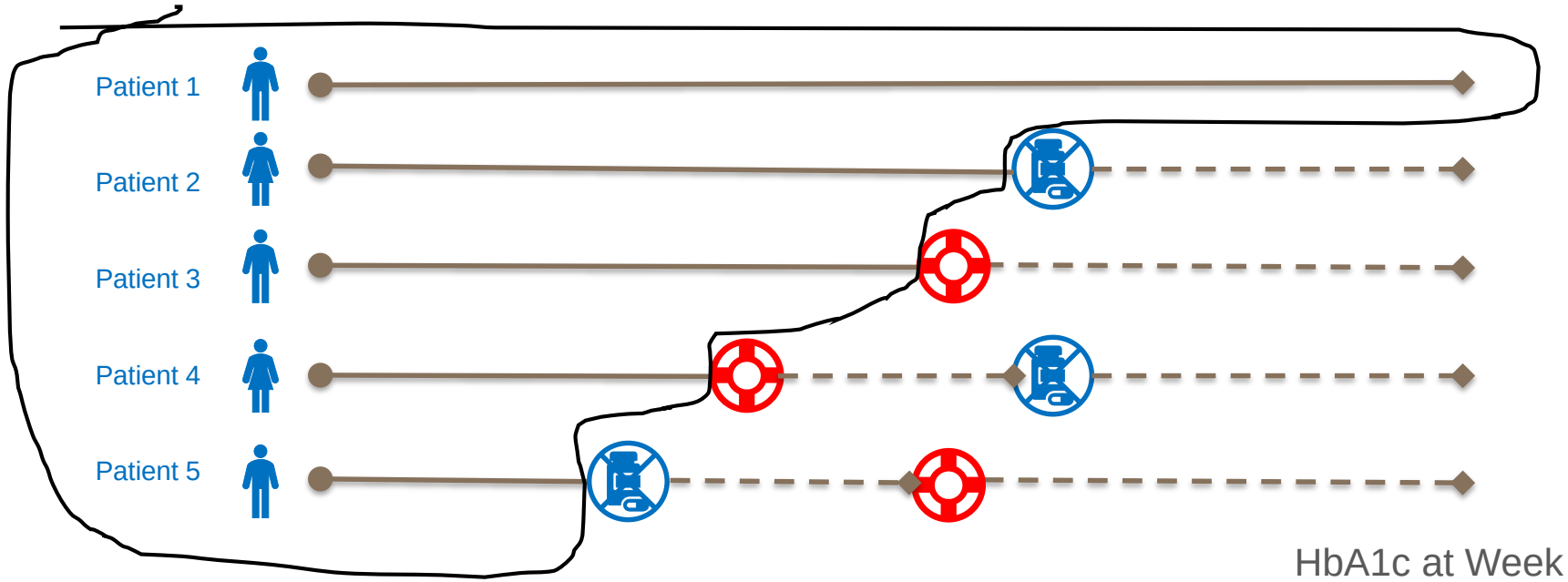




Prediction or imputation as though IMP is continued



Estimand 2 (Pure / If Only) –Partial Patient Journeys



Only data collected until the first intercurrent event is useful to evaluate this question

According to the Addendum:

Rescue medication is reflected according to the **hypothetical strategy**

Treatment discontinuation is reflected according to the **hypothetical strategy**

PIONEER 1 Study results

Frequency of intercurrent events:	14 mg	Placebo
Discontinuation of IMP	24 (13.7%)	19 (10.7%)
Rescue medication*	7 (4.0%)	35 (19.7%)

*initiated before or after discontinuation of IMP

Endpoint: Change from baseline HbA1c at week 26

Results related to Estimand 1 (confounded/reality)

14 mg* Mean	Placebo* Mean	Difference between means (95% CI)	P-value
-1.4%	-0.3%	**-1.1%** (-1.3% , -0.9%)	P<0.001

*with rescue medication as required, irrespective of discontinuation of IMP

Results related to Estimand 2 (pure/if only)

14 mg Mean	Placebo Mean	Difference between means (95% CI)	P-value
-1.5%	-0.1%	**-1.4%** (-1.7% , -1.2%)	p<0.001

PIONEER 1 Study Results

Estimand 1 (Confounded / Reality)	Estimand 2 (Pure / If Only)
What is the difference between means in change from baseline HbA1c after 26 weeks in patients with Type 2 diabetes treated with oral semaglutide 14 mg versus placebo...	What is the difference between means change from baseline HbA1c after 26 weeks in patients with Type 2 diabetes treated with oral semaglutide 14 mg versus placebo...
...irrespective of adherence to IMP and with use of rescue medication as required?	**...as though patients always adhered to IMP and as though rescue medication is unavailable?**
Estimate: -1.1%	**Estimate: -1.4%**

One endpoint, two different questions (estimands),
=> two different answers!

Diabetes Obes Metab. 2019;21:2203–2210.

Discussion – Motivation and Rationale for Choice of Estimands

Q1: Why did the PIONEER team consider writing estimands into the protocol even before the ICH E9 draft addendum was released?

Q2: Did the choice of estimands affect study conduct?

Q3: What did the clinicians want do know?

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Conclusions and Recap Learning Outcomes	Mel and Sue
Q & A	Nanco + All

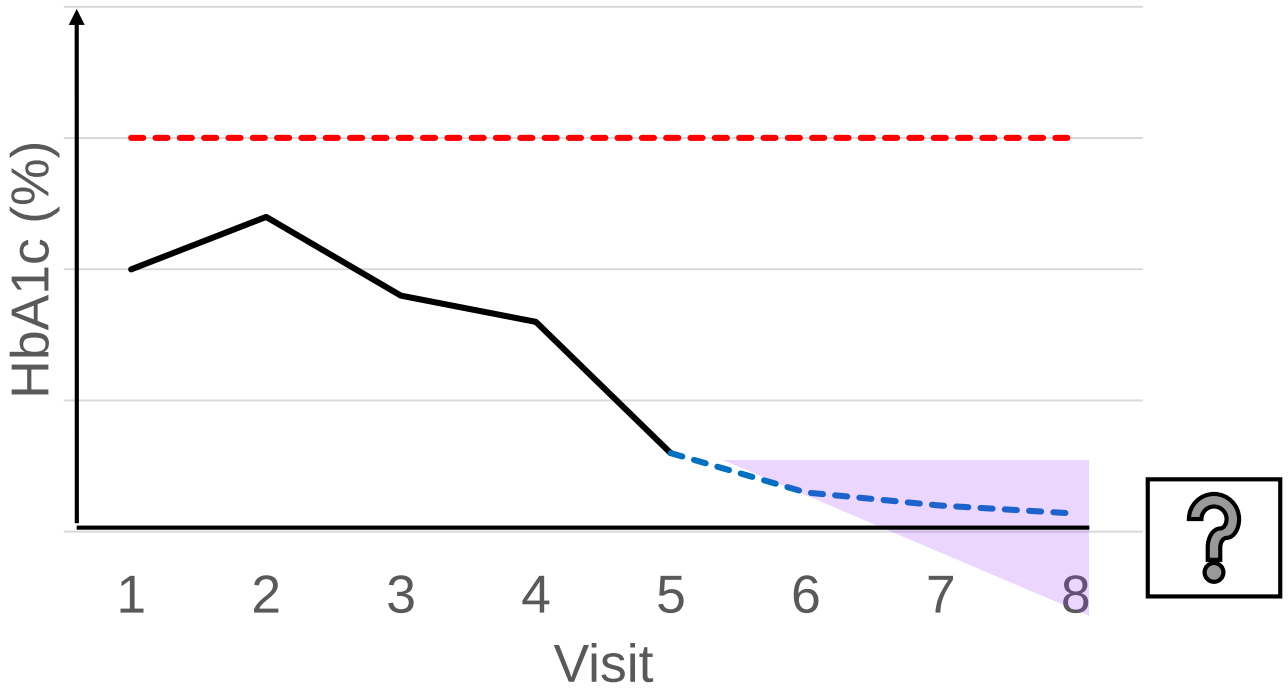
Are Different Stakeholders Interested in Different Questions?

- Patients
- Regulators
- Prescribers
- Payers [health technology assessment bodies (e.g. NICE), private health companies etc]

If Only Patients Always Tolerated IMP?

If some patients cannot tolerate the new treatment, is answering this question useful for decision making?

Prediction or imputation as though IMP is continued



A Regulator's Question (EMA Guideline) – the "Fusion Recipe"!

What is the difference between means in

change from baseline HbA1c after 26 weeks,

in patients with Type 2 diabetes,

treated with
oral semaglutide 14 mg versus placebo*
Irrespective of adherence to IMP and

as though rescue medication is unavailable?

*(as an adjunct to diet and exercise)

Population-level summary measure

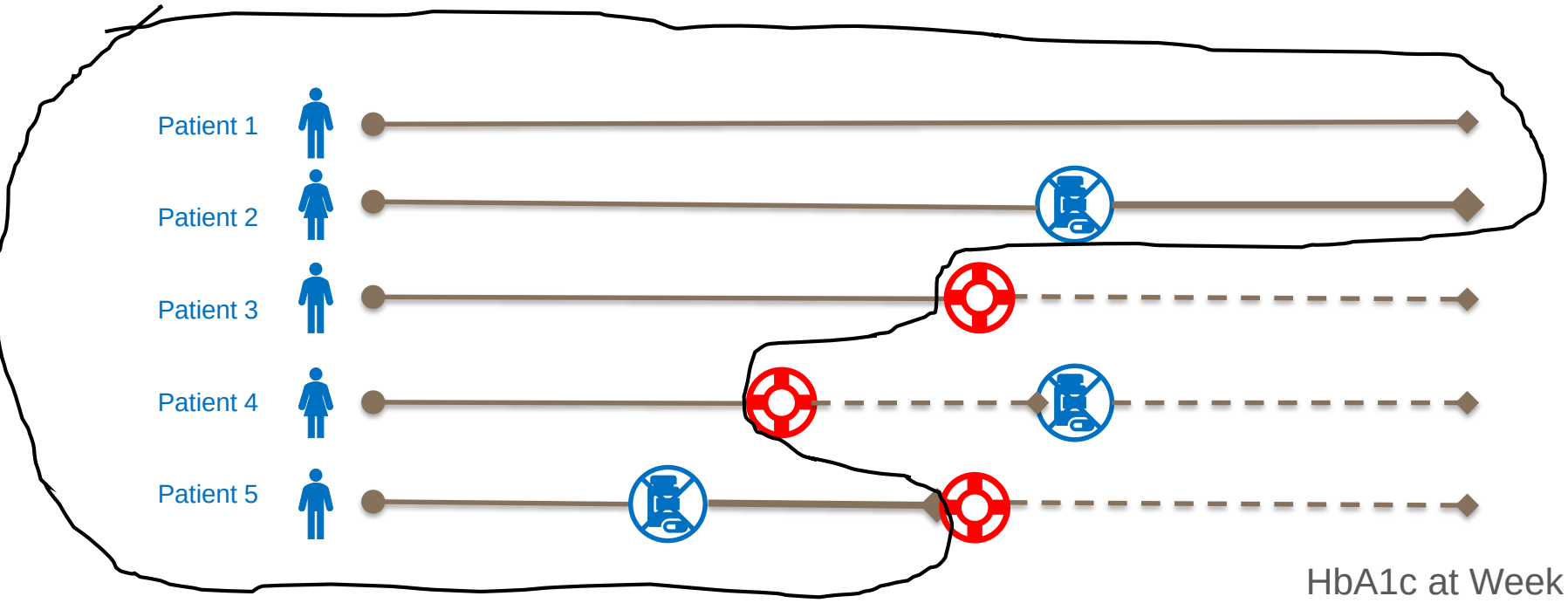
Endpoint

Population

Treatment Conditions

Strategies for Intercurrent Events

Fusion Recipe – Partial Patient Journeys



Only data collected until rescue intake is useful to evaluate this question

According to the Addendum:

Rescue medication is reflected according to the **hypothetical strategy**

Treatment discontinuation is reflected according to the **treatment policy strategy**

Discussion – Considering Different Points of View

Q1: What are the benefits of formulating clinical questions in terms of estimands?

Q2: Can you think of other estimands which may be relevant from another point of view

(e.g. from a patient perspective)?

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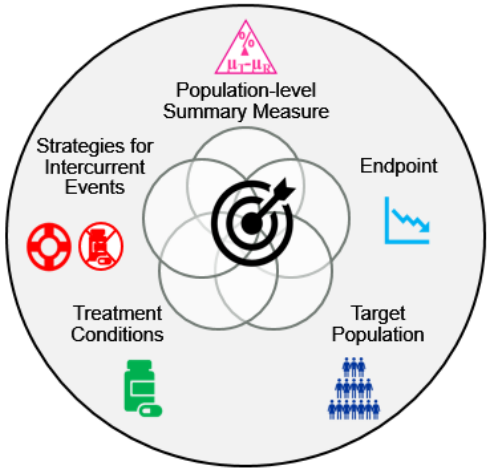
Conclusions – PIONEER 1

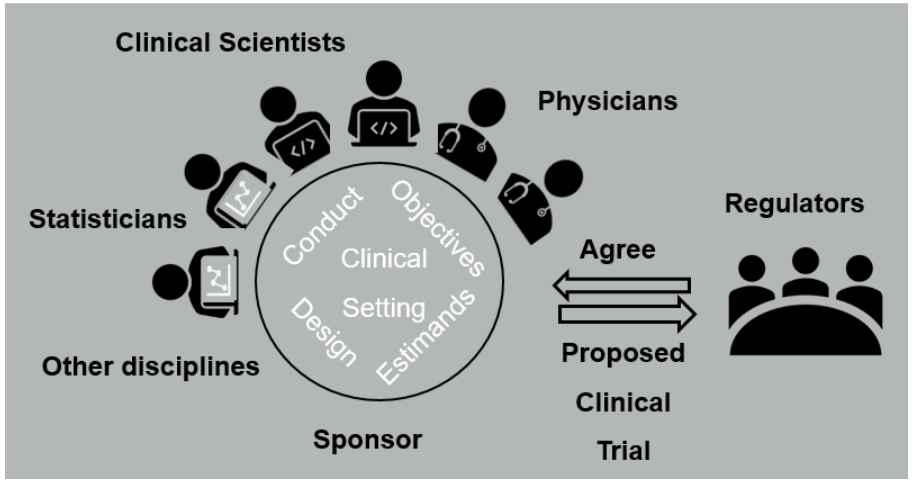
- PIONEER 1 was a trial which PIONEERed estimand thinking
  - Two estimands were specified in the protocol, both defined with the same endpoint
  - Two estimands = Two different answers
  - Presentation of results in press release and manuscripts reflected the results from both estimands
  - Oral semaglutide approved based on the PIONEER program by
    - FDA September 2019 and EMA in April 2020
      - The estimate (results) of estimand 1 (confounded/reality) were presented in the labelling for both US and Europe

Conclusions – The Estimand

The Estimand **WHAT** type of soup?



Recipe Ingredients



The Estimator (statistical methods) **HOW** to cook the soup

The Estimate of the treatment effect (numerical result) **RESULT!** The tasty soup!

Recipe book = PROTOCOL

Final Thoughts

- The estimand is a powerful tool which can help to frame questions of interest to different stakeholders:
  - Physicians, patients, regulators, payers
- It’s no longer all about the endpoint... but it’s all about the question …precisely what we want to find out (the estimand)....

...and importantly you will always have written down your recipe!

Recap of Learning Outcomes

- To discuss the **definition** of the estimand using **simple language** and to be able to identify **intercurrent events**
- Recognize the **benefits** of following the estimand framework (ICH E9 (R1) addendum) in the context of a clinical trial, in order to:
  - **Gain alignment** on the **question(s) of interest**
  - **Frame questions** which may be of **interest** to **different stakeholders**
  - **Be transparent**

The Estimands Academy for Trial Teams

"Bringing estimands to *life* through real case studies"

Webinar 2 coming soon!

- A new case study will be described (respiratory)
- Training will focus on the strategies to reflect intercurrent events in the clinical question of interest (estimand)

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Q & A	Nanco + All

Thank you

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Watch out for webinar 2 – coming soon!!

References

- Wiley Review Article (2019): Aroda et al, Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: The PIONEER 1 randomized clinical trial as an example
  - https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.13804
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