The Estimands Academy for Trial Teams

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

Webinar 3: Estimands from trial planning to publication in medical journals: The ETHOS trial.

19th November 2021 3-4:30 pm UK /4-5:30 pm CET/10-11:30 am EST

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)

[+]Co-Lead *Adhoc member C = Clinician

Institution	Member
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	Mette Josiassen
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	Amel Besseghir

Disclaimer

- Opinions are those of the presenters and are not necessarily the views of AstraZeneca.

Acknowledgements

Our sincere thanks to:

- AstraZeneca for allowing us to use the ETHOS case study.
- To EFPIA/EFSPI for sponsoring and promoting the webinar.
- To EIWG members for the lively discussion and comments on the slides.
- To Melanie Wright, Sue McKendrick and Judith Anzures-Cabrera for support with the Q&A

Agenda

Introduction and Acknowledgements	David Wright (AstraZeneca) & Paul Dorinsky (AstraZeneca)
Learning Outcomes	David
An introduction to the ETHOS study	Paul
Reminder of the Estimand Framework	David
Using the framework with ETHOS	David
3 possible estimands	David
Clinical view	Paul
How should estimands be communicated in medical journals	David
Conclusions and Recap Learning Outcomes	David
Q & A	David and Paul

Introductions

	**David Wright is Head of Statistical Innovation at AstraZeneca and is also a member of the** EIWG training team (ex MHRA)	AstraZeneca
	**Paul Dorinsky** is a Global Clinical Head **at AstraZeneca**.	AstraZeneca

Learning Outcomes

- To discuss the definition of the estimand using simple language and to be able to identify intercurrent events
- Understand different estimand strategies that could be of interest in trials in Chronic Obstructive Pulmonary Disease (COPD).
- Recognize the benefits of following the estimand framework (ICH E9 (R1) addendum) in the context of COPD, in order to:
  - Frame questions which may be of interest to different stakeholders
  - Be transparent when communicating trial results in publications in medical journals

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Some abbreviations

- *COPD:* Chronic obstructive pulmonary disease

- *ICS*: inhaled corticosteroid (e.g. budesonide)
- *LABA*: long-acting β_2-agonist (e.g. formoterol fumarate)
- *LAMA: long-acting muscarinic antagonist (e.g.* glycopyrrolate)

- *SABA*: short-acting β2-agonist,
- *SAMA*: short-acting muscarinic antagonist,
- *BID*: twice daily,
- *MDI*: metered dose inhaler.
- Dual combinations
- Triple combinations

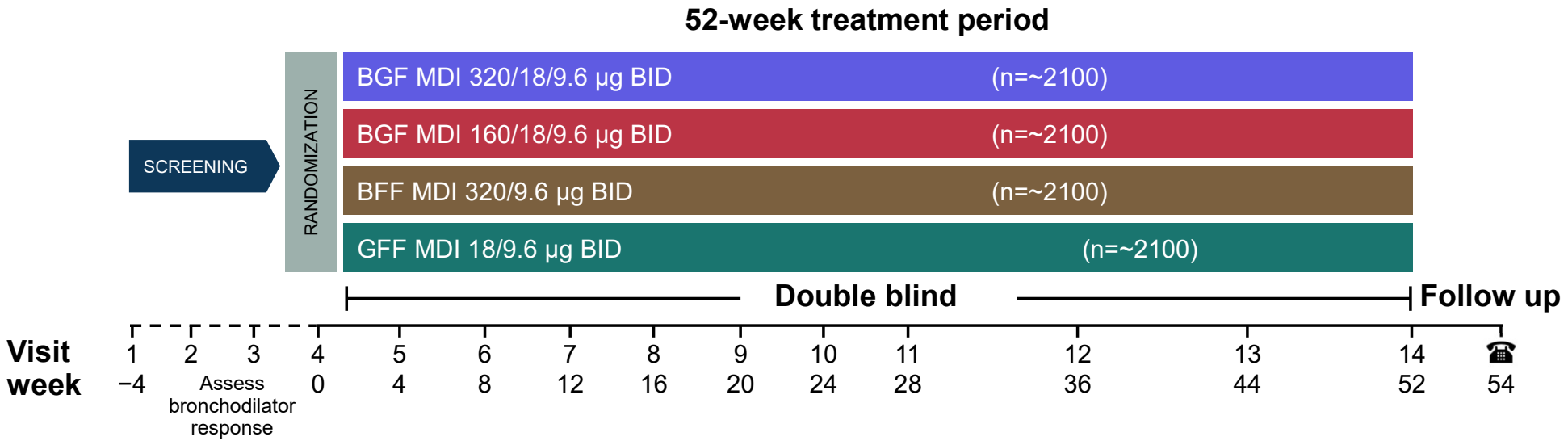
- LOE: Lack of Efficacy
- IMP: Investigational Medicinal Product

ETHOS treatment arms

- **BGF** = triple ICS/LAMA/LABA (budesonide, glycopyrronium, and formoterol fumarate)
- **BFF** = dual ICS/LABA (budesonide and formoterol fumarate)
- **GFF** = Bevespi – dual LAMA/LABA (glycopyrronium and formoterol fumarate)

Is BGF (triple combination) superior to BFF and GFF (both dual combinations)?

ETHOS study design (NCT02465567)



Key inclusion criteria
- Age 40–80 years
- Symptomatic on two or more inhaled maintenance treatments
- Postbronchodilator FEV_1 must be ≥25% to <65% predicted normal value
- History of moderate/severe COPD exacerbation

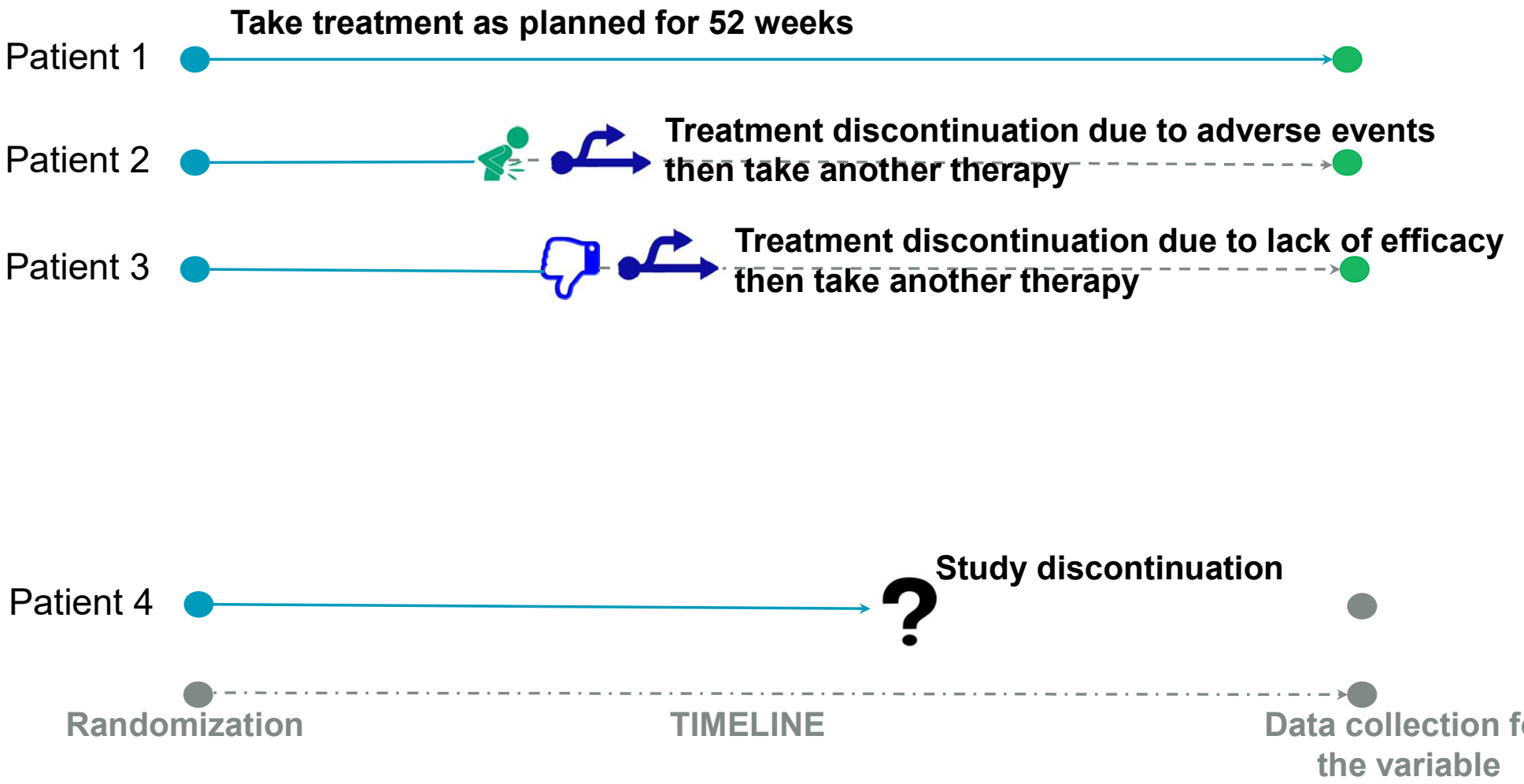
Primary endpoint
- Rate of moderate/severe COPD exacerbations

ETHOS study design and rationale published in Respiratory Medicine

Results published in NEJM

Veeva ID: Z4-22118; Date of preparation: January 2020; Date of expiration: March 2020

What can happen to a patient after initiation of treatment



Observations

- Events occurring after treatment initiation can affect either the interpretation or the actual measurements associated with the clinical question of interest.

- Discontinuation of assigned treatment is an example of such an event in ETHOS. The reason for discontinuation provides important information about the benefit of treatment.
- If a patient discontinues assigned treatment early in the study and then takes another medication and experiences more (or less) exacerbations later in the trial than expected that is likely to be due to the subsequent therapy they received not the therapy they were initially assigned to.

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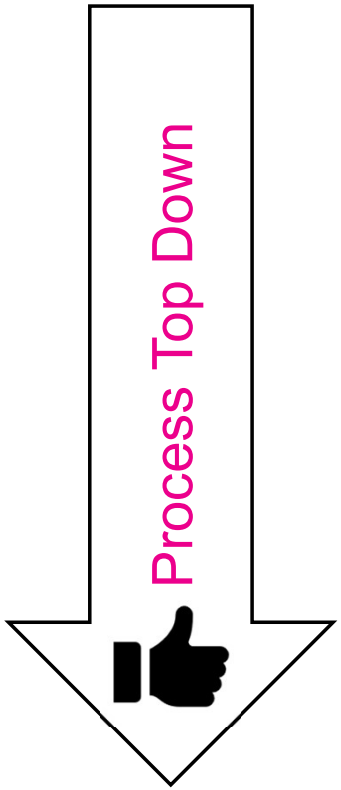
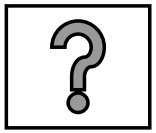
Introduction to the Estimand Framework



Trial Objective — **WHAT we want to find out**

Estimand — precisely described



Study Design

Main Estimator ← Statistical Methods

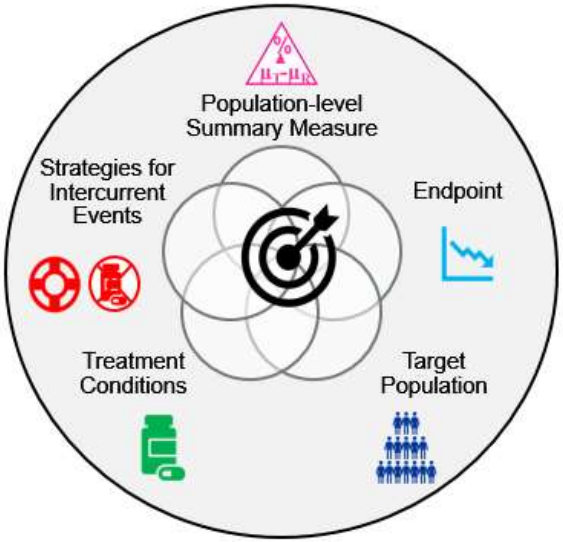
Main Estimate ← Numerical Result

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

The Estimand

Precise description of

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



Population-level summary measure

Endpoint

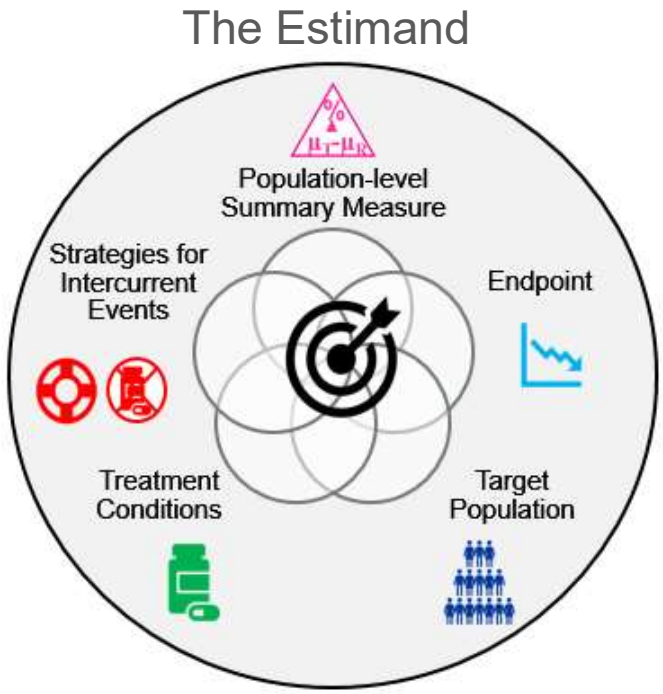
Population

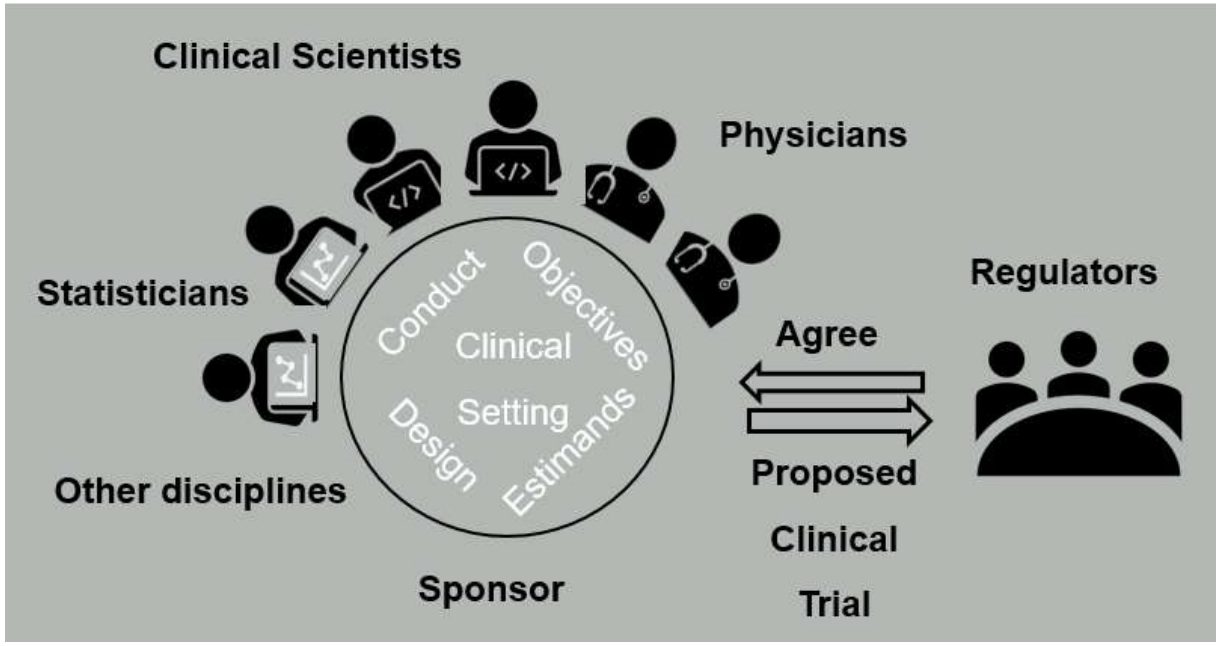
Treatment Conditions

Strategies for Intercurrent Events

Multi-disciplinary Discussions during Protocol Development

…Who Decides on the choice of estimand?





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

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ETHOS – Main intercurrent event of interest

Assigned treatment discontinuations

1. Due to Lack of Efficacy
2. Due to an Adverse Event
3. Due to other reasons

1 and 2 are evidence against the assigned treatment. 3 it is unclear.

Question: Are data collected after a patient discontinues assigned therapy (and starts another therapy) relevant to understanding the efficacy of the assigned therapy?

5 Strategies for Intercurrent Events

Irrespective of	Include in Outcome	Scenario in which event does not occur	Prior to occurrence	As part of target population definition
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest	• A scenario is envisaged in which the intercurrent event would not occur	• Scientific question is about what happened prior to the intercurrent event • Outcome after intercurrent event is considered irrelevant	• Population is defined by those in whom the intercurrent event would or would not occur
Treatment Policy	**Composite**	**Hypothetical**	**While on Treatment**	**Principal Stratum**

Hypothetical estimand

What is the annual rate of

Moderate to severe exacerbations

in patients with symptomatic moderate to severe COPD currently treated with dual or triple inhaled therapy,

treated with BGF 320/18/9.6
versus GFF (18/9.6),
as though patients who discontinued treatment (regardless of reason) continued that treatment

Population-level summary measure

Endpoint

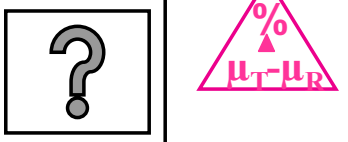
Population

Treatment Conditions

Strategies for Intercurrent Events

Attributable Estimand – a hybrid of a composite and hypothetical estimand

What is the annual rate (poor response assumed if discontinued for attributable reasons (*i.e.* due to LOE or AEs)) of
Moderate to severe exacerbations
in patients with symptomatic moderate to severe COPD currently receiving dual or triple therapy,
treated with BGF 320/18/9.6
versus GFF (18/9.6),
as though patients who discontinued treatment for non attributable reasons continued on treatment



Population-level summary measure

Endpoint

Population

Treatment Conditions

Strategies for Intercurrent Events

Treatment Policy Estimand

What is the annual rate of

Moderate to severe exacerbations

in patients with symptomatic moderate to severe COPD currently receiving dual or triple therapy,

treated with BGF 320/18/9.6
versus GFF (18/9.6),
irrespective of treatment discontinuation

Population-level summary measure

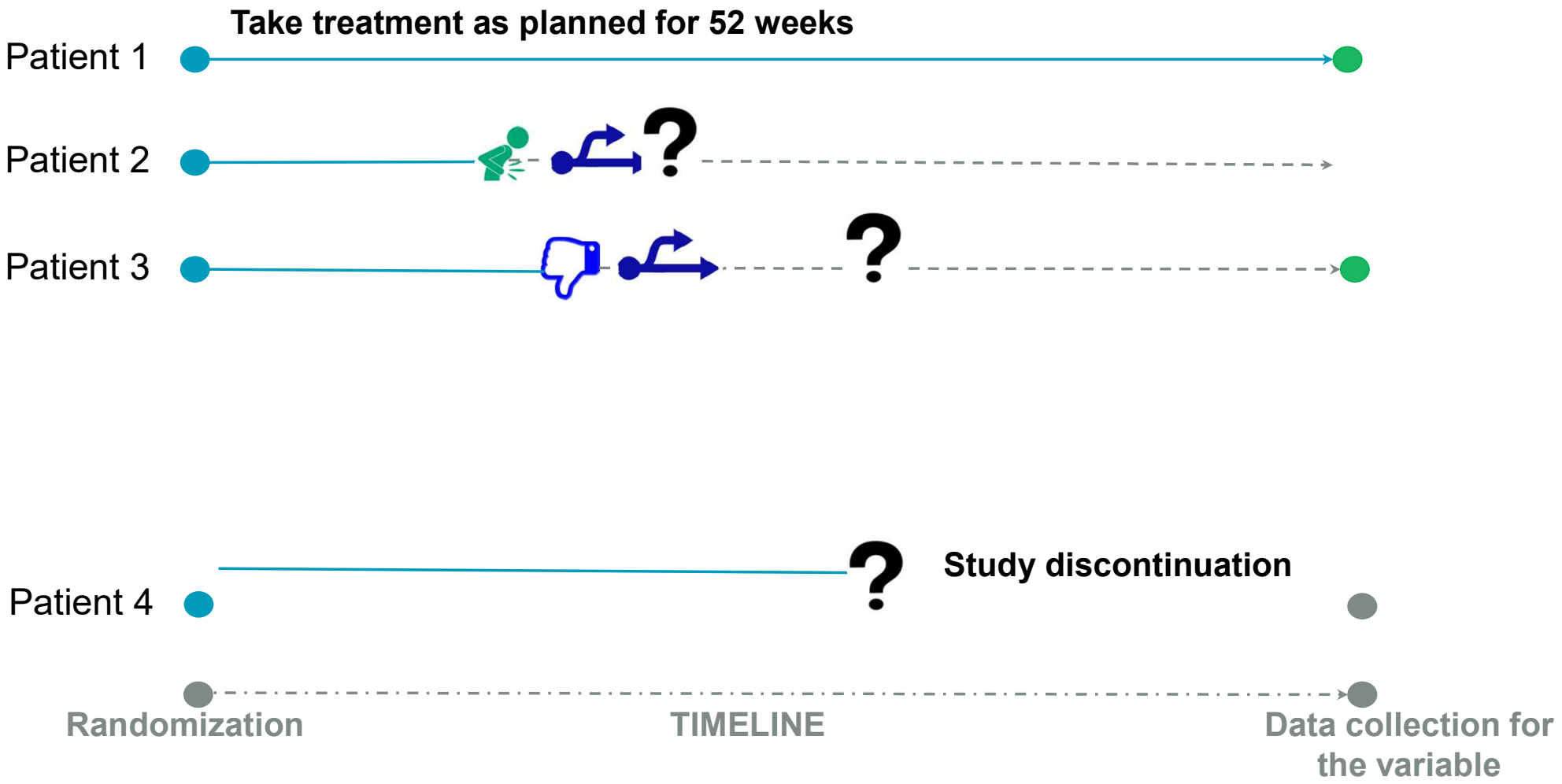
Endpoint

Population

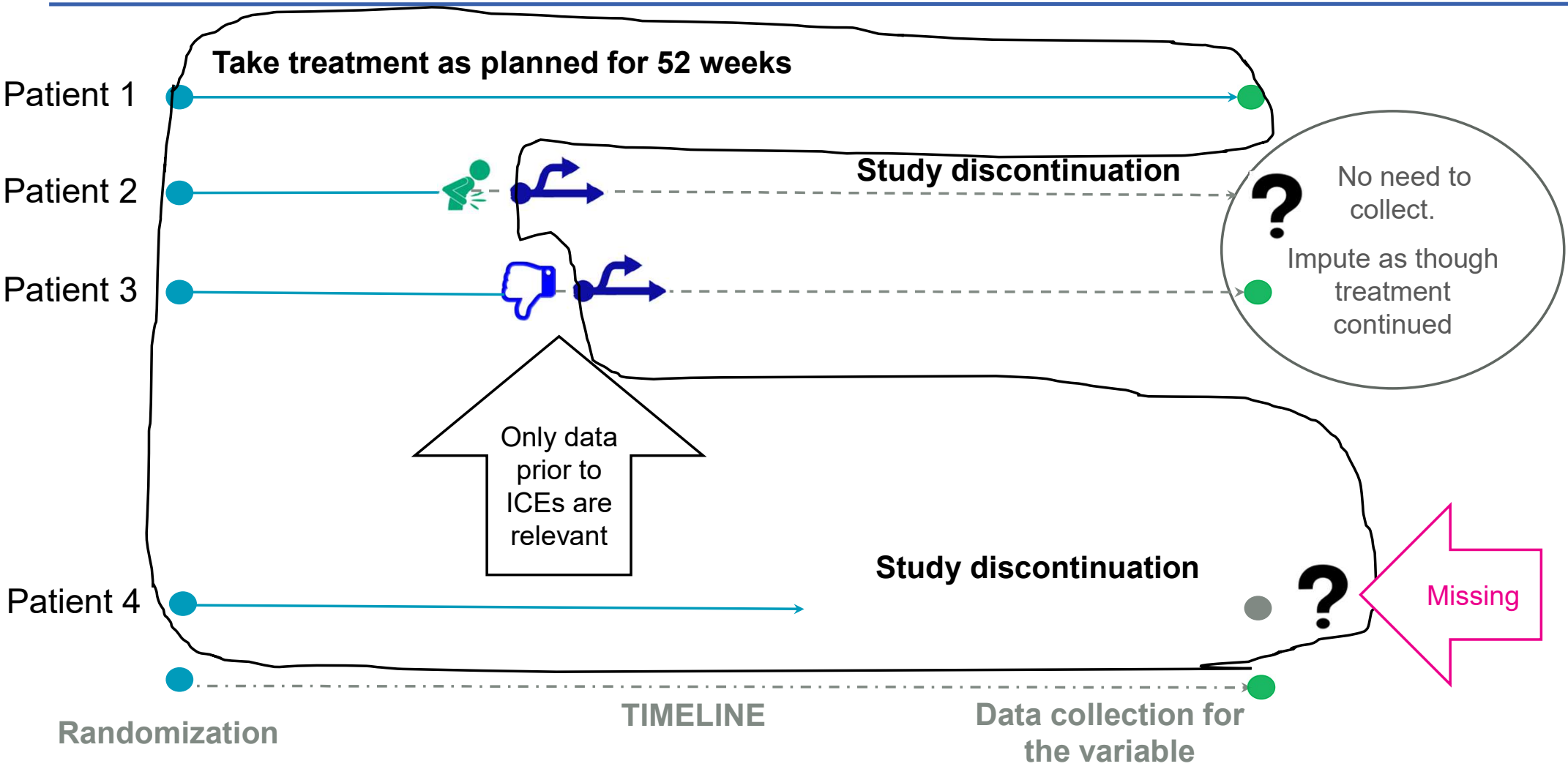
Treatment Conditions

Strategies for Intercurrent Events

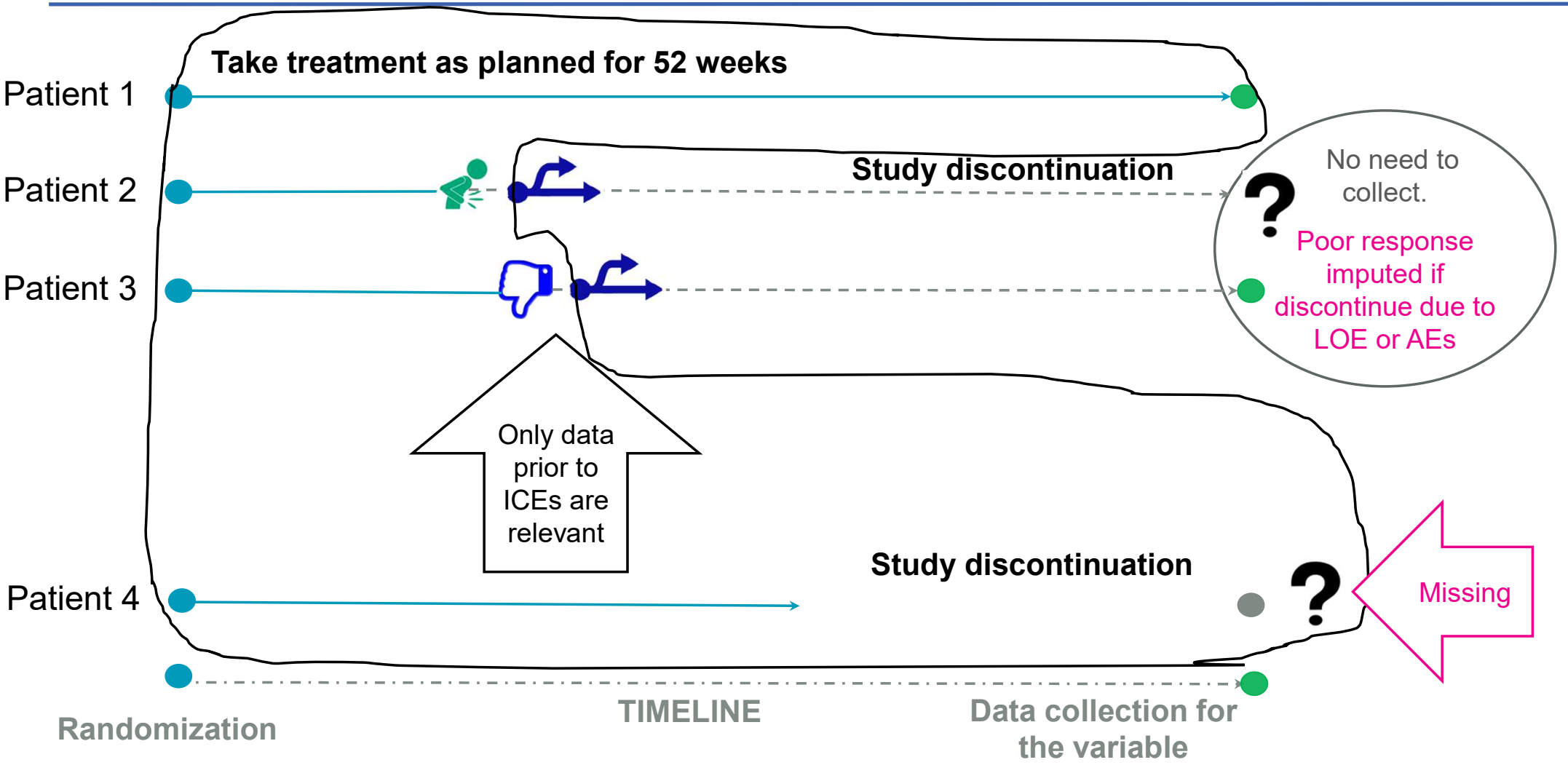
Missing Data



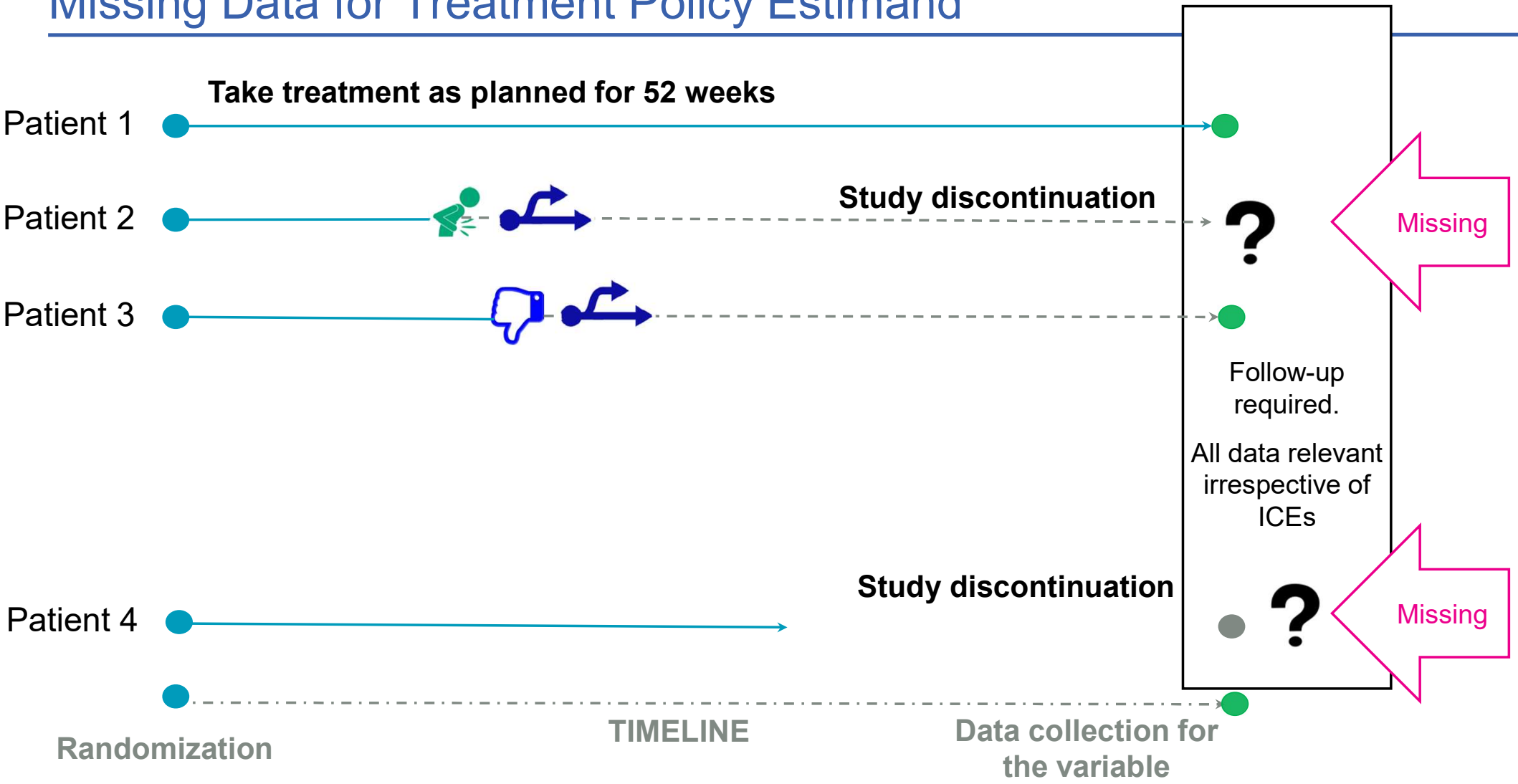
Missing Data for Hypothetical Estimand



Missing Data for Attributable Estimand



Missing Data for Treatment Policy Estimand



What do you think?

Time to hear what you think. For the purposes of regulatory decision making (i.e. to decide whether or not BGF has demonstrated efficacy) which estimand strategy would you choose to handle treatment discontinuation?

1. Hypothetical Estimand (as though patients who discontinued treatment continued treatment)
2. Attributable Estimand (Mix of Composite and Hypothetical depending on reason for treatment discontinuation)
3. Treatment policy Estimand (irrespective of treatment discontinuation)

VOTE NOW:

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Clinical view - Which estimand is most relevant to making the decision whether or not to approve triple therapy (BGF)?

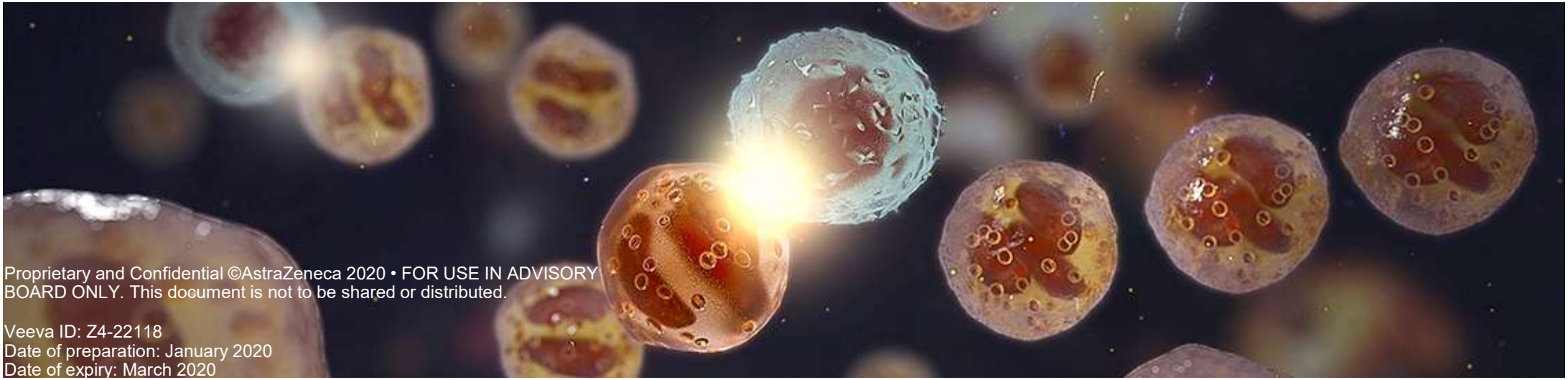
Hypothetical estimand (primary estimand in study (referred to as the efficacy estimand) assumes patients who stop taking treatment behave like people who continued taking treatment

Treatment policy includes efficacy data collected on other therapies. This could give misleading results.

Attributable estimand penalizes patients who can’t tolerate the drug due to lack of efficacy or adverse events to give a more informed view on the efficacy of the assigned therapy.

I would vote for the attributable estimand

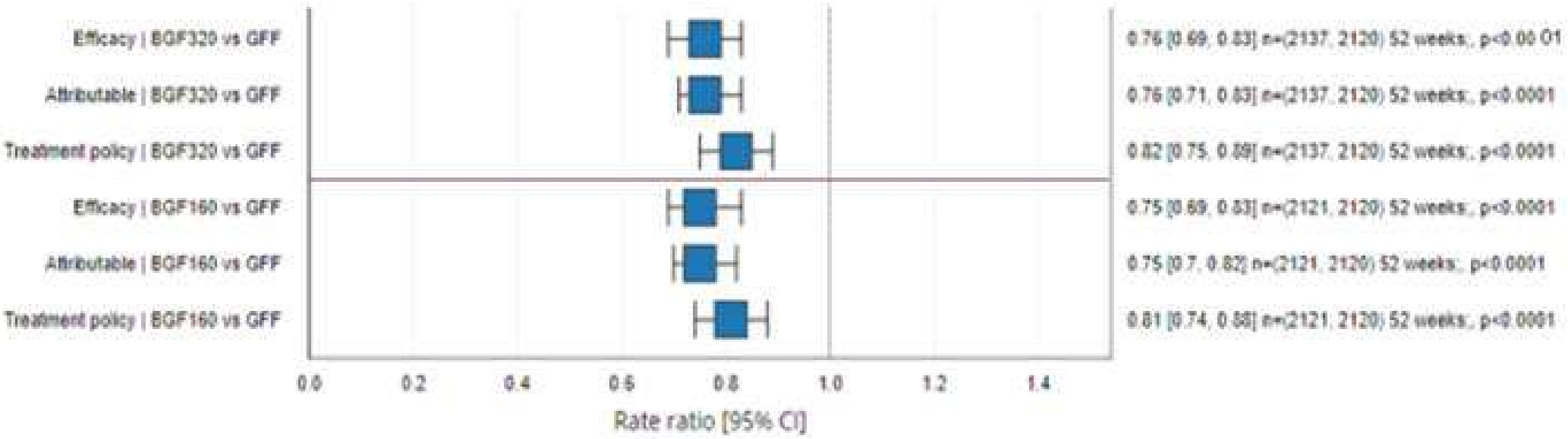
ETHOS Study Primary Endpoint Results



Veeva ID: Z4-22118
Date of preparation: January 2020
Date of expiry: March 2020

Rate of moderate/severe COPD exacerbations

BGF320 and BGF160 vs GFF (all estimands)



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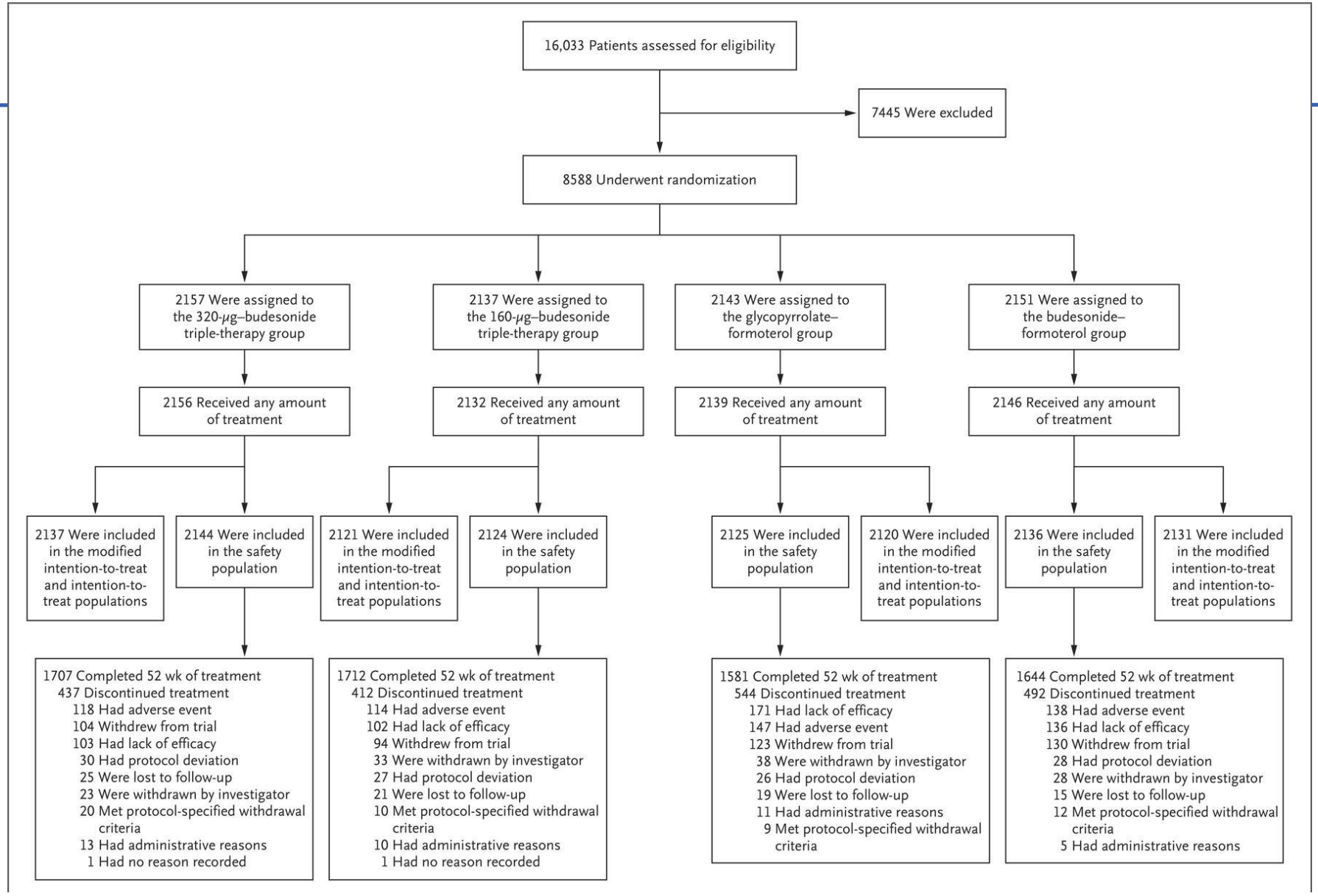
16,033 Patients assessed for eligibility
7445 Were excluded
8588 Underwent randomization
2157 Were assigned to the 320-μg–budesonide triple-therapy group
2137 Were assigned to the 160-μg–budesonide triple-therapy group
2143 Were assigned to the glycopyrrolate–formoterol group
2151 Were assigned to the budesonide–formoterol group
2156 Received any amount of treatment
2132 Received any amount of treatment
2139 Received any amount of treatment
2146 Received any amount of treatment
2137 Were included in the modified intention-to-treat and intention-to-treat populations
2144 Were included in the safety population
2121 Were included in the modified intention-to-treat and intention-to-treat populations
2124 Were included in the safety population
2125 Were included in the safety population
2120 Were included in the modified intention-to-treat and intention-to-treat populations
2136 Were included in the safety population
2131 Were included in the modified intention-to-treat and intention-to-treat populations
1707 Completed 52 wk of treatment
437 Discontinued treatment
118 Had adverse event
104 Withdrew from trial
103 Had lack of efficacy
30 Had protocol deviation
25 Were lost to follow-up
23 Were withdrawn by investigator
20 Met protocol-specified withdrawal criteria
13 Had administrative reasons
1 Had no reason recorded
1712 Completed 52 wk of treatment
412 Discontinued treatment
114 Had adverse event
102 Had lack of efficacy
94 Withdrew from trial
33 Were withdrawn by investigator
27 Had protocol deviation
21 Were lost to follow-up
10 Met protocol-specified withdrawal criteria
10 Had administrative reasons
1 Had no reason recorded
1581 Completed 52 wk of treatment
544 Discontinued treatment
171 Had lack of efficacy
147 Had adverse event
123 Withdrew from trial
38 Were withdrawn by investigator
26 Had protocol deviation
19 Were lost to follow-up
11 Had administrative reasons
9 Met protocol-specified withdrawal criteria
1644 Completed 52 wk of treatment
492 Discontinued treatment
138 Had adverse event
136 Had lack of efficacy
130 Withdrew from trial
28 Had protocol deviation
28 Were withdrawn by investigator
15 Were lost to follow-up
12 Met protocol-specified withdrawal criteria
5 Had administrative reasons

Communication

As you can see explaining different estimands is complex and there can be quite subtle differences between different estimands.

However, if patterns of treatment discontinuation for attributable reasons are quite different in different treatment arms different estimands can lead to quite different estimates of treatment benefit.

It is therefore important that different estimands can be thoroughly explained when communicating the results of a study.

Although here all estimands produce clearly positive results, even here the size of the clinical benefit is slightly greater with the efficacy and attributable estimands. Which one do you think should be included in the product label? Be communicated to the patient? Be used to decide if this drug should be reimbursed?

Issues with Communication in medical journals

Space is very limited – often a request to reduce the amount of explanation of approach used,.

In this case some description of estimands used was included.

In the future greater space needs to be given to

- The clinical objective(s) of the study
- How this leads to the choice of primary estimand and other estimands that might be needed to evaluate the benefits of treatment
- Space should also be given to explain why different estimands might be useful for different stakeholders who might have a different clinical objective

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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 pre-specified the approach you want to use.

Final Thoughts

- In this specific example the fact that patients can stop taking assigned medication and then receive any triple therapy (free combination or a different triple to that in the trial) produces data post treatment discontinuation that is not relevant to the clinical question of interest i.e. should the triple combination of BGF be used to treat COPD patients.
- This naturally leads to considering alternative estimands to treatment policy.
- This case only considers one intercurrent event there can be multiple that affect the outcome of interest and these can be handled in different ways (i.e. some treatment policy, some hypothetical etc…)

Learning Outcomes

- To discuss the **definition** of the estimand using **simple language** and to be able to identify **intercurrent events**
- Understand the choice of estimands using the ETHOS trial as an example
- 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**
- Understand the benefits of including estimands in publications of trial results in medical journals

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Watch out for more webinars coming in 2022

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References

- Triple Inhaled Therapy at 2 Glucocorticoid doses in moderate-to-very severe COPD NEJM 2020 Rabe et al
  - Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD | NEJM
- ICH E9 (R1) addendum on Estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
  - https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf)