Ulrike Fischer, Kathi Künnemann, Azuka Iwobi,
Maarten van Dijk, Seyma Öztürk, Habib Esmaeili

An attempt to translate estimands into plain language

staburo DATA SCIENCE

INTRODUCTION

ESTIMANDS

Describe the treatment effect a study seeks to assess using 5 attributes[1]:

Population	participants in the study
Endpoint	measurements taken of **each participant** to evaluate the treatment effect
Treatment	intervention used to obtain a treatment effect
Intercurrent event handling strategies	*define* the treatment effect by specifying how to address events in participants after treatment initiation (intercurrent events), e.g., how to handle missing and observed data
Population-level summary	summary measure **across all participants;** e.g., difference between groups = '*treatment effect*'

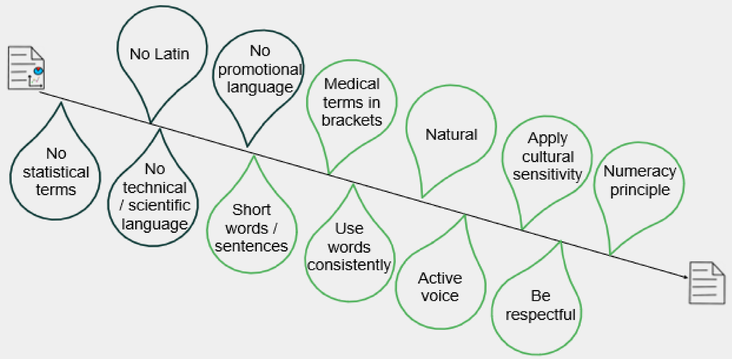
INTERCURRENT EVENTS (ICE)

- Occur in a participant after treatment initiation
- Affect either the interpretation or the existence of the endpoint

The 5 ICE handling strategies according to ICE E9 (R1)[1]:

Treatment policy	outcome value is used regardless of the ICE
Hypothetical	outcome value is not used after ICE, imagines a hypothetical scenario in which the ICE had not occurred
Composite	outcome value is a pre-defined outcome value, ICE is incorporated in the measurement of interest
While-on-treatment	outcome value is not used after ICE
Principal stratum	outcome value is considered only for those who did not experience an ICE

PLAIN LANGUAGE CHARACTERISTICS[2]



METHODS

We searched clinicaltrials.gov for trials with defined estimands and publicly available protocols. We extracted the primary estimands, their attributes and strategies for intercurrent event handling and translated them into plain language. We compared the translations of different trials to identify similarities and propose suggestions for guidance.

RESULTS

Example 1: Type 2 diabetes (T2DM)[3]

SCIENTIFIC LANGUAGE	PLAIN LANGUAGE
Adults with T2DM, HbA1c between 7.0 to 9.5%, treated with diet / exercise only	**In this trial, researchers wanted to find out if the new medicine, semaglutide, could lower high blood sugar (diabetes) more than the pretend medicine (placebo) in 26 weeks.**
Change from baseline to week 26 in HbA1c	Before the trial, the patients tried to lower their blood sugar. They did this only by eating healthily and exercising. In this trial, researchers compared 3, 7, and 14 mg semaglutide to a pretend medicine (placebo). Patients got semaglutide as a tablet once a day. Researchers measured each participant's blood sugar levels over 26 weeks.
Semaglutide (3, 7, 14 mg) vs placebo, oral tablet once daily	**Researchers used all values, including the values of patients who did not take their semaglutide as planned. For example, they included the fact that a patient took other blood sugar-lowering drugs or if a patient forgot to take their semaglutide. Researchers did this because they wanted to understand semaglutide's effect in real life.**
Treatment policy (treatment adherence, rescue medication)	
Adjusted mean difference in HbA1c at week 26 (dose-control comparison 'as randomized')	

Example 2: Obesity[4]

SCIENTIFIC LANGUAGE	PLAIN LANGUAGE
Adults with BMI 27.0 $\frac{kg}{m^2}$, without T2DM and 1 unsuccessful dietary effort to lose weight	**In this trial, researchers wanted to find out if a new medicine, BI 456906, could help patients with obesity lose weight better than a pretend medicine (placebo).**
Change from baseline to week 46 in body weight (%)	Before the trial, the patients tried to lose weight by eating healthily and less, but it did not work. Researchers compared 0.6, 2.4, 3.6, and 4.8 mg BI 456906 to a pretend medicine (placebo). The patients got BI 456906 as an injection once a week. Researchers measured each participant's weight over 46 weeks.
BI 456906 (0.6, 2.4, 3.6, 4.8 mg) vs Placebo, once weekly subcutaneously	**Researchers used all values of patients who had no COVID-19. They also used the values of patients who stopped their treatment with BI 456906 before week 46.** **In case patients got COVID-19 researchers used values as if the patient had had no COVID-19.**
Treatment policy (non-pandemic related), Hypothetical (pandemic-related)	
Adjusted mean difference in weight at week 46 (dose-control comparison 'as randomized')	

Example 3: Asthma[5]

SCIENTIFIC LANGUAGE	PLAIN LANGUAGE
Adults with moderate to severe asthma, airway reversibility of ≥ 12% and 200 mL in FEV1	**In this trial, researchers wanted to find out if a new medicine, GSK37772847, could help patients with repeated asthma attacks to control their asthma better.**
Percentage of participants with loss of asthma control over 16 weeks	In this trial, researchers compared 10 mg per kg to a pretend medicine (placebo). The patients got GSK37772847 as an infusion in their veins once a week. Patients also received two other Asthma medications: fluticasone propionate (500 mg) and salmeterol (50 mg). Researchers measured each participant if they lost their asthma control over 16 weeks.
GSK37772847 10mg/kg vs Placebo, intravenous infusion every 4 weeks	**Researchers used all observed values of patients who** • **took other medications that helped to control asthma,** • **did not take their fluticasone propionate and salmeterol as planned,** • **got pregnant.** **In case patients died or stopped their medication early researchers used values as if the patients were alive or had continued treatment.**
Treatment policy (prohibited/concomitant medications, pregnancy), Hypothetical (treatment discontinuation due to an AE/SAE, death)	
Median rate ratio (GSK**37772847**/ placebo) of loss of asthma control at week 16	

CONCLUSION

Because estimands describe the treatment effect, we believe it is important to make them understandable to everyone, including patients and the public.

This is what we found:

The attributes 'population-level summary' and 'intercurrent events' are the most difficult to translate:

- **'Population-level summary'** mainly uses highly technical mathematical language which is not helpful for a lay audience. Translating this in intuitive terms makes it understandable

  Incorporating the hypothesis into the treatment effect adds clarity, however, one loses language neutrality by doing this

- **'Intercurrent events'** affect the treatment effect. Explaining why they affect the treatment effect by giving examples increases understanding

  Limiting the ICE to those that happened, saves space and avoids unnecessary details

Keeping the attribute information concise adds clarity:

- Create a context for the actual numbers by keeping the estimands close to the actual results
- Focus on the primary and patient-relevant estimands

DISCUSSION

- Simplifying estimands will improve clarity and transparency in clinical trials by ensuring that the lay audience truly understands what research questions a trial seeks to address
- Additionally, easy-to-understand estimands will greatly improve the standardization of their terminology and enhance understanding within trial teams
- We see this poster as a starting point for future research:
  - The translation of estimands in plain language needs to be investigated on a larger scale. In this initial study, we looked at 11 trials with estimands in three different indications: diabetes type 2, obesity and asthma. We present one example of each indication here.
  - It is necessary to explore the extent to which translations of statistical analyses or terms in plain language enhance the understandability of the treatment effect
  - How the translation of estimands can exploit multi-media techniques, e.g., images, audio, animation, and video.

REFERENCES

[1] US Food and Drug Administration. ICH E9 (R1) statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials, 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf..
[2] Good lay summary practice guide, October 2021. https://health.ec.europa.eu/system/files/2021-10/glsp_en_0.pdf
[3] ClinicalTrials.gov ID: NCT02906930
[4] ClinicalTrials.gov ID: NCT04667377
[5] ClinicalTrials.gov ID: NCT03207243

ClinicalTrials.gov IDs of the other trials:
Type 2 diabetes: NCT03495102, NCT03214380.
Obesity: NCT03548935, NCT04657003, NCT02963935.
Pulmonary disease: NCT02465567, NCT02497001, NCT02924688.

Staburo GmbH, Aschauer Str. 26a, 81549 Munich, Germany, info@staburo.de, https://www.staburo.com