Joint PSI/EFSPI, PHUSE, ASA Safety Working Group Webinar Series

Scientific Evaluation of Safety Data: A Learning and Decision-Making Approach

8 October 2026, hosted by PSI: - *Introduction to Safety Assessments in Clinical Trials &*
- *Implementation Process of Safety Surveillance in Ongoing Studies*

10 November 2026, hosted by ASA: - *Estimands for Single Study and Aggregated Safety Analysis &*
- *Estimating and Comparing the Incidence of Adverse Events with Clinical Trial Data Focusing on Oncology Trials: A Safety Estimand Perspective*

January 2027, hosted by ASA: - *AI Enhanced Tools for Drug Safety Analytics*

March 2027, hosted by PHUSE: - *Communication – Barriers to Implementation*

Today's speakers

Joint PSI/EFSPI, PHUSE, ASA Safety Working Group Webinar Series | 8 October 2026



Naomi Givens

Statistics Director, GSK

Facilitator



Rima Izem

Director in Biostatistics, Novartis

Introduction to Safety Assessments in Clinical Trials



Katarina Hedman

Statistical Science Director, AstraZeneca

PHUSE Package of Educational Slide Decks on Safety Estimands



Matthias Trampisch

Expert TAM Statistician, Boehringer Ingelheim

Beyond Individual Cases: Operationalizing FDA IND Safety Reporting for Anticipated SAEs



Matteo Pedone

Principal Statistician, GSK



Alex Spiers

Statistics Leader, GSK

From Theory to Practice: Implementing BDRIBS for Blinded Safety Surveillance

Why now?

Year	
2026	PHUSE Safety Analytics Working Group: educational slide decks on the implementation of estimands in safety analysis
2025	US FDA (CDER), Standard Safety Tables and Figures: Integrated Guide, Version 2.0
	US FDA Guidance for Industry: Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices
	US FDA Guidance for Industry: Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies
2024	US FDA webinar: Statistical Considerations for Premarketing Risk Assessment (16 May 2024)
	US FDA Guidance for Industry: Use of Data Monitoring Committees in Clinical Trials
2022	ICH E19: A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials
2021	ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials
2018	US FDA Draft Guidance for Industry: Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products

Co-authors Part 1 October 8, 2026,

Introduction to Safety Assessments in Clinical Trials

- Rima Izem, Advanced Quantitative Sciences, Novartis, Basel, Switzerland
- Katarina Hedman Biometrics CVRM, AstraZeneca, Gothenburg, Sweden

  On behalf of Estimands in Safety Analytics Project Team in PHUSE Safety Analytics Working Group

Disclaimer

The content should not be interpreted as a binding standard and/or information required by regulatory authorities.

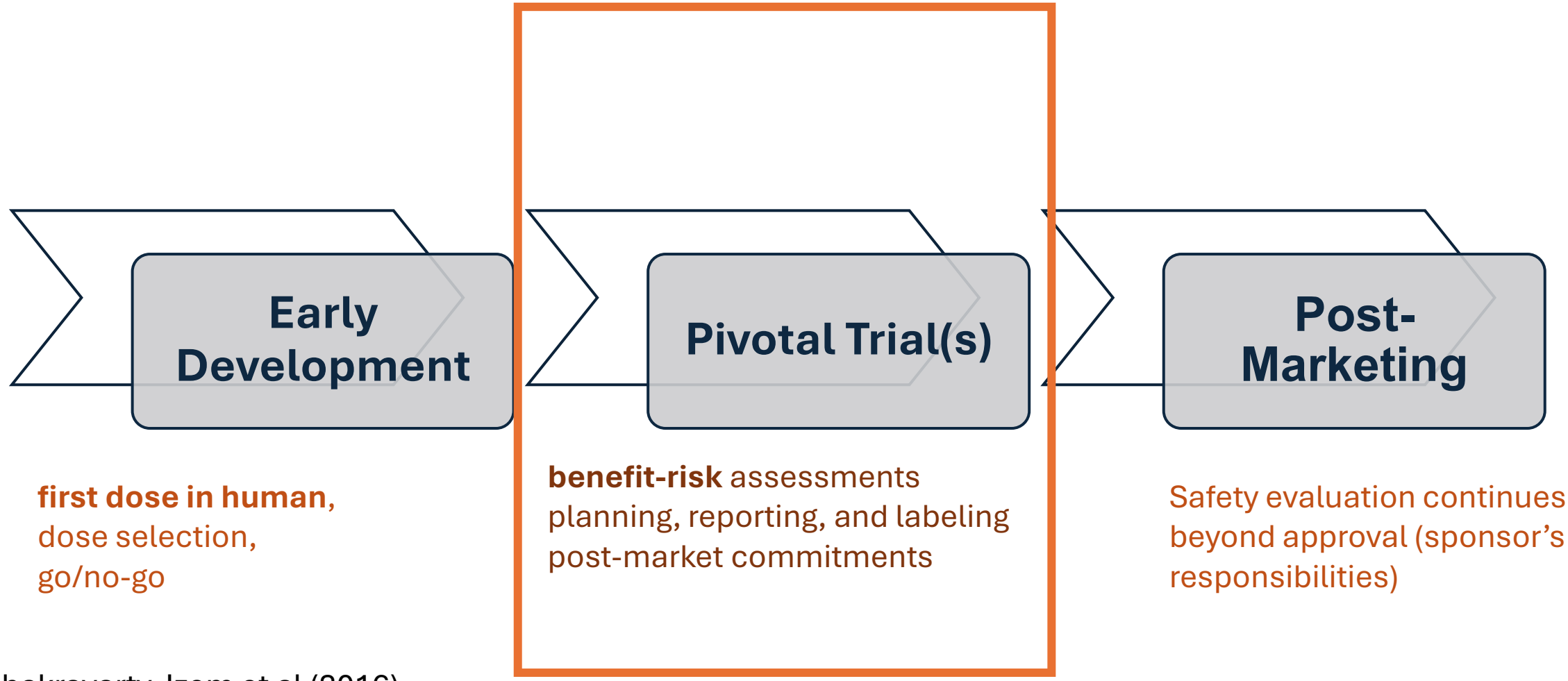
Key messages

- The goals of safety data collection and analyses in clinical trials are to protect patient participating in the trial (knowns, and unknowns risks) and characterize the benefit-risk of the product

- The two-tier safety approach triages (Tier 1: general safety profile) assessments with broad questions and scalable analytics from (Tier 2: specific safety questions) assessments with focused safety topics and in-depth analytics

- The Estimand framework principles apply to safety analyses (Tier 1 and Tier 2)

Safety throughout the drug development lifecycle



Chakravarty, Izem et al (2016)

Safety is critical to benefit-risk



Risk Benefits

Pink Sheet >> Product Reviews >> Post-Marketing Regulation & Studies

UK MHRA Joins List Of Regulators Scrutinizing Drug X

Jun 08 2026 • By Neena Brizmohun • 3 min read

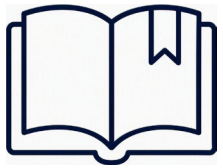
Safety differentiation: emerging competitive edge in drug development

Marianne Uteng[1], Laszlo Urban[2], Dominique Brees[1], Patrick Y. Muller[3], Gerd A. Kullak-Ublick[4,5], Page Bouchard[2], Gervais Tougas[4] and Salah-Dine Chibout[1]

[1] Novartis Institutes for Biomedical Research, Translational Medicine, Pre-Clinical Safety, Basel, Switzerland
[2] Novartis Institutes for Biomedical Research, Translational Medicine, Pre-Clinical Safety, Cambridge, MA, USA
[3] Novartis Pharma AG, Global Drug Development, Basel, Switzerland
[4] Novartis Pharma AG, Global Drug Development, Chief Medical Office and Patient Safety, Basel, Switzerland
[5] Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

References: (Left) Pink Sheet (2026), Uteng et al (2019)

Safety knowns and unknowns: key concepts



RSI

Reference Safety Information Section of the **Investigator Brochure**



SmPC

Summary of Product Characteristics (EMA)



USPI

US Prescribing Information



SUSAR

Suspected Unexpected Serious Adverse Reaction



AESI

Adverse Event of Special Interest



ADR

Adverse Drug Reaction



ASAE

Anticipated Serious Adverse Event

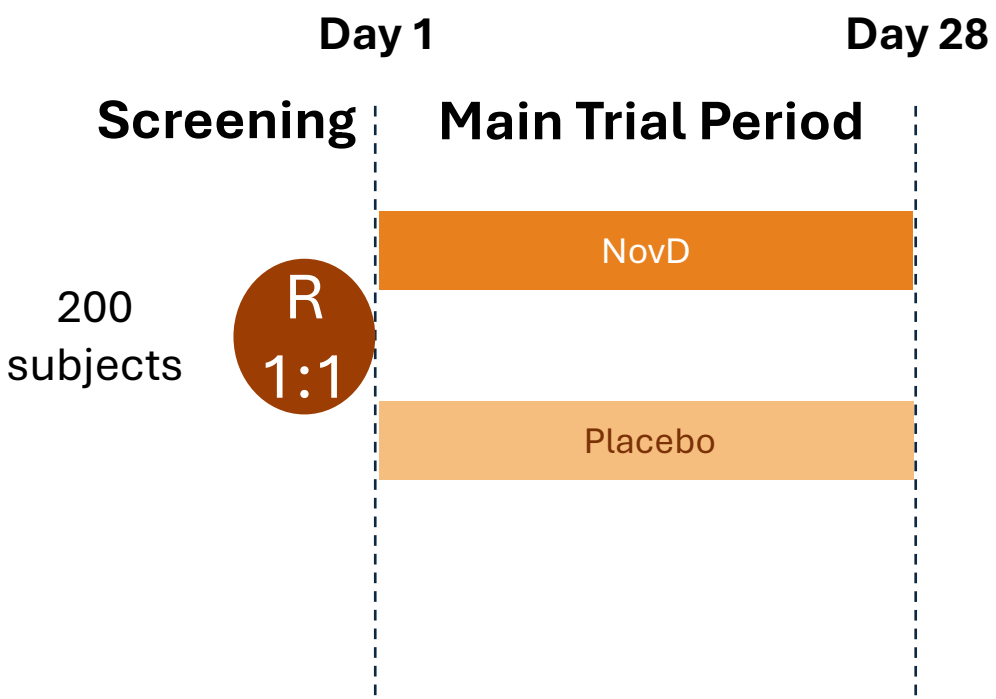
STOI

Safety Topic Of Interest

Safety planning: protecting trial participants

- Document assessment of the safety knowns and unknowns in the protocol and Statistical Analysis Plan
- Standardize data collection of AESI and ADRs in the trial and mitigate the risks when possible
- Evaluate the (summary measure of) risk of each anticipated AE
- **Plan safety monitoring and reporting during the trial (individual reports and aggregate reports, blinded/unblinded) and at trial completion**

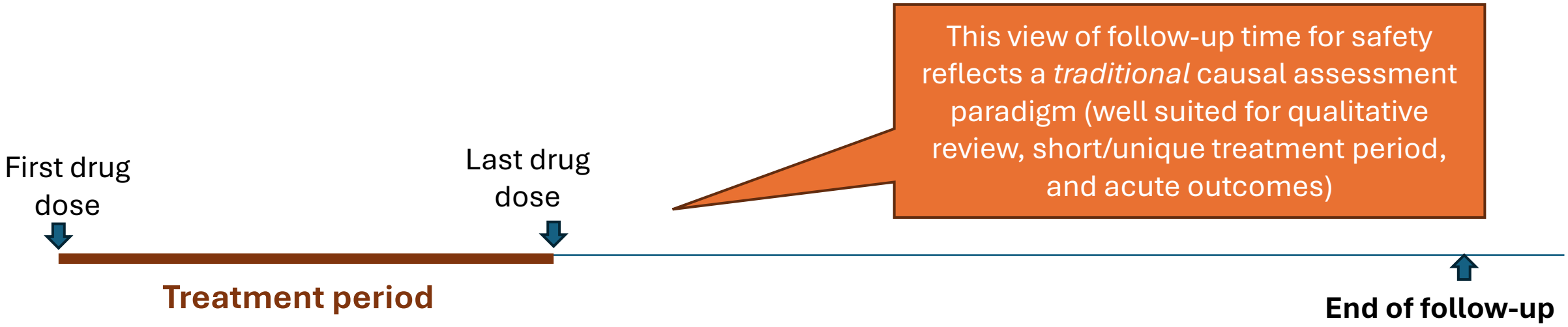
Toy example



Incidence of some adverse events

Term (MedDRA)	NovD	Placebo	Risk difference (%)
Urinary tract infection	4	2	2%
Herpes zoster	2	0	2%
Pneumonia	1	0	1%
Serious, infection and infestation	2	1	1%

Time: typical safety periods in the patient journey

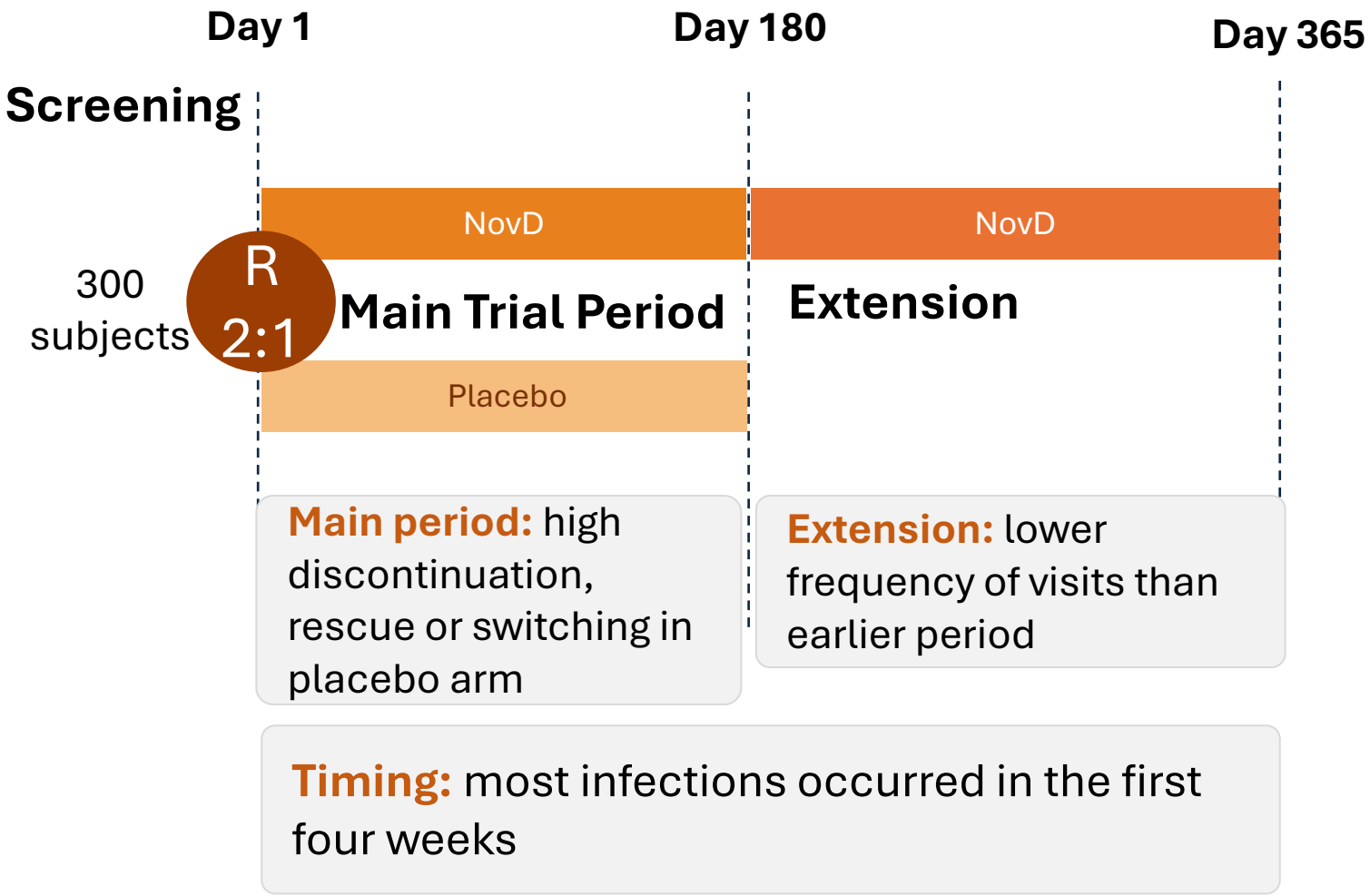


On-treatment period or at-risk ascertainment period
(e.g., pre-set 30 days after the last drug dose, or 5 x half-life whatever is larger)

On-study period starts at first drug and ends at the end of follow-up for each patient (e.g., pre-set maximum follow-up time)

On-treatment vs. on-study? (see FDA webinar (2024) DeMets & Cook (2019), Yang & Wittes (2019))

Reality?

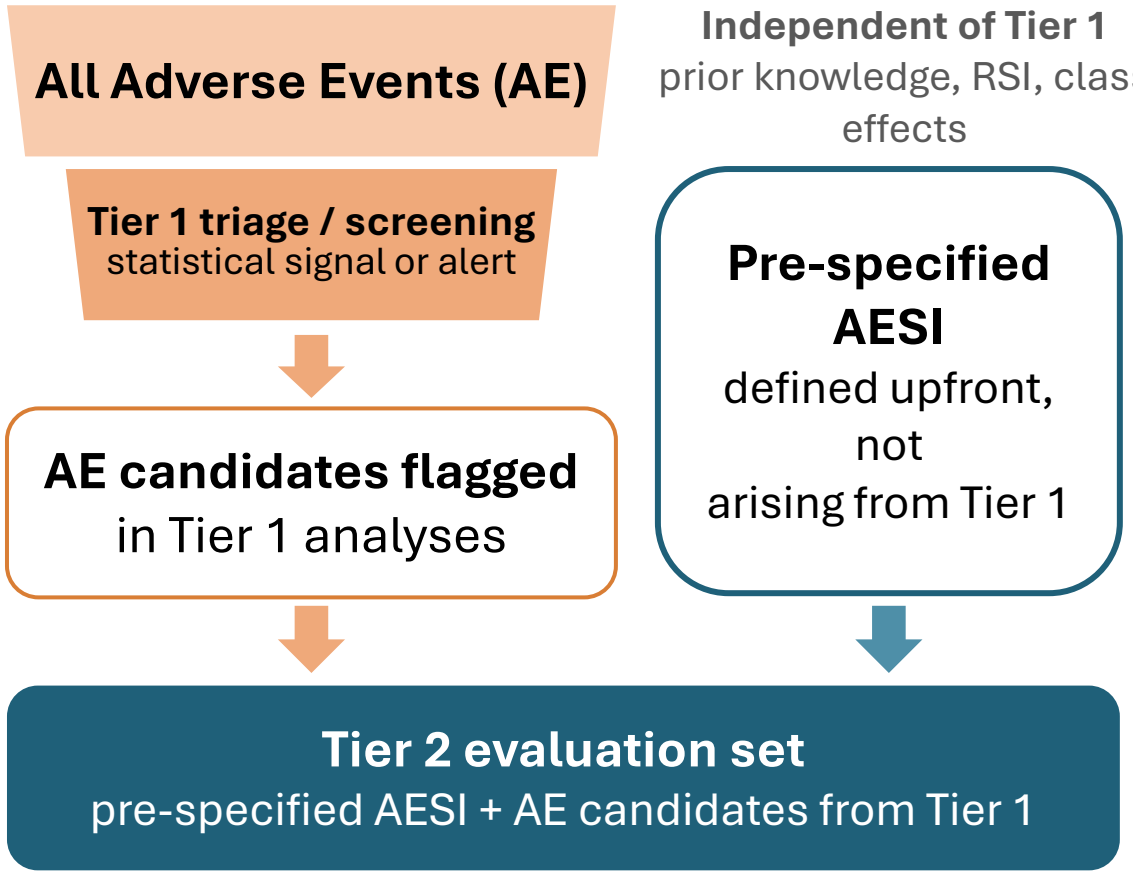


Serious infections and infestations (on-treatment)

NovD: 18 events (9%)
Placebo: 8 events (8%)

Risk?

Safety planning and reporting: two-tier approach



Tier 1: Overall safety profile

Aim: AE triage or screening to select candidates with a statistical signal or alert for further in-depth evaluation

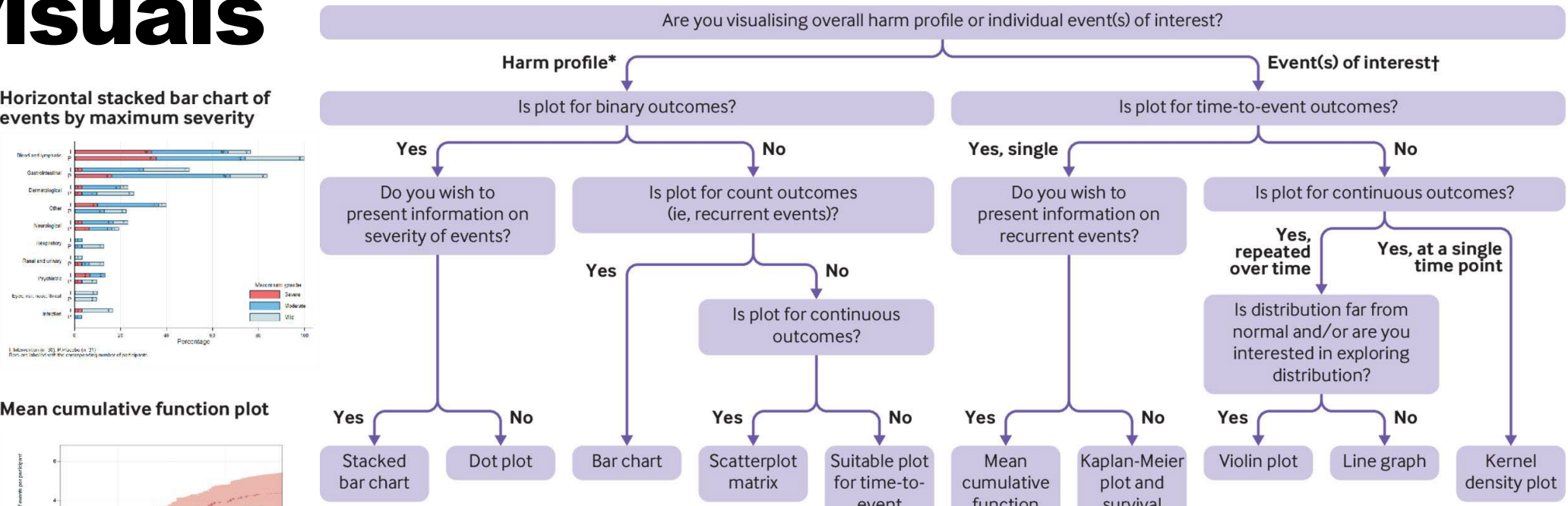
Methods: Scalable reporting and analyses (e.g., fully using MedDRA hierarchy, use of graphics), potentially run sequentially for safety monitoring

Tier 2: Specific safety questions

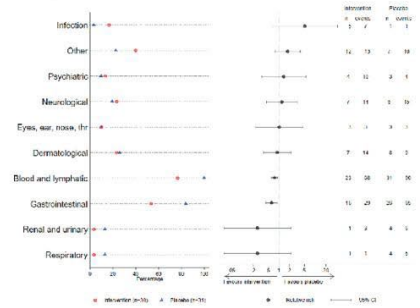
Aim: Inform benefit-risk assessment at marketing approval with (pre-specified) estimand(s) and estimation strategies for each AESI

Methods: Granular analyses tailored to each question of interest, guided through the estimand framework

Tier 1 visuals

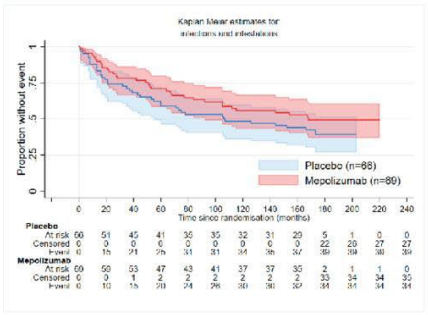


Dot plot

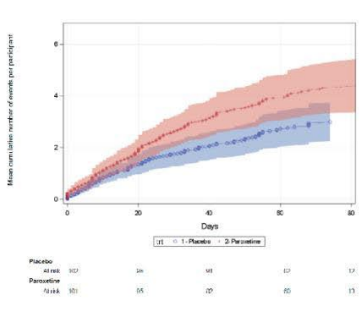


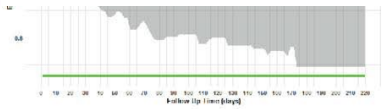
Horizontal stacked bar chart of events by maximum severity

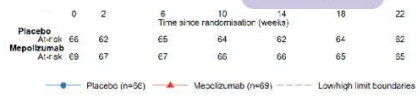
Kaplan-Meier plot



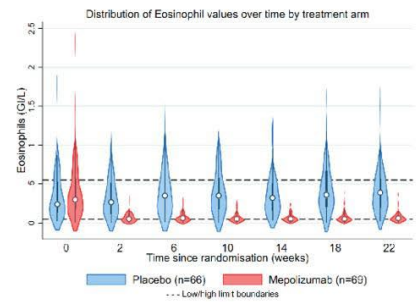
Mean cumulative function plot



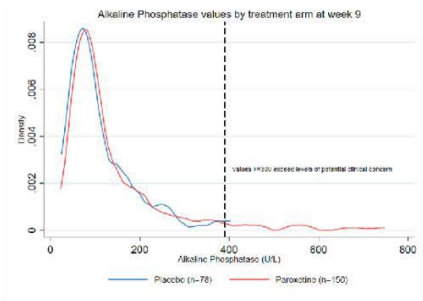




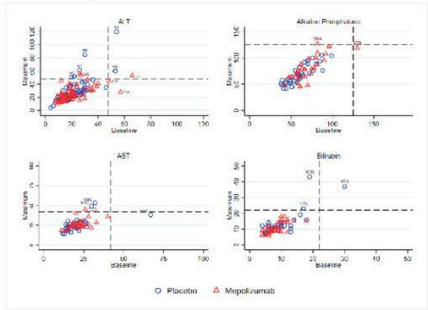
Violin plot



Kernel density plot



Scatterplot matrix



Rachel Phillips et al. BMJ 2022;377:bmj-2021-068983

©2022 by British Medical Journal Publishing Group

What does FDA say?

Statistical Perspective

- Trials should generally include plans to assess efficacy and safety outcomes through trial end in all randomized participants and to carry out on-study analyses
- Additional on-treatment safety analyses may also be of interest, particularly for signal detection, in some settings

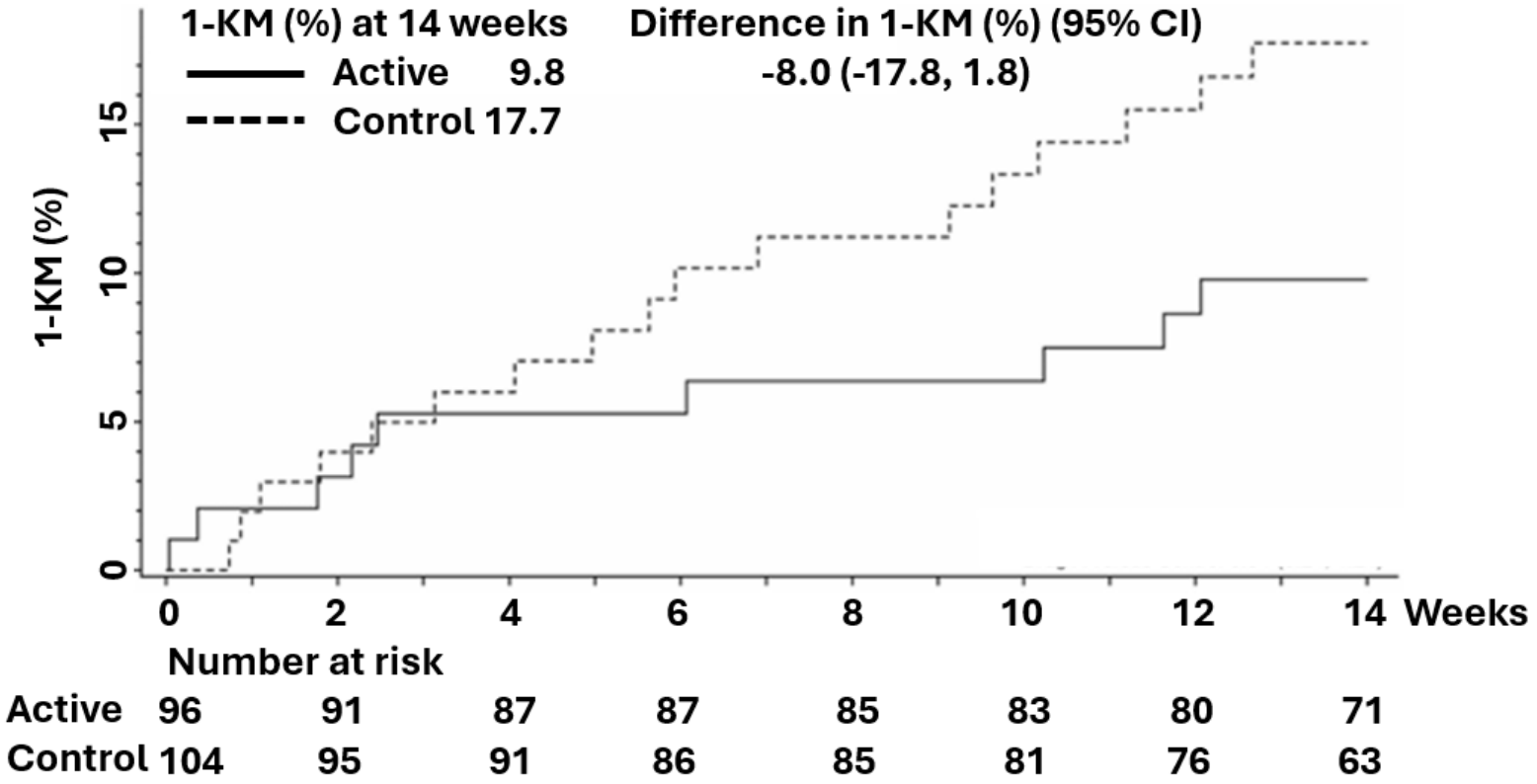
Cumulative Incidence Considerations

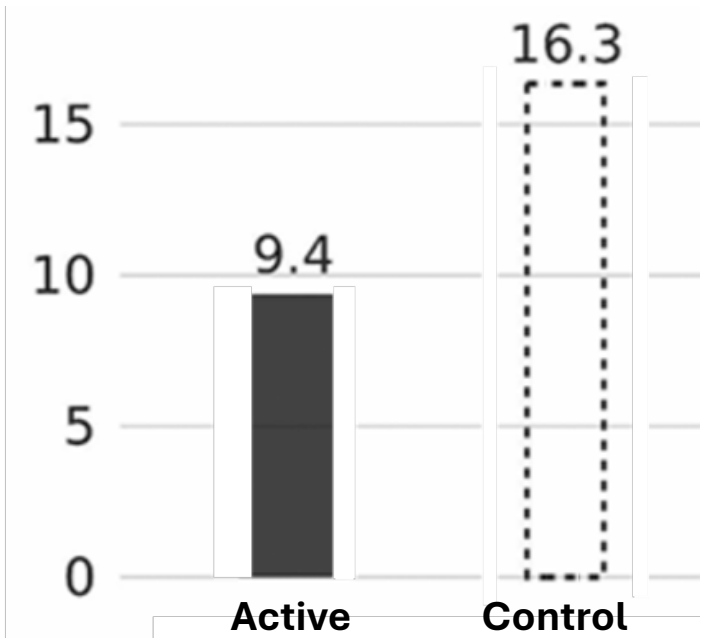
- Cumulative incidence **in given period** (e.g., 1 year) focuses on snapshot of risk **through single time point**
  - May not be sensitive to differences at earlier or later time points
  - Can look at incidence **over time** (e.g., in Kaplan-Meier plots) to help address this
- When participants are followed for **different lengths of time**, simple calculation of n/N (i.e., crude proportion) is **not appropriate**
  - Can occur by design (time-to-event trials) or in fixed duration trials with participant dropout
  - **Reliable estimation requires more complex methods (e.g., Kaplan-Meier, Aalen-Johansen)**

41

FDA webinar on Statistical Considerations for Premarketing Risk Assessment 2024

Modern Safety Analysis Versus Traditional





Modification of figure in Hedman K, Lisovskaja V et al. 2024. A safety estimand for late phase clinical trials where the analysis period varies over the subjects. Clinical Trials. 2024; 21(4):483-490. doi: 10.1177/17407745241230933.

Advice – planning and reporting safety

Tier 1 (Statistical signal detection)

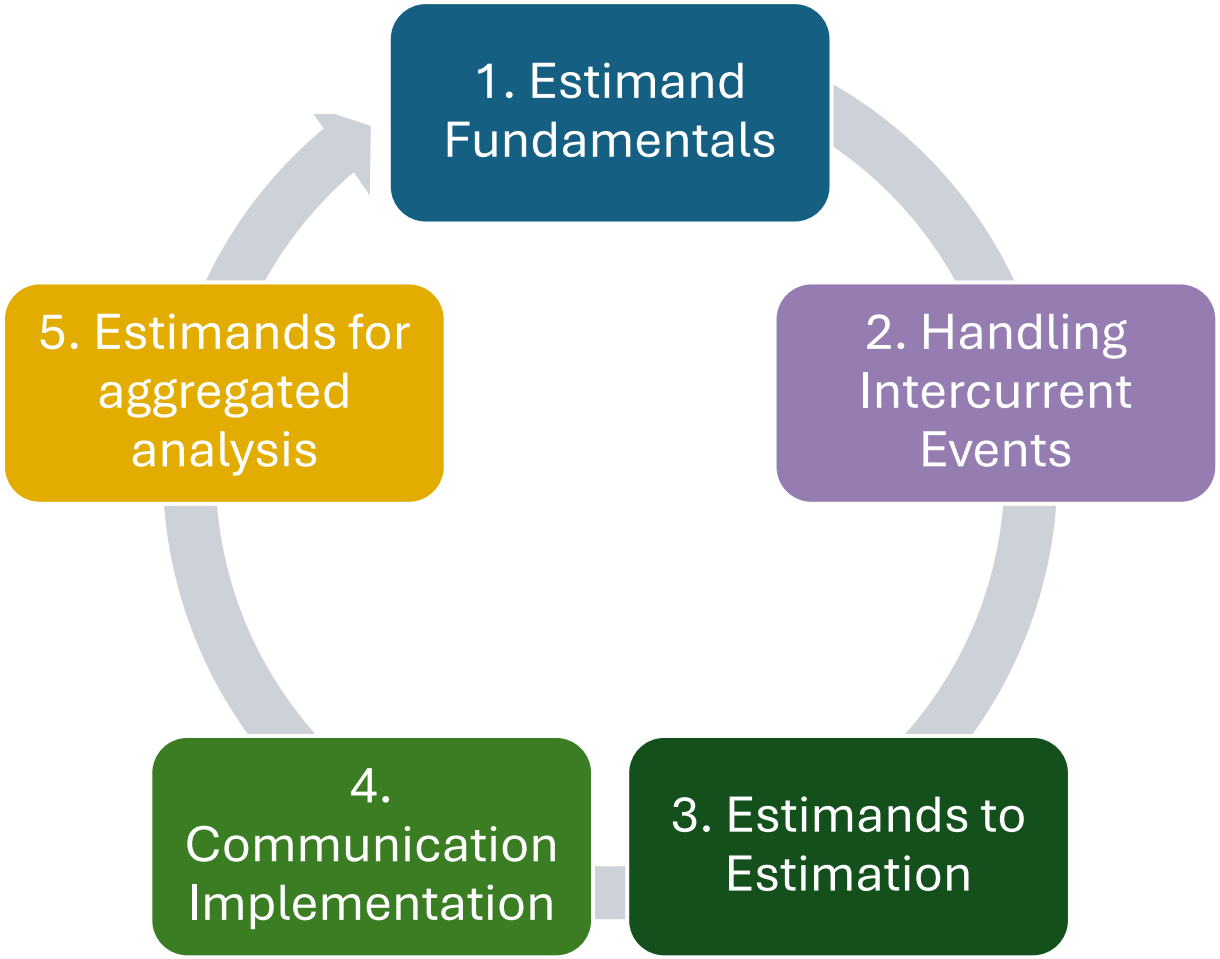
- Report risk % or rate per unit of time for each AE and AE grouping (eg MedDRA SOC & PT)
- Prospectively define explicitly the follow-up and tailor this period to exposure(s) and/or to the comparisons of interest
- Define what constitutes an “alert” for further analyses (e.g., higher than expected for this indication, or higher in treatment A vs. treatment B)
- Use graphics to help with the alert process

Tier 2 (Quantification of STOI)

- Use estimand framework to translate questions of interest into design and analyses considerations
- Discuss important intercurrent events such as change in exposure (e.g., treatment discontinuation, rescue therapy, or concomitant therapies)
- Consider the impact of terminal events (e.g., death) and/or competing risks (e.g., bleeding for anticoagulant therapy, non-CV death for CV outcomes)

STOI Safety topic of interest

PHUSE Estimands in Safety Analytics Project



Building capability in safety analysis:
Package of educational slide decks and upcoming webinars **to operationalize the estimand framework for the safety analyses** in clinical trials

What Does FDA Say?

Statistical Considerations for Premarketing Risk Assessment May 2024

Design and Analysis Plan Principles

- Consider appropriate design and analysis plan elements **prior to Phase 3** to ensure reliable safety evaluation
  - Improved planning improves quality and reliability of safety data
- Appropriate analysis approaches for both AESIs and for descriptive assessment of general safety for signal detection

AESIs are Outcomes identified prior to the trial as plausibly affected by the drug (e.g., based on class effects, biologic plausibility, non-clinical findings, or early-phase results)

Focus on Estimation and Uncertainty

- Key aspects of safety and benefit-risk assessment
  - Estimation of magnitudes of potential adverse effects
  - Degree of confidence there is not unacceptable harm in context of benefits
- Motivates two goals in safety evaluation
  - Estimation of magnitude of harm (point estimate)
    - Interest in **causal effect**: typically requires randomized comparison unless safety outcome does not occur naturally in population
  - Estimation of uncertainty around magnitude of harm (e.g., confidence interval)
    - Upper CI bound important to consider magnitude of harm ruled out with high confidence

FDA webinar on Statistical Considerations for Premarketing Risk Assessment (2024)

Estimand, Estimator, Estimate

Target of estimation = WHAT TO ESTIMATE

Safety Objective → To evaluate the safety and tolerability of the investigational treatment.

Clinical Question → E.g., in adults with hypertension, what is the percentage of hypotension occurring by 3 months after initiation of Treatment A, compared with placebo?

Estimand → The "recipe" for obtaining an answer to the clinical question.

Statistical method of estimation = HOW TO ESTIMATE

Estimator → E.g., Within treatment group incidence proportion and its treatment difference.

THE RESULT

Estimate → E.g., the incidence proportion for an adverse event was 10% higher in treatment A group than in the placebo group.

ICH E9(R1) guidance and training

Write clear and well-structured estimand statements

Study Design: A 12-week placebo-controlled study period, randomization to 1 mg of baxdrostat, 2 mg of baxdrostat, or placebo.

Primary Safety Question: In adults with uncontrolled and resistant hypertension, what is the percentage of hyperkalemia by 12 weeks after initiation of baxdrostat 2 mg compared with placebo?

Estimand:

Population: Adults with uncontrolled and resistant hypertension

Treatment: Baxdrostat 2 mg or placebo

Summary measure: Probability of occurrence of hyperkalemia; implemented by incidence proportion estimator using the on-study analysis period



Intercurrent events with handling strategies:

- Ignoring treatment discontinuation and changes in background medications **(treatment policy strategy)**
- No imputation of data after death and using incidence proportion estimator **(while-alive strategy)**

Flack, Azizi et al 2026 - https://www.nejm.org/doi/full/10.1056/NEJMoa2507109

PHUSE Safety Library



https://sway.cloud.microsoft/GDFDyqfElW4nkjQy?ref=Link

References

- Chakravarty, A. G., Izem, R., Keeton, S., Kim, C. Y., Levenson, M. S., & Soukup, M. (2016). The role of quantitative safety evaluation in regulatory decision making of drugs. *Journal of Biopharmaceutical Statistics*, *26*(1), 17-29.
- Uteng, M., et al, (2019). Safety differentiation: emerging competitive edge in drug development. *Drug discovery today*, *24*(1), 285-292.
- DeMets DL, Cook T. Challenges of Non–Intention-to-Treat Analyses. *JAMA*. 2019;321(2):145–146.
- Yang F, Wittes J et al. 2019. Beware of on-treatment safety analyses. Clinical Trials. 2019; 16(1): 63-70.
- Hedman K, Lisovskaja V et al. 2024. A safety estimand for late phase clinical trials where the analysis period varies over the subjects. Clinical Trials. 2024; 21(4):483-490.
- PHUSE Safety Library: https://sway.cloud.microsoft/GDFDyqfElW4nkjQy?ref=Link
- CIOMS VI - Management of Safety Information from Clinical Trials (https://cioms.ch/wp-content/uploads/2017/01/Mgment_Safety_Info.pdf)
- Phillips, R, et al. "Visualising harms in publications of randomised controlled trials: consensus and recommendations." *bmj* 377 (2022).

Glossary of terms

Documents describing the knowns in safety:

- **Reference Safety Information (RSI)**: mandatory part of the investigator brochure (Section 6) providing a concise summary list of all “Adverse Events” (AE) considered to be expected for reporting purposes
- **Summary of Product Characteristics (SmPC)**: An EMA document describing the properties and the officially approved conditions of use of a medicine.
- **US Prescribing information (USPI)** The FDA-approved prescribing information for healthcare professionals in the United States.

- **Adverse Events of Special Interest (AESI)** adverse event of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. (CIOMS VI)
- **Adverse Drug Reactions (ADR),** an AE suspected to be related to the drug based on individual assessment by investigator or aggregate reports
- **Anticipated serious adverse event (ASAE)** serious adverse events that are likely to occur in the study population because the adverse events (1) reflect consequences of participants’ underlying disease or factors such as age and (2) are events that may occur in the study population unrelated to an effect of a drug (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population).
- **Suspected Unexpected Serious Adverse Reactions (SUSAR):** any event not listed in the RSI for unauthorized products or SmPC/USPI for authorized products
- Safety Topic of Interest (STOI: A pre-specified or emerging safety concern associated with a medical product that is selected for focused monitoring, analysis, or evaluation in post-marketing surveillance or regulatory safety assessments.