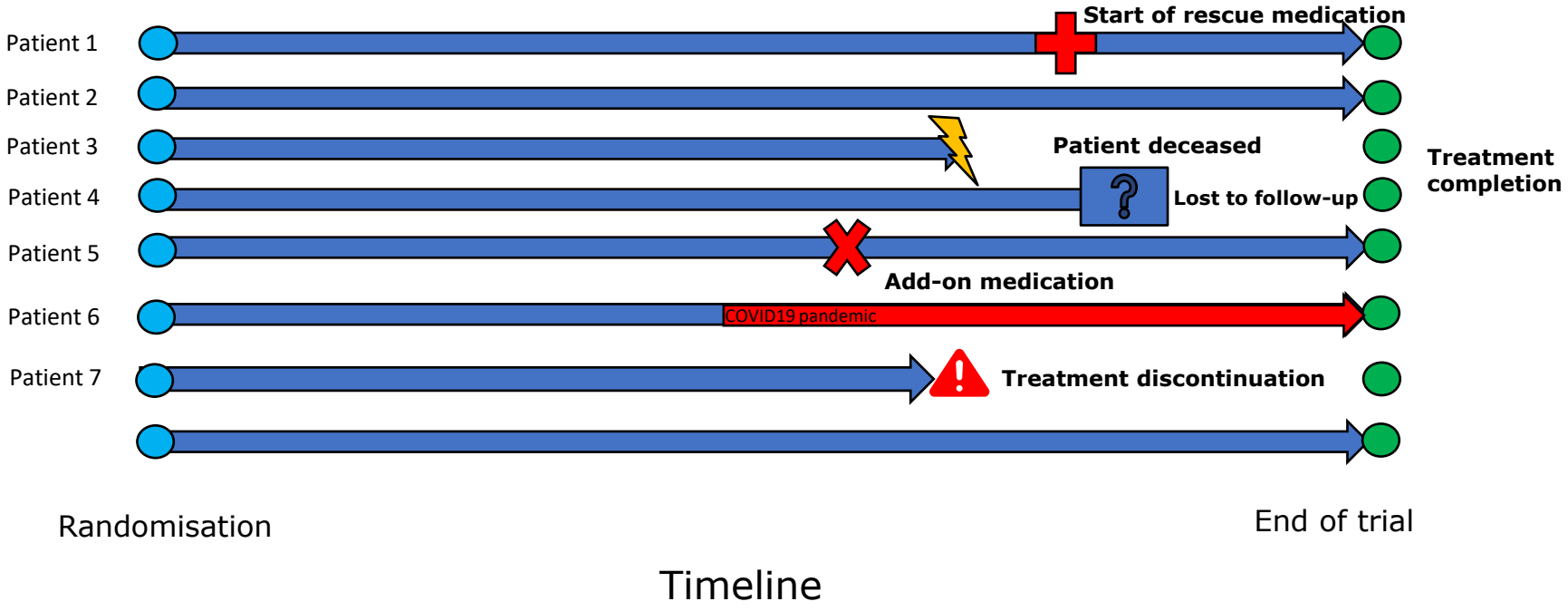
ICH E9(R1) estimand framework & CDISC

Marian Mitroiu, PhD

12 May 2023

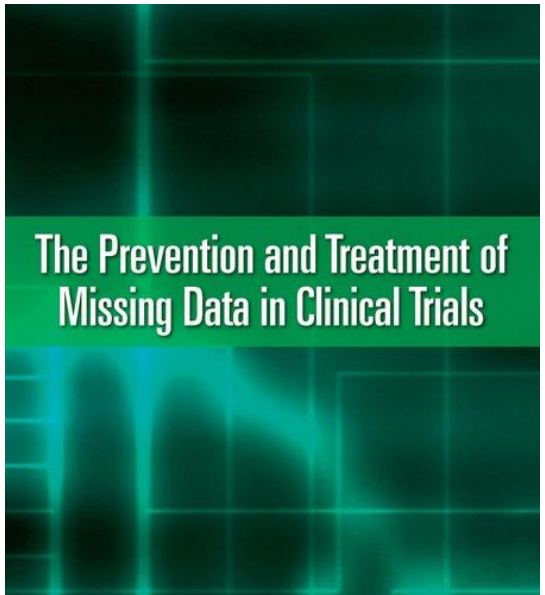
Estimands session at IX CDISC Italian User Network

Patient journeys in a trial



ICH E9(R1) Timeline

- 2010 US National Research Council report on missing data (& estimands)
- E9(R1) Expert Working Group
  - Oct 2014 Concept Paper
  - August 2017 Step 2b
  - December 2019 final version step 5



ICH
harmonisation for better health

Final Concept Paper
E9(R1): Addendum to Statistical Principles for Clinical Trials
on
Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials
dated 22 October 2014
Endorsed by the ICH Steering Committee on 23 October 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2017
EMA/CHMP/ICH/436221/2017
Committee for Human Medicinal Products

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
Step 2b

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

Status: *Step 5*

Implementation status:

ANVISA, Brazil - In the process of implementation; Date: 1 December 2023;

COFEPRIS, Mexico - Not yet implemented;

EC, Europe - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/436221/2017

FDA, United States - Implemented; Date: 11 May 2021; Reference: Posted on FDA, United States website

HSA, Singapore - Implemented; Date: 1 November 2019; Reference: HSA, Singapore webpage: Guidance documents for clinical trials

Health Canada, Canada - Implemented; Date: 21 July 2020; Reference: File #: 20-109237-45

MFDS, Republic of Korea - In the process of implementation; Date: 1 January 2022;

MHLW/PMDA, Japan - In the process of implementation;

MHRA, UK - Implemented; Date: 1 July 2020;

NMPA, China - Implemented; Date: 25 January 2022; Reference: NMPA, China Announcement No. 16 (2021)

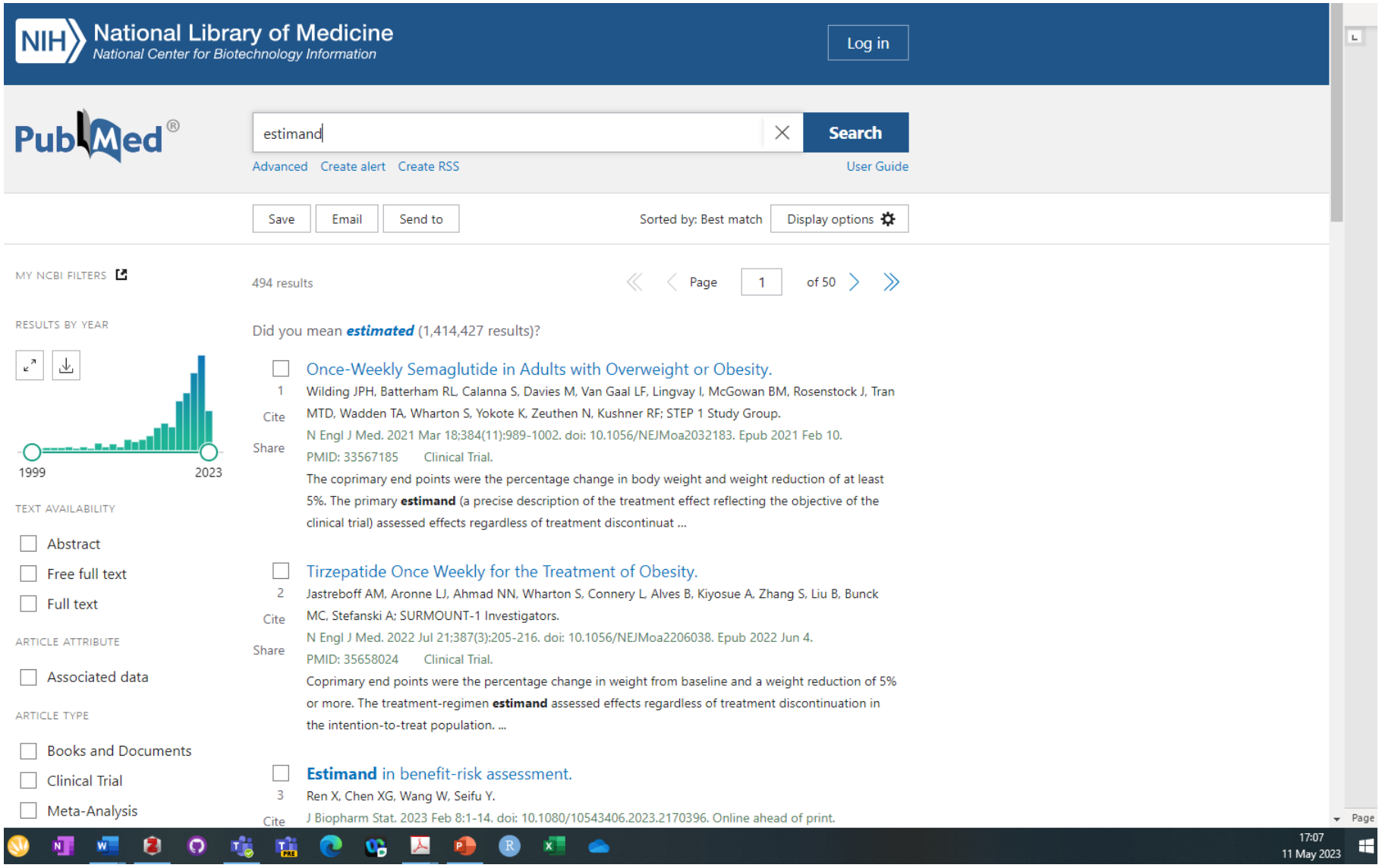
SFDA, Saudi Arabia - Not yet implemented;

Swissmedic, Switzerland - Implemented; Date: 30 November 2019;

TFDA, Chinese Taipei - Implemented; Date: 9 February 2021; Reference: Updated-Announcement for ICH Guidelines Recognition List

TITCK, Turkey - Not yet implemented;

Estimands in literature



Estimands in Regulatory guidance?

the control group during a pre-defined post-vaccination interval.

Guideline on clinical evaluation of vaccines
EMEA/CHMP/VWP/164653/05 Rev. 1

Page 15/21

- The required number of events (i.e. cases) has been accumulated. This case-driven approach may be most appropriate when the rate of accumulation of cases is less certain.

The primary analysis should be aligned to an agreed target of estimation (estimand) as determined by the trial objective. Examples of issues to consider when defining a target of estimation include the target population about which confirmatory conclusions are to be drawn and adherence to the treatment schedule. Depending on the specific situation there could be others, including events such as death that preclude observation of the variable of interest.

ing factors such as the expected proportion

Estimands

The concept of estimands, defined as 'a precise description of the treatment effect reflecting the clinical question posed by the trial objective' (ICH E9(R1)), is equally important for SATs as for RCTs. However, due to the uncontrolled nature of SATs, some concepts from the estimands framework are more difficult to apply, specifically in relation to the five estimand attributes:

- Treatment ('The treatment condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made…', ICH E9(R1)): In SATs, only the investigational treatment is administered, and there is no alternative treatment condition to which a direct comparison can be made with the data derived from the SAT.
- Population: See Section 4.2.
- Variable (or endpoint): See Section 4.1.
- Handling of intercurrent events: Intercurrent events are defined as 'Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest' (ICH E9(R1)). In SATs, intercurrent events are only observed for the investigational treatment arm which poses an additional challenge in relation to their interpretation and handling and even the timing of treatment initiation may be less clear than in RCTs.
- Population-level summary: See definition of treatment effect estimate in this section and Section 4.4.

Conceptually, appropriateness of a SAT depends on whether it can address the targeted estimand of interest. Specific problems associated with this are addressed in Section 4.

Treatment effect of interest

Following ICH E9, a treatment effect is 'an effect attributed to a treatment in a clinical trial. In most trials the treatment effect of interest is a comparison (or contrast) of two or more treatments'. For the purpose of this reflection paper, the term treatment effect of interest refers to the comparison (contrast) of the summary measure under the experimental treatment to the summary measure under the alternative of the trial population not being treated with the experimental treatment (counterfactual). This term is used in this reflection paper in the context of assessing whether there is an effect attributable to treatment and of (unbiased) estimation of the size of the treatment effect.

Isolation of treatment effect

There is no general statistical or methodological definition for the concept of isolating a treatment effect. For the purpose of this reflection paper, the following definition is adopted. If observed individual outcomes in a SAT for the defined endpoint within the designated follow-up could not have occurred without active treatment in any patient who entered the trial, the SAT is able to isolate the

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation
EMA/CHMP/50424/2021

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(i) COVID-19 potentially affecting trial participants directly and

(ii) COVID-19 related measures a

on trial integrity and interpretability i
analysis of the accumulating trial data
of study participants during the trial,
treatment effect. It is understood tha
monitoring activities and should prim
blinded data with the intent to inform
not with the usual intent to confirm tl
should focus on quality and reliability
consider the impact of intercurrent ev
arising from the COVID-19 pandemic
estimand framework provides a comp

2. Missing Data and Intercurrent Events

Subjects may have missing data in the study for various reasons (e.g., subject's refusal to continue in the study, worsening of conditions or emergence of adverse events, subject's failure to meet scheduled appointments for evaluation). Subjects may also have intercurrent (post-randomization) events that affect either the interpretation or the existence of the measurements associated with the question of interest (e.g., noncompliance with the protocol for various reasons, use of rescue medication due to lack of efficacy, death). Missing data and intercurrent events can introduce problems such as bias, misleading inference, loss of precision and loss of power, which make it hard to interpret the trial outcome.

The ICH (Internal Council for Harmonization) E9(R1) Addendum introduces the concept of an estimand, which is a precise description of the treatment effect reflecting the clinical question posed by a particular study objective.[21] The trial protocol of a BE study should include the following components of an estimand: (1) the treatment of interest and alternative treatment(s) to which comparison will be made: e.g., test drug compared with reference drug; (2) the analysis population for BE assessment; (3) the variable (or endpoint) to be measured for each subject (e.g., AUC or C_{max}); (4) the specification of how to account for intercurrent events in assessing the scientific question of interest (for example, in a comparative clinical endpoint BE study with

[19] Fieller, E., Some Problems in Interval Estimation, 1954, Journal of the Royal Statistical Society, 16(2): 175-185.
[20] For example, see Sun, W., S. Grosser, and Y. Tsong, 2017, Ratio of Means vs. Difference of Means as Measures of Superiority, Noninferiority, and Average Bioequivalence, Journal Biopharmaceutical Statistics, 27(2): 338-355.
[21] Guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*, Revision 1 (May 2021).

9

deviations accordingly and capture related reasons.

The war in Ukraine may impact ongoing clinical trials in aspects that are shared with the COVID-19 pandemic. In this regard, Sponsors are encouraged to consult the EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing trials – Revision 1, and take into consideration other relevant points discussed there that are also applicable in this context. Likewise, it is recommended to seek Scientific Advice early in the process if substantial modifications to the current protocol and/or analysis plan are considered necessary. These aspects related to impact of the war on trial design elements, recruitment, data collection, analysis and interpretation of results will be thoroughly reflected upon during requests for EMA Scientific Advice and the assessment of affected clinical trial data submitted to the EMA for Marketing Authorisation Application.

Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials
EMA/214249/2022

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Statistical Approaches to Establishing Bioequivalence

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) David Coppersmith at 301-796-9193.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2022
Biopharmaceutics

Revision 1

8.1.2. Target of estimation in the prodromal AD /MCI due to AD
Preclinical AD setting

In the prodromal/MCI setting, patients are not from the beginning of the trial on a st
background therapy. The initiation of a non-investigational symptomatic treatment sl
as an intercurrent event that will influence the measurement of the outcome variable
be addressed in the estimand. As above, the treatment effect 'if symptomatic medica
been introduced' could be an appropriate target of estimation, providing that reliable
estimation can be identified. An alternative strategy might be to integrate the event
(e.g. to define a non-responder as a patient with a certain degree of progression or v
additional symptomatic medication).

Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease
CPMP/EWP/553/95 Rev.2

Estimands initiatives in pharma industry?

After **over 250 episodes** of The Effective Statistician Podcast and many webinars, I'm very happy to invite you to **the first conference of The Effective Statistician**.

The conference will take place on **April 25th, 2023**.

And you will get the registration for **free**.

The conference will **start at 1pm CET (7am East Coast US)** and **end at 6pm CET (noon East Coast US)**.

The **5 hours** will be filled with short presentations (15-20 minutes each) and Q&A sessions.

Those, who have registered, will also get access to the recordings of the conference.

We will cover a great collection of topics, which will be relevant to statisticians in healthcare:

- Estimands
- Bayesian approaches in early development
- Medical affairs statistics
- Digital health applications
- Simulation of studies and development plans
- Network meta-analysis
- Working effectively as a researcher
- Leading without authority
- Optimizing your processes

Join Today | Login | Latest News

Neuroscience-Estimands European SIG

Home / SIGs / Neuroscience-Estimands

Purpose

This SIG will have two connected topics:

1. General biostatistics Neuroscience community
2. Working groups on estimands in neuroscience and other topics in neuroscience

Publications and slide decks

The group did work on the impact of Covid-19 pandemic on clinical trials in Neuroscience and provides recommen
regular updates.

The impact of Covid-19 on clinical trials in NS V1.0 final

https://oncoestimand.github.io/oncowg_webpage/docs/

Office Ho... | HowTo - Home | Delve – Marian Mitr...

Oncology estimand WG | About | Task forces | Health authority interactions | Publications | Events

1 Purpose
2 Become a member
3 Link to this page
4 Latest updates of this page

Oncology estimand working group

A cross-industry international working group

Last change: 13 Oktober, 2021

1 Purpose

Find on this webpage information on the working group on estimands in oncology.

2 Become a member

The general spirit of the working group is inclusive. If you'd like to contribute in one or the other way, we propose you first reach out to your company's representative(s) (if applicable) and align within your company who is best placed to contribute to which task force. After that is clarified reach out to the WG leads - contact details available here.

3 Link to this page

Link to this page: http://www.oncoestimand.org.

baselbiometrics.github.io/home/docs/

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News on this site

- 2022/12/16: Added recording and slide decks of joint EFSPI & BBS virtual event on "Addressing intercurrent events: Treatment policy and hypothetical strategies (Day 2)".
- 2022/12/14: Added recording of Next Generation Networking Seminar.
- 2022/12/09: Added recording and slide decks of joint EFSPI & BBS virtual event on "Addressing intercurrent events: Treatment policy and hypothetical strategies (Day 1)".

The ICH E9(R1) estimands framework

- *"This addendum presents a structured framework to **strengthen the dialogue between disciplines** involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as **between sponsor and regulator** regarding the treatment effect(s) of interest that a clinical trial should address."*

The estimand definition

Estimand:

A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

The intercurrent event definition

Intercurrent Events:

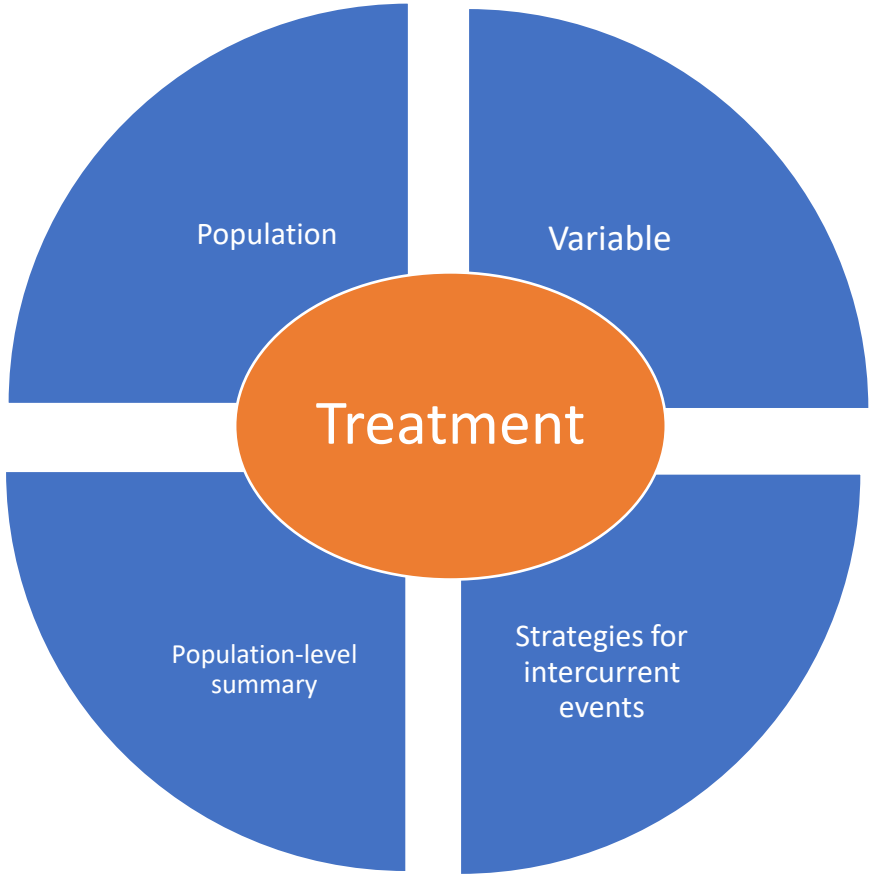
Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Missing data definition

Missing Data:

Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.

Estimand attributes



Strategies for intercurrent events

- Treatment policy strategy
- Hypothetical strategy
- Composite variable strategies
- While on treatment strategies
- Principal stratum strategies

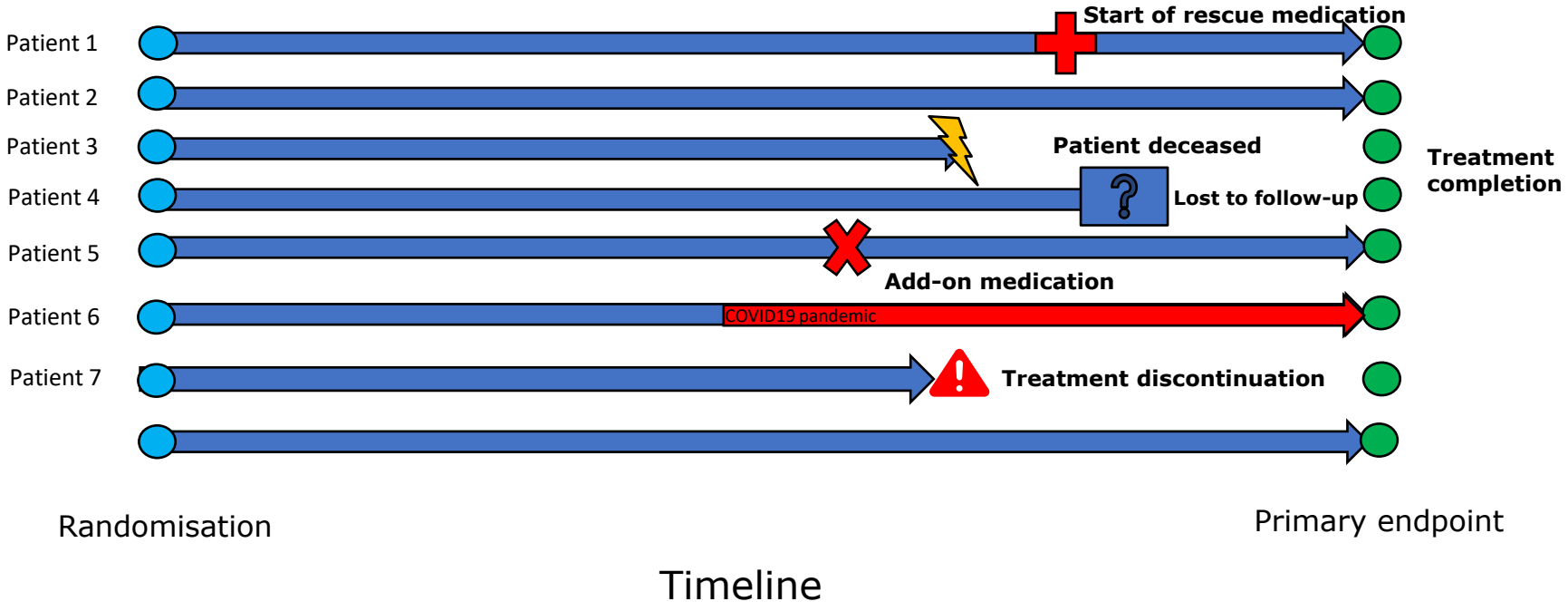
Strategies for intercurrent events

- Treatment policy strategy

(Actively!) Ignore the intercurrent event

- it requires complete subject follow-up

Patient journeys in a trial (TP)

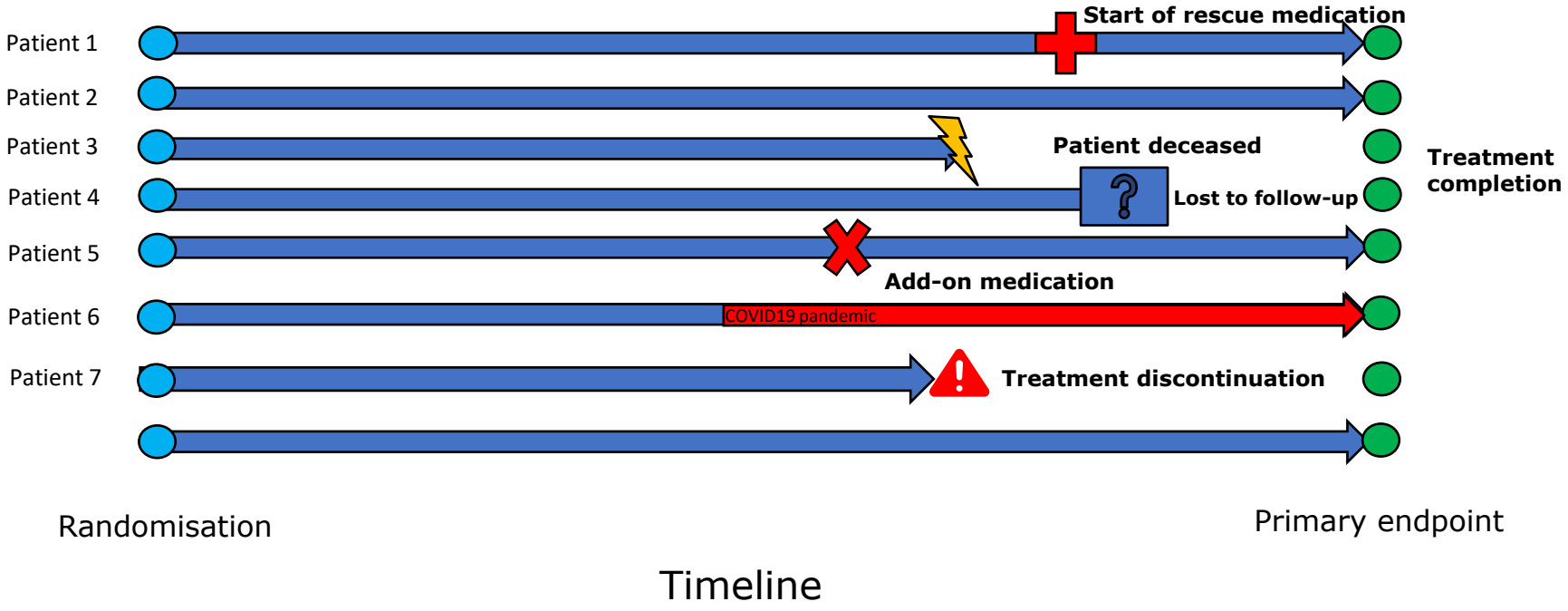


Strategies for intercurrent events

- Hypothetical strategy

Envisage a scenario where the intercurrent event would not occur

Patient journeys in a trial (Hyp)



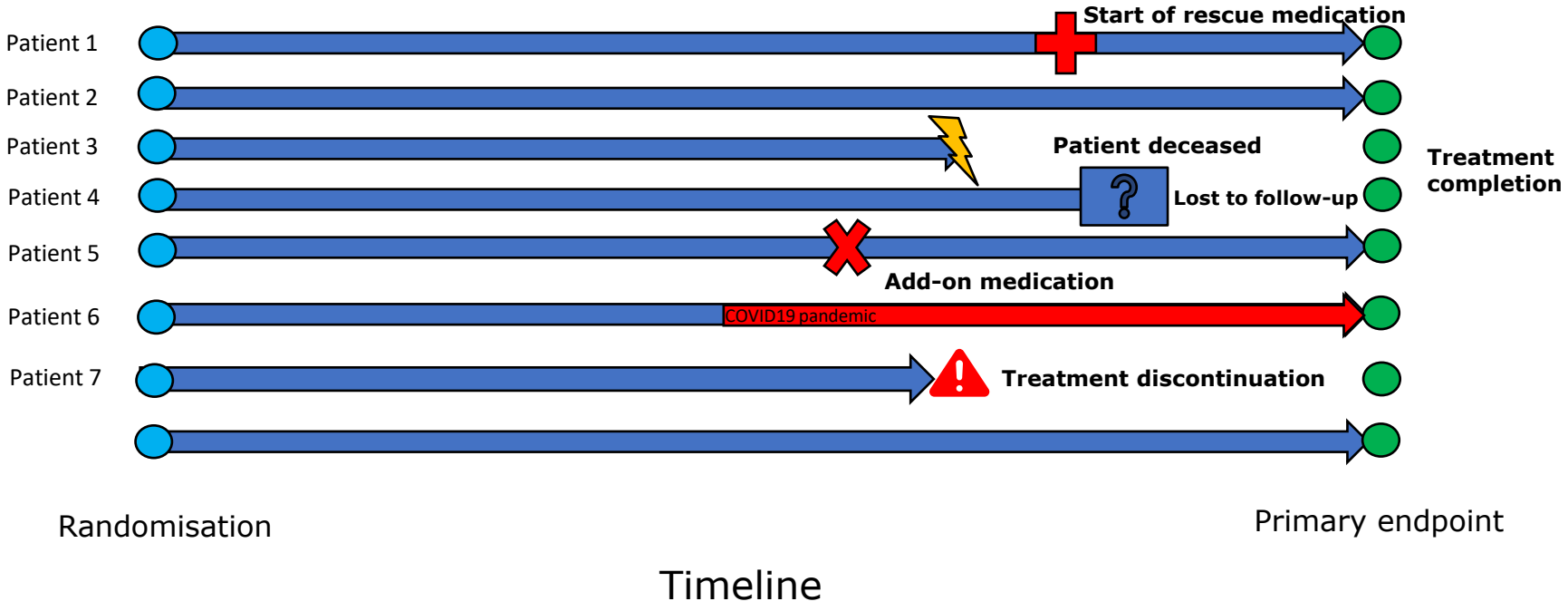
Strategies for intercurrent events

- Composite variable strategies

Consider the intercurrent event as part of the variable.

Could be an event or could be a certain value if scores are used.

Patient journeys in a trial (Comp)



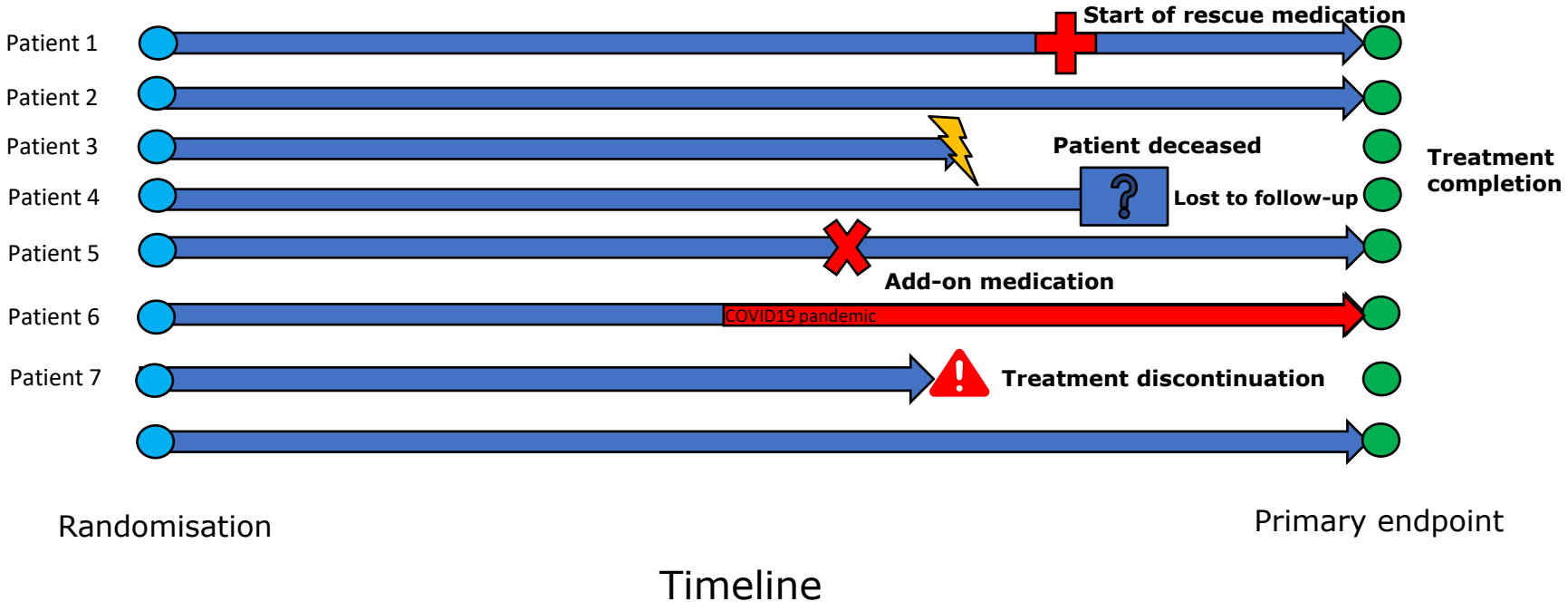
Strategies for intercurrent events

- While on treatment strategies

Interest is in the patient's trajectory prior to the intercurrent event.

Use only outcome values before the intercurrent event.

Patient journeys in a trial (WoT)



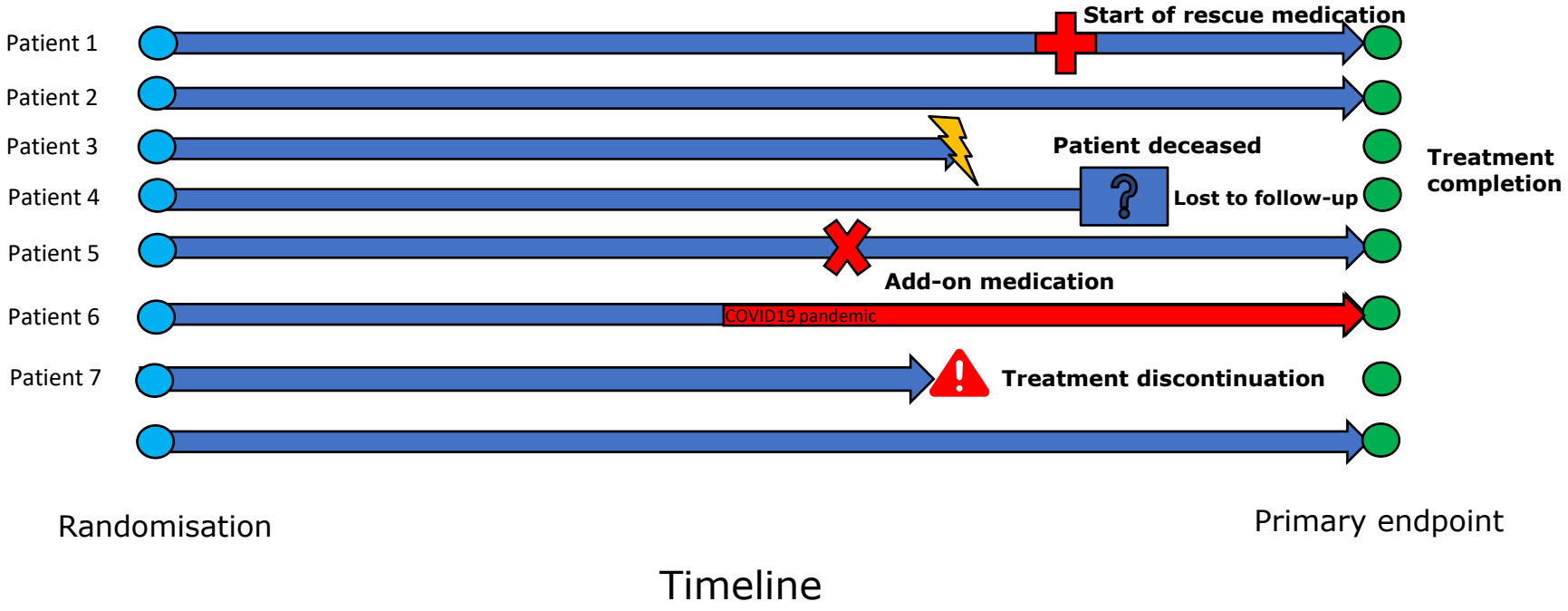
Strategies for intercurrent events

- Principal stratum strategies

Interest is in a certain subpopulation that would/would not experience a certain intercurrent event of interest

!= subgroup/PP…

Patient journeys in a trial (PS)



What do ICH E9(R1) and CDISC have in common?

- Nothing and a lot, at the same time

ICH E9(R1) Guideline

A.1. PURPOSE AND SCOPE

To properly inform decision making by pharmaceutical companies, regulators, patients, physicians and other stakeholders, clear descriptions of the benefits and risks of a treatment (medicine) for a given medical condition should be made available. Without such clarity, there is a concern that the reported "treatment effect" will be misunderstood. This addendum presents a structured framework to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect(s) of interest that a clinical trial should address.

A.4. IMPACT ON TRIAL DESIGN AND CONDUCT

The design of a trial needs to be aligned to the estimands that reflect the trial objectives. A trial design that is suitable for one estimand might not be suitable for other estimands of potential importance. Clear definitions for the estimands on which quantification of treatments effects will be based should inform the choices that are made in relation to trial design. This includes determining the inclusion and exclusion criteria that identify the target population, the treatments, including the medications that are allowed and those that are prohibited in the protocol, and other aspects of patient management and data collection. If interest lies, for example, in understanding the treatment effect regardless of whether a particular intercurrent event occurs, a trial in which the variable is collected for all subjects is appropriate.

Avoiding or over-simplifying the process of discussing and constructing an estimand risks misalignment between trial objectives, trial design, data collection and method of analysis. Whilst an inability to derive a reliable estimate might preclude certain choices of strategy, it is important to proceed sequentially from the trial objective and an understanding of the clinical question of interest, and not for the choice of data collection and method of analysis to determine the estimand.

phuse working group with multiple subteams

advance.phuse.global/display/WEL/Implementation+of+Estimands+%28ICH+E9+%28R1%29%29+using+Data+Standards

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PHUSE Advance Hub | Spaces | Search

WORKING GROUPS

PAGE TREE

- Working Groups
  - Data Transparency
  - Data Visualisation & Open Source
  - Emerging Trends & Technologies
  - Nonclinical Topics
  - Optimizing the Use of Data Stand
    - Management of ODS Regulator
    - Bioresearch Monitoring (BIMO)
    - (BIMO) Bio-research Monitoring
    - **Implementation of Estimands**
    - Best Practices in Data Standards
    - Clinical Integrated Study Data &
    - SDTM ADaM Implementation FA
    - Electronic Data Submission in Ja
  - Real World Evidence
  - Risk Based Monitoring
  - Safety Analytics
- Deliverables
- Working Group Events
- Hot Topics
- Useful Information
- Working Groups Events Archive
- Working Groups Archive

Space tools

Pages / ... / Optimizing the Use of Data Standards

Implementation of Estimands (ICH E9 (R1)) using Data Standards

Created by , last modified by Lauren White on May 03, 2023

Project Scope

Impact assessment of the estimands framework and recommendations/best practices (where applicable) for implementing the framework in the following areas:

- Data Collect Design/CDASH
- SDTM
- ADaM (including handling of intercurrent events, missing data imputation) – Analysis Displays
- cSDRG and ADRG

Development of new standards is not in scope, and any impact findings that may necessitate new standard development will be shared with CDISC for their consideration. Examples may be created on how to implement the framework by using permitted extensions to the existing data standards.

Project Leads	Email
Chris Price (Roche)	chris.price.cp1@roche.com
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Paula Rowley (PHUSE Project Assistant)	paula@phuse.global

Objectives & Deliverables	Timelines
Submit abstracts for multiple conferences	Q2 2023
Develop draft White Paper for internal project review prior to PHUSE Working Group Review and Public Review	Q3 2023

Project Members	Organisation
Lauren Shinaberry	Abbvie
Liping Sun	FDA
Lisa Lin	FDA
Marc Walton	Janssen Research & Development
Marian Mitroiu	Biogen
Matt Baldwin	Amgen
Mindy Mo	Bayer
Munish Mehra	Tigermed

Documentation to Data

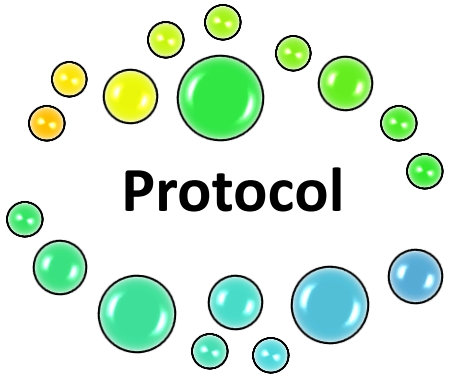
Get **sufficiently detailed answers** during collection

Annotated CRF

Data Collection

cSDRG

SDTM



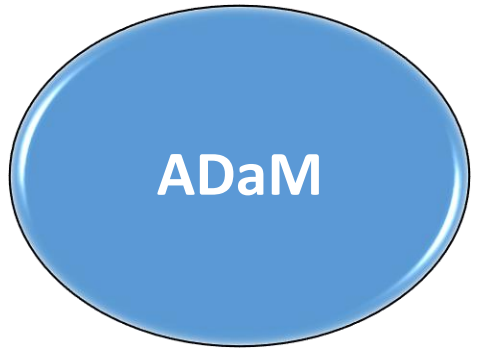
Describe the study objective in terms of the estimands framework (**WHAT**)

SAP

Statistical details on estimand (**WHAT detailed**), link estimands to their estimators (**HOW performed statistically**)

ADRG
Define.xml

HOW the relevant aspects of estimands were **implemented** in the data. New section on estimands in CSDRG & ADRG



Dedicated datasets and variables to document the traceability of estimands and impact in the data

Data Collection & Tabulation

Need for Data Collection Enhancements

- Accurate collection of intercurrent events is critical in defining estimands and constructing the estimators

- Granular data collection of the reasons for treatment discontinuations (e.g., AE, LoE, condition improved, AE & LoE etc…)

Data collection enhancements enable to use the prespecified strategies to handle intercurrent events based on the underlying reasons

Commonly Observed Intercurrent Events

Direct Consequences of Treatment

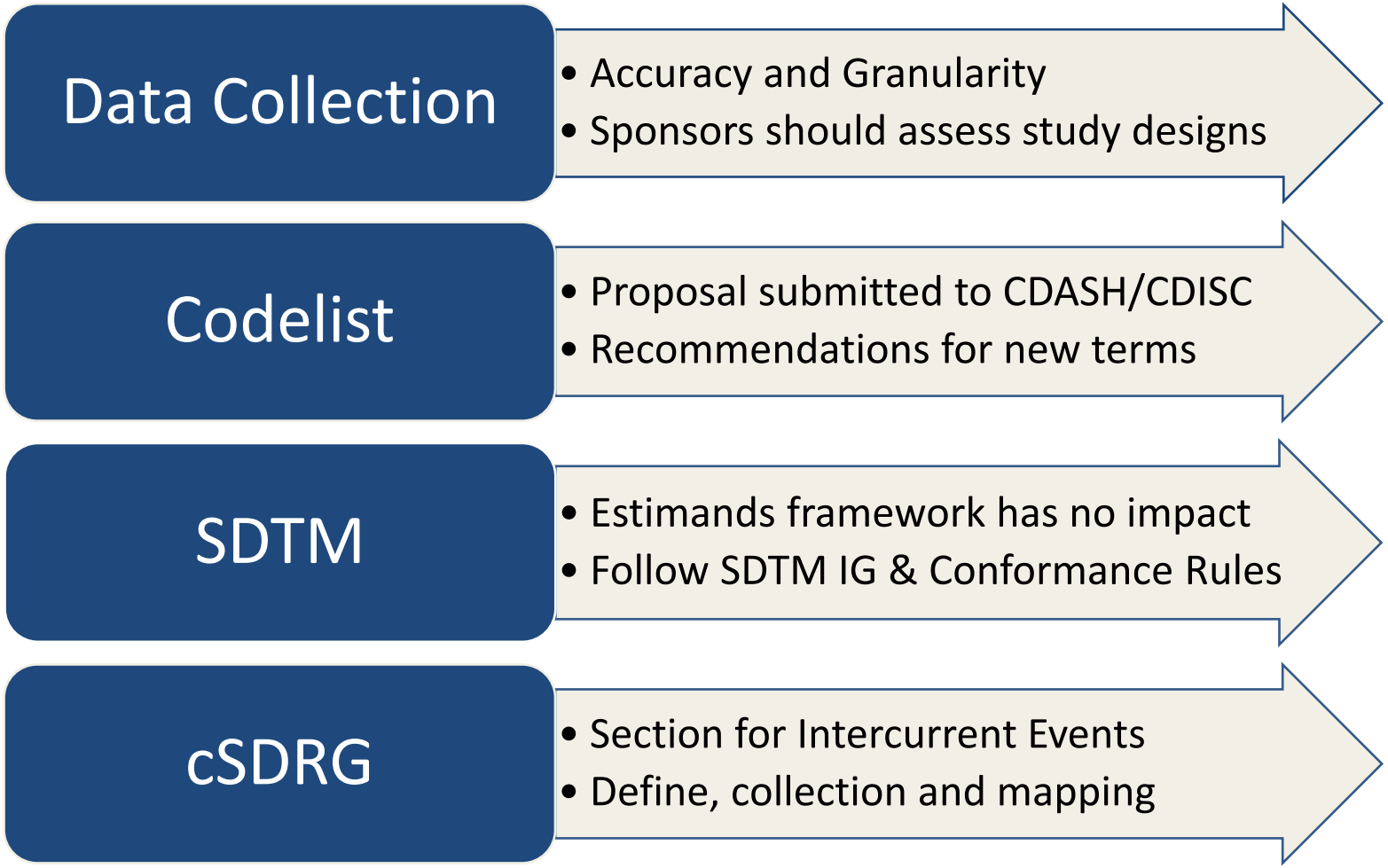
- Treatment Discontinuation
- Treatment Interruption
- Infusion Interruption
- Dose Adjustment
- Treatment Delay

Additional / Alternative Treatment

- Concomitant Medication
- Concomitant Procedure
- Subsequent Cancer Surgery*
- Subsequent Radiotherapy*

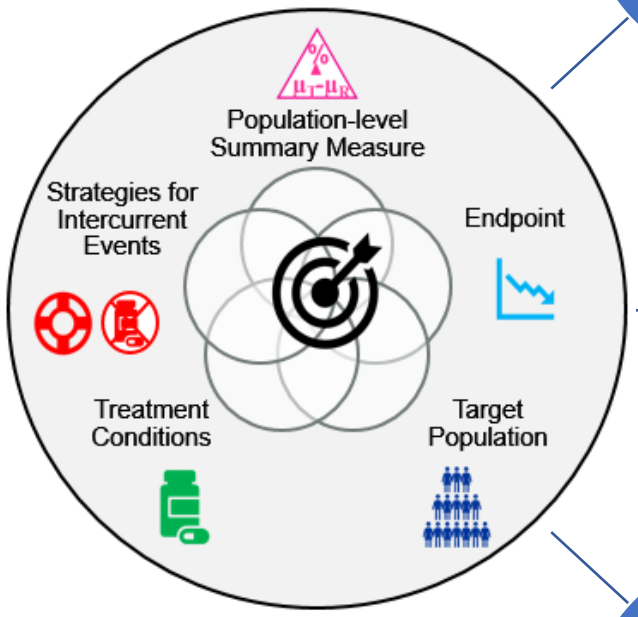
*oncology

Data Collection & Tabulation - Summary




Data
Analysis

Estimands Impact on Analysis



Analysis

- Mapping intercurrent events
- Identifying subjects and data points for estimand-based analyses
- Enhanced ADaM dataset guidance is needed

Traceability

- Documentation
- Estimands description and implementation

Flexible Solutions

- Based on user needs
- Proposed examples will be offered in white paper

NEW Intercurrent Events Dataset (ADICE)

- Documents intercurrent events across all estimands
- Facilitates traceability and inclusion of intercurrent events into other datasets
- OCCDS structure (one record per intercurrent event)
- This is an ***optional*** and supportive dataset to consolidate all intercurrent events in one place

USUBJID	ASEQ	ATERM	ADECOD	ASTDT(M)	AENDT(M)	SRCDOM	SRCVAR	SRCSEQ

- Optional columns per estimand:
  - **ESTzzSTR**: Strategy (e.g., treatment policy) for handling the intercurrent event for estimand zz
  - **ESzzGRID**: Group multiple intercurrent events affecting a datapoint for estimand zz

NEW ADaM Dataset Variables

- ADSL (Subject-Level)

USUBJID	[…]	FASFL	SAFFL	EST01FL	EST02FL	ESTzzFL

  - **ESTzzFL**: Subjects considered in all estimand zz estimations

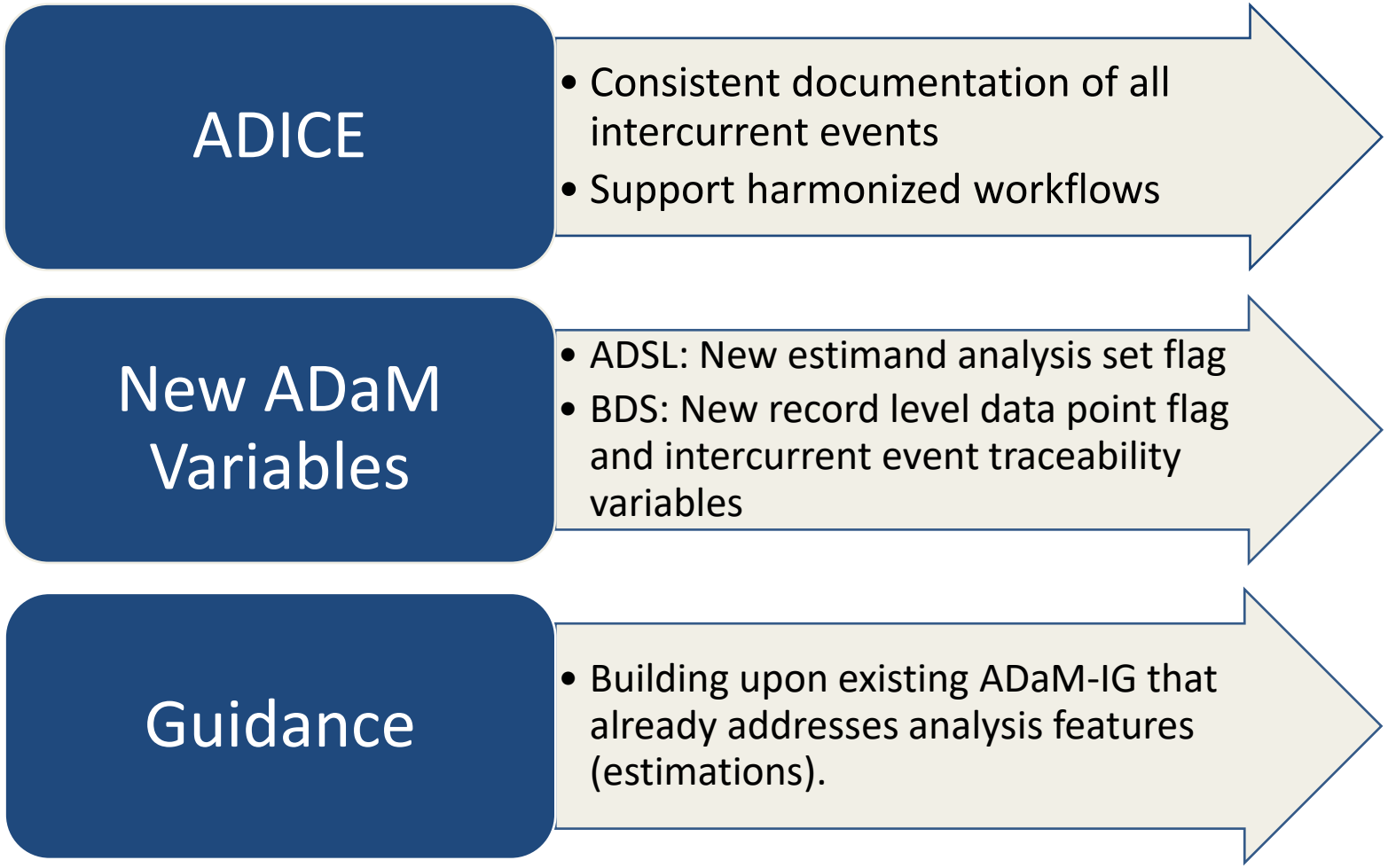
- BDS (Basic Data Structure)

USUBJID	PARAMCD	AVISIT	[…]	AVAL	CHG	DTYPE	ICESEQzz	EST01RFL	EST02RFL	ESTzzRFL

  - **ESTzzRFL**: Record-level datapoints considered in all estimand zz estimations
  - **ICESEQzz**: Links the intercurrent event(s) impacting the datapoint for estimand zz
    - Point to **ASEQ** of the single intercurrent event affecting the datapoint
    - Point to **ESzzGRID** of the multiple intercurrent events affecting the datapoint (advanced)

    Note: if ADICE is not implemented: **ICEDOMzz** and **ICEVARzz** link to SDTM source
  - Similar for OCCDS and ADaM OTHER structures

Data Analysis - Summary



’Data analysis’ becomes more complex & granular – ‘Data derivation’ + ‘Estimation’

Conclusion & Next Steps

Conclusion – E9(R1) & CDISC

Cross-functional interaction critical

Impacts protocol, data collection and data analysis

Different implementation approaches may be appropriate

Need to update/extend existing data standards

Consistent implementation of estimands is beneficial

Thank you!

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