Global Biometrics & Data Sciences / Cell Therapy Biostatistics

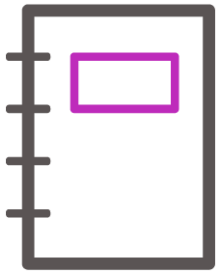
Estimands in the context of cell therapy development

BBS Webinar on "Statistical challenges in the clinical development of CAR T-cell therapies"
22nd March 2021

Alessandro Previtali, MSc
Senior Manager, Principal Statistician

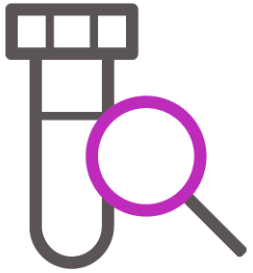
Bristol Myers Squibb™

The storyline of this (brief) talk



Part 1) Introduction on ICH E9(R1)

Key take-home messages from the ICH E9(R1) addendum on estimands and sensitivity analyses



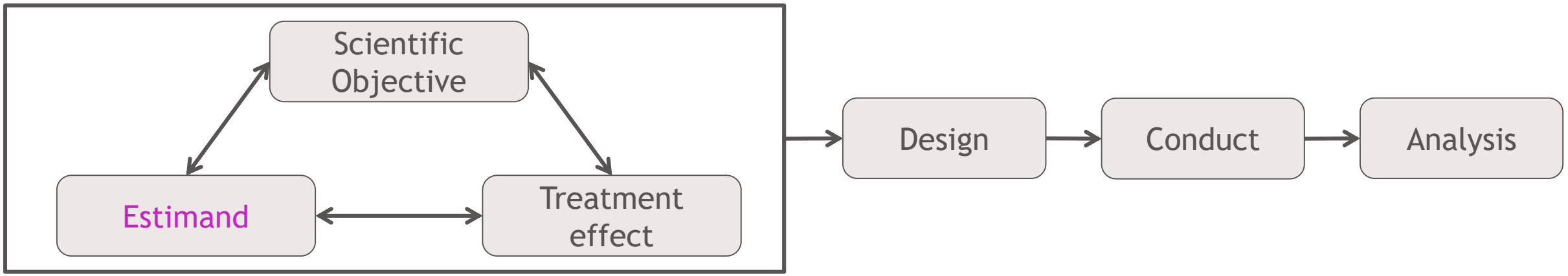
Part 2) Application of the estimand framework to cell therapy

An example in a late-stage CAR T-cell trial

The estimand

An estimand is the target of estimation

- It precisely describes the treatment effect reflecting the clinical question posed by a given clinical trial objective
- It is to be defined alongside with trial objective and treatment effect of interest
- It is the main determinant for aspects of trial design, conduct and analysis



The 5 attributes of an estimand

Treatment

What is being assessed/compared in the trial

Population

Patients target by the clinical question

Variable

Endpoint to be obtained for each patient to address the clinical question

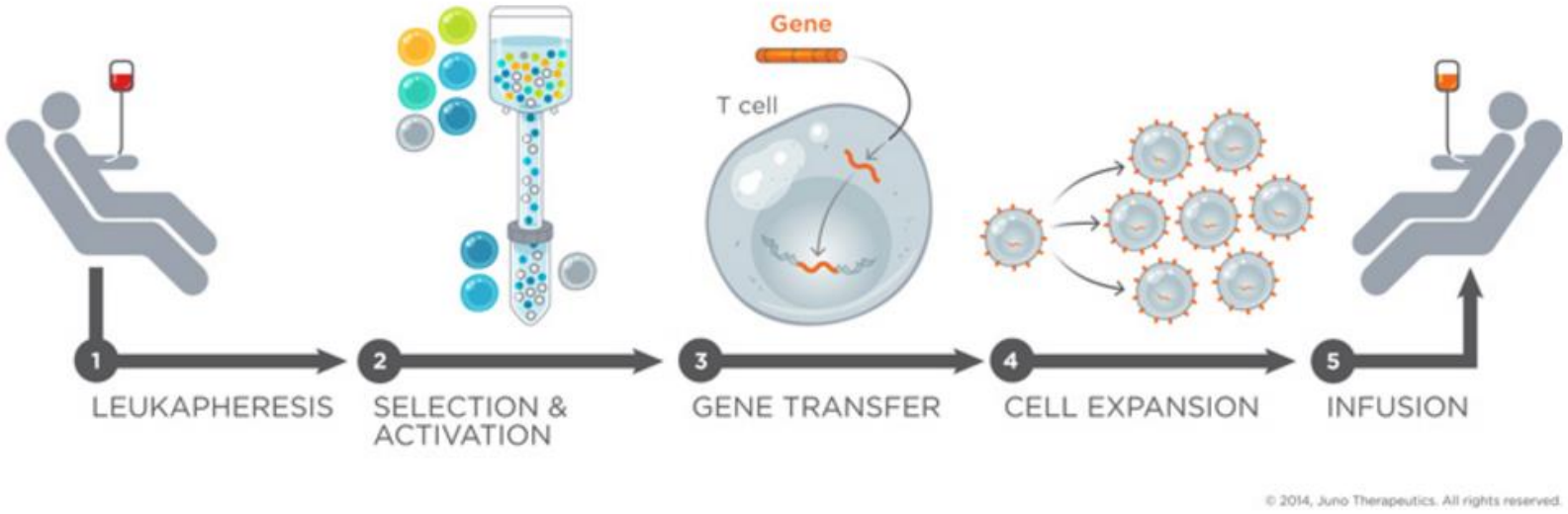
Intercurrent events

Events occurring after treatment start/randomisation that affect either the interpretation or the existence of the variable

Population-level summary

Basis for comparison between treatment conditions

Overview of CAR T-cell therapy



A living drug

The modified T-cells recognise cancer cells, activating an immediate immune response as well as persisting in the system providing potential long-term clinical effects

Vein-to-vein turnaround time

Typically, the turnaround time from leukapheresis to infusion takes from 4 to 6 weeks

Logistic and clinical limitations

CAR T-cells are produced on an individual-patient basis, which makes it complex and expensive. Also, in a number of patients, the desired immune response has been associated with serious toxic effects, such as CRSs and NTs

Underlying objectives of the trial

To evaluate efficacy and safety of CAR T-cell therapy (preceded by bridging therapy [BT], if needed, and lymphodepletion) compared to standard of care (SOC) in adult patients with haematological malignancy

Description of the primary estimand

Treatment

<u>Experimental arm</u>
BT (if needed) + Lymphodepletion + CAR T-cell infusion

<u>Control arm</u>
SOC + HDCT[a] + HSCT[b]

Population

Adult patients with haematological malignancy

Variable

Event-free survival (EFS): time from randomisation to disease progression, death, start of a new anti-cancer therapy or stable disease at first response assessment

Intercurrent events

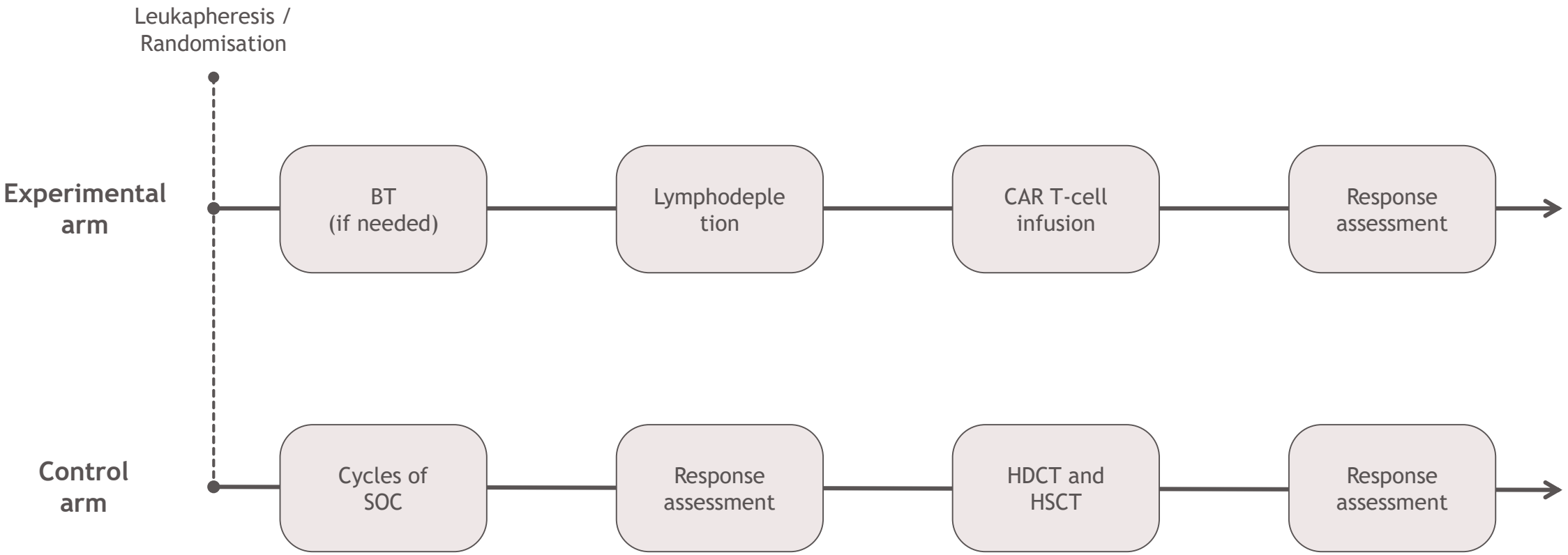
Identified through subject's journey analysis (see next slide)

Population-level summary

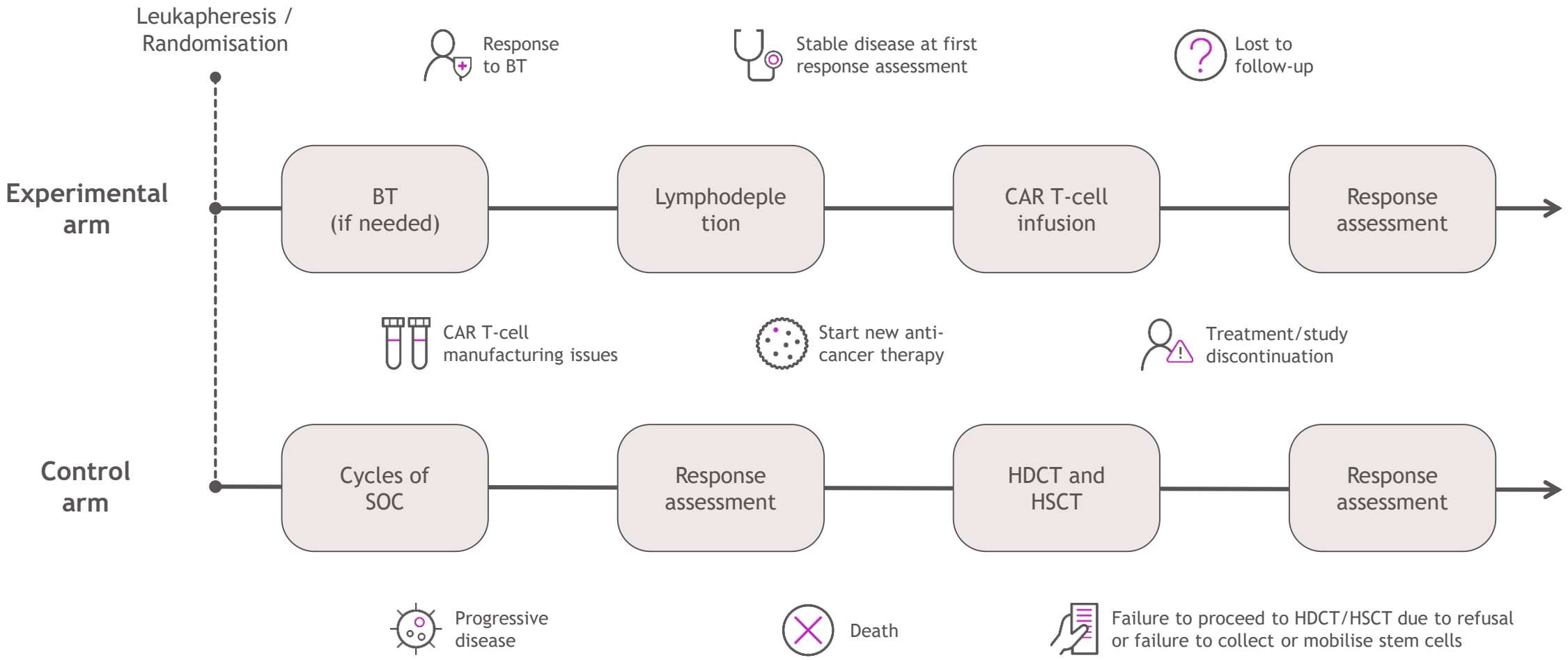
HR, based on (stratified) Cox model (assuming proportional hazards)

[a] high dose chemotherapy
[b] hematopoietic stem cell transplant

Patient's journey



Patient's journey and potential intercurrent events



Addressing intercurrent events for the primary estimand

Intercurrent event	Strategy	Justification
Stable disease at first response assessment Start new anti-cancer therapy Progressive disease Death	Composite	Undesired outcome incorporated into the definition of EFS
Response to BT CAR T-cell manufacturing issues	Treatment policy	Event ignored in the EFS assessment – this would reflect clinical practice in real-world setting
Lost to follow-up Treatment/study discontinuation Failure to proceed to HDCT/HSCT due to refusal or failure to collect or mobilise stem cells	Hypothetical	Not part of treatment strategy, and affecting the observation and interpretation of further assessments (i.e., censoring at last adequate response assessment before event)

Putting everything together

	Primary Estimand	
Treatment	BT (if needed) + Lymphodepletion + CAR T-cell infusion vs SOC + HDCT + HSCT	
Population	Adult patients with hematological malignancy	
Variable	EFS	
Intercurrent events	**Intercurrent event**	**Strategy**
	Stable disease, PD, start new therapy, death	Composite
	Response to BT, manufacturing issues	Treatment policy
	Lost to FUP, trt/study disc, failure to go to HSCT	Hypothetical
Population-level summary	HR, based on (stratified) Cox model (assuming proportional hazards)	

Conclusions and future topics for research

- Sensitivity analyses and supportive estimands should be added to the primary estimand
  — Including safety estimands
- Other intercurrent events that are specific to CAR T-cell trials?
- How the objectives should be written within the estimand framework
- Definition of estimands that are compound/disease/therapeutic area/phase-specific?
- Impact on trial documentation and on processes for trial design

Acknowledgments, in alphabetical order

- Daniel Li
- James Lymp
- Lily Peng
- Marc Glettig
- Marie-Laure Casadebaig
- Revathi Ananthakrishnan

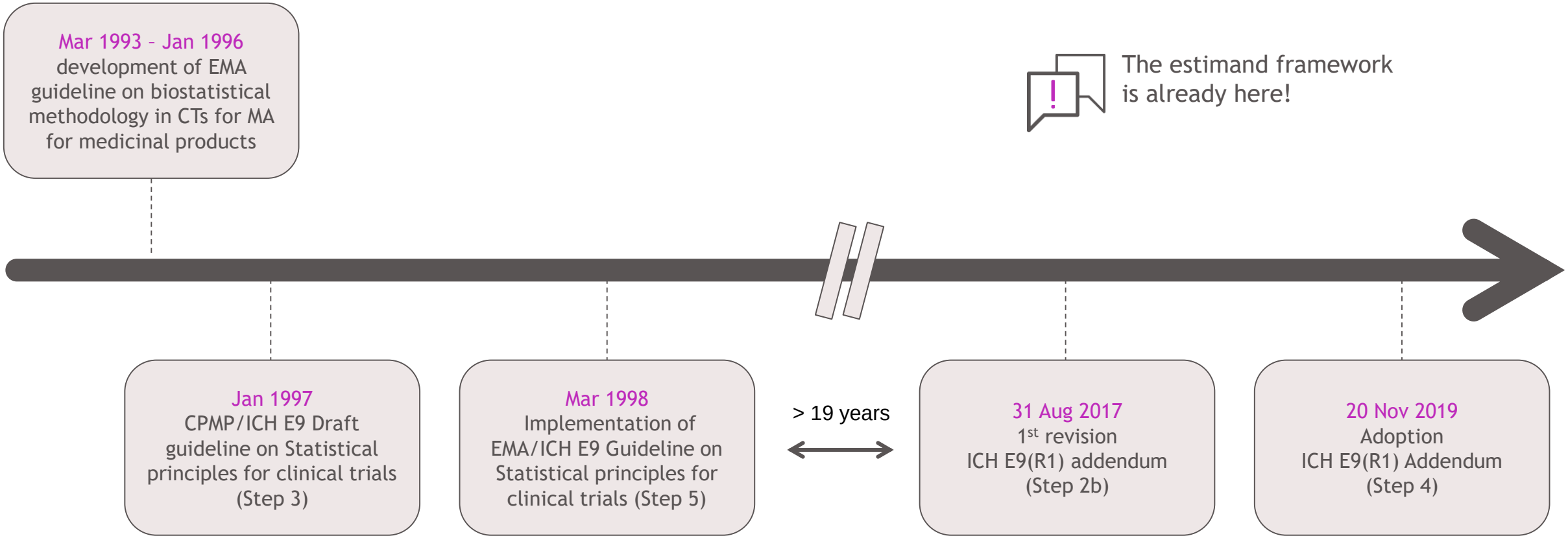
Thank you

Contact information
e-mail: Alessandro.Previtali@bms.com

Bristol Myers Squibb™

Back-up

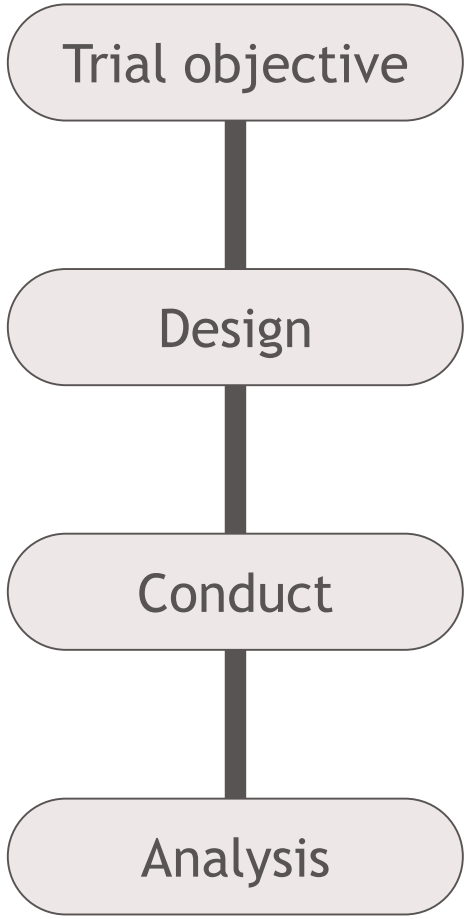
The ICH E9(R1) addendum is the first revision of ICH E9 guideline since its implementation in March 1998



The purpose of the ICH E9(R1) addendum

- To ensure alignment between the objectives posed by the trial and the analytical/statistical part
- To facilitate the dialogue between disciplines (i.e., statistics, clinical, regulatory affairs, commercial, etc…) and stakeholders (i.e., sponsor, regulators, etc…)
- To define common ground to discuss the treatment effect of interest

There are concerns in how the treatment effect of interest is currently defined!



Strategies for addressing intercurrent events

Treatment policy

The occurrence of the intercurrent event is considered irrelevant

Hypothetical

A scenario is envisaged in which the intercurrent event would not occur

Composite variable

The intercurrent event is incorporated into the definition of the variable

While on treatment

Response to treatment prior to the occurrence of the intercurrent event is of interest

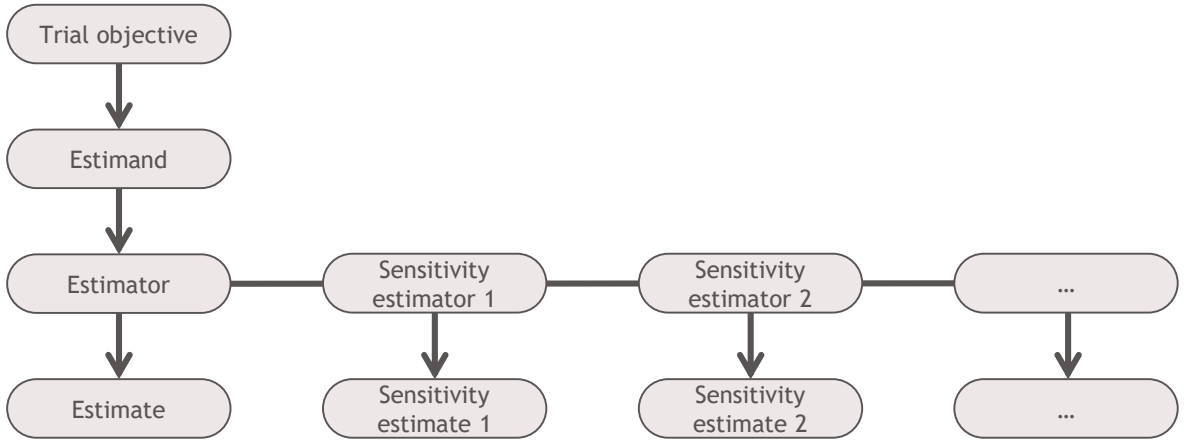
Principal stratum

The target population might be taken to be the “principal stratum” in which an intercurrent event would occur

Supportive analyses

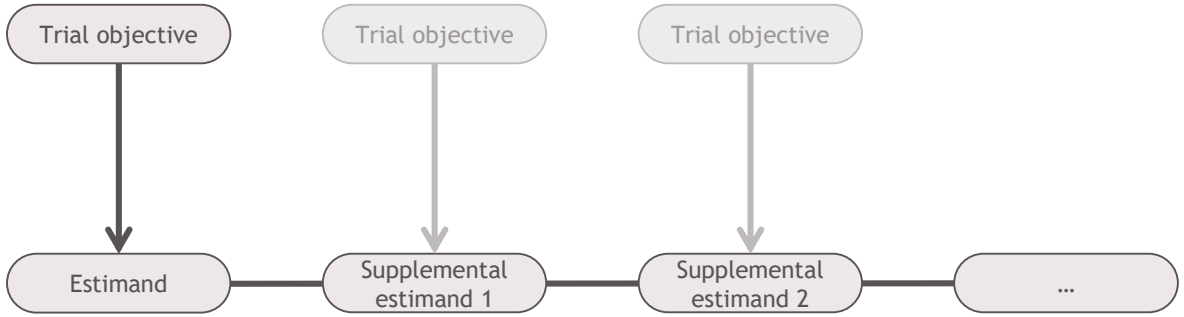
Sensitivity analyses

Inferences based on a particular estimand should be robust to limitations in the data and deviations from the assumptions used in the statistical model for the main estimator



Supplemental estimands

Supplementary analyses for an estimand should be conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect



Supportive analyses

Sensitivity analyses

Same estimand, different assumptions:

- EFS as assessed by the investigator
- Unstratified Cox-PH model as population-level summary (assuming proportional hazards)
- Censoring for 2 or more consecutive missing assessments
- Restricted mean survival approach or piecewise stratified Cox-PH model (in case the proportional hazard assumption is violated)
- Etc.

Supplemental estimands

Different estimand, or same estimand based on a different analytical approach:

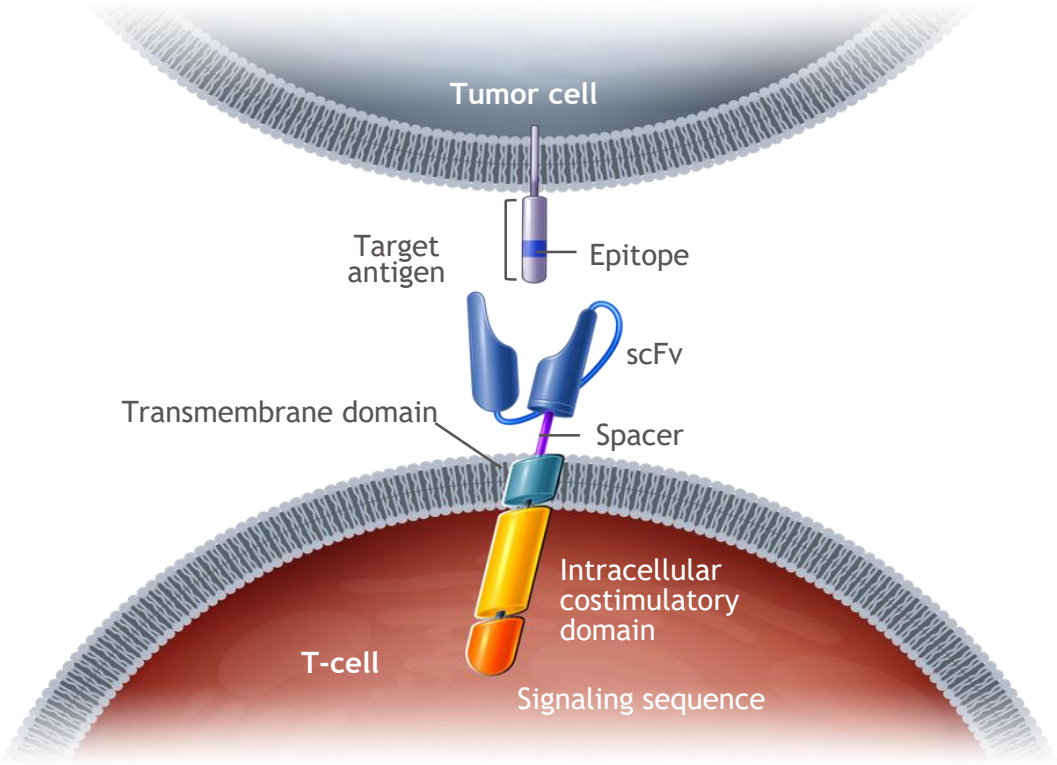
- For EFS
  - Different population attribute (i.e., per-protocol set)
  - Covariate-adjusted analysis (multivariate Cox regression analysis)
- Treatment effect based on complete response rate (CRR), progression-free survival (PFS) or overall survival (OS)
- Treatment effect for PFS/OS adjusted for cross over (RPSFT, IPCW, 2-stage model) or censored at subsequent anti0cancer therapy
- Safety profile assessment (i.e., safety estimands)
- Etc.

Putting everything together

	Primary Estimand		Supportive estimand 1		Supportive estimand 2	
Treatment	BT (if needed) + Lymphodepletion + CAR T-cell infusion vs SOC + HDCT + HSCT		BT (if needed) + Lymphodepletion + CAR T-cell infusion vs SOC + HDCT + HSCT		BT (if needed) + Lymphodepletion + CAR T-cell infusion vs SOC + HDCT + HSCT	
Population	Adult patients with hematological malignancy		Adult patients with hematological malignancy		Adult patients with hematological malignancy	
Variable	EFS		CRR		OS	
Intercurrent events	**Intercurrent event**	**Strategy**	**Intercurrent event**	**Strategy**	**Intercurrent event**	**Strategy**
	Stable disease, PD, start new therapy, death	Composite	Response to BT, manufacturing issues, Stable disease, PD	Treatment policy	Death	Composite
	Response to BT, manufacturing issues	Treatment policy	Lost to FUP, trt/study disc, failure to go to HSCT, start new therapy, death	While-on-treatment	Start new therapy	Hypotetical
	Lost to FUP, trt/study disc, failure to go to HSCT	Hypothetical				
Population-level summary	HR, based on (stratified) Cox model (assuming proportional hazards)		Proportion + Confidence Interval		HR, based on (stratified) Cox model (assuming proportional hazards)	

Chimeric Antigen Receptor (CAR) T-cell

- Autologous T-cells genetically engineered to express a chimeric antigen receptor (CAR) specific for a tumor-associated antigen
- CARs combine the antigen-binding property of monoclonal antibodies with the lytic capacity and self-renewal of T-cells
- Unlike T-cell receptors (TCRs), CARs enable high specificity of targeting an antigen in a major histocompatibility complex (MHC)-independent manner



Abramson JS, et al: *J Clin Oncol*. 2018; 36(abstr 7505). Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. Chicago, IL; June 1-5, 2018.

References

- Abramson JS, et al: *J Clin Oncol*. 2018; 36(abstr 7505). Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. Chicago, IL; June 1-5, 2018
- Akacha, M., F. Bretz, and S. Ruberg, *Estimands in clinical trials - broadening the perspective*. Stat Med, 2017. **36**(1): p. 5-19
- Ilya Lipkovich, Bohdana Ratitch & Craig H. Mallinckodt (2020) *Causal Inference and Estimands in Clinical Trials*, Statistics in Biopharmaceutical Research, 12:1, 54-67
- Degtyarev, E., et al., *Estimands and the Patient Journey: Addressing the Right Question in Oncology Clinical Trials*. JCO Precision Oncology, 2019(3): p. 1-10
- *ICH E9 Statistical principles for clinical trials* 1998
- *ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials*. 2019
- Ratitch, B., et al., *Choosing Estimands in Clinical Trials: Putting the ICH E9(R1) Into Practice*. Ther Innov Regul Sci, 2019
- Steven Sun, Hans-Jochen Weber, Emily Butler, Kaspar Rufibach, Satrajit Roychoudhury, *Estimands in Hematologic Oncology Trials*. Pharmaceutical statistics, 2021


Bristol Myers Squibb™