The Estimands Academy for Trial Teams

"Bringing estimands to *life* through case studies"

Webinar 4: Proposing Estimands from Different Perspectives

Patient, Clinician, Regulator, Health Technology Assessor and Statistician

30th March 2023 2-3:30 pm UK / 3-4:30 pm CET / 9-10:30 am EST

EFPIA / EFSPI Estimand Implementation Working Group (EIWG)

EIWG brings together statisticians and clinicians to support the estimand journey

Estimand Implementation Working Group (EIWG) Members 16 March 2023

Institution	Member
AMGEN	Mary Elliott-Davey
astellas	Antonia Morga
AstraZeneca	David Wright
BAYER	Vivian Lanius
Boehringer Ingelheim	James Bell
Chiesi	Stefano Vezzoli
ClinChoice	**Amel Besseghir+**
CONSILIUM Salmonson & Hemmings	Rob Hemmings*
EUROPEAN MEDICINES AGENCY	Lorenzo Guizzaro
GILEAD	Susanne Crowe
gsk	**Chrissie Fletcher+**
	Tricia Byers
	Millie Wang (C)
Independent consultant	Oliver Keene
IQVIA	Maria Efstathiou

Institution	Member
janssen	Stefan Englert
LEO	Kyle Raymond
Lundbeck	**Nanco Hefting+** (C)
	Mette Josiassen
medac	Michael Tribanek
Medicines & Healthcare products Regulatory Agency	Khadija Rantell
MERCK	Armin Schueler
METRONOMIA	Volker Schoder
mundipharma	Nick Manamley
NOVARTIS	Melanie Wright
novo nordisk	Helle Lynggaard
	Rikke Mette Agesen (C)
	Christian Pipper
	Pepa Polavieja

Institution	Member
Pfizer	Maria Dilleen
	Rod Junor (C)
PPD Part of Thermo Fisher Scientific	Sue McKendrick
	Nikolay Stoyanov (C)
PT Stat Consulting	Paul Terrill
Roche	Judith Anzures-Cabrera
SCENDEA	Beatrice Panico (C)
SERVIER	Estelle Lambert
ucb	Christian Loesch
	Katsumi Yoshida
UCL	Brenan Kahan
	Ian White
VectivBio Transforming Lives	Carrie Lie

+Co-Lead *Adhoc member C = Clinician

Acknowledgements

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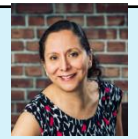
- To EFPIA/EFSPI for sponsoring and promoting the webinar.
- PSI for hosting the webinar (recording will be made available open access)
- To EIWG members for the lively discussion and comments on the slides.

Disclaimer:

1. This webinar gives an illustration of different perspectives and possible thinking but not intended to be taken as the perfect solution
2. Opinions are not necessarily the views of all our respective companies or representative of the roles we play (regulators or HTAs)

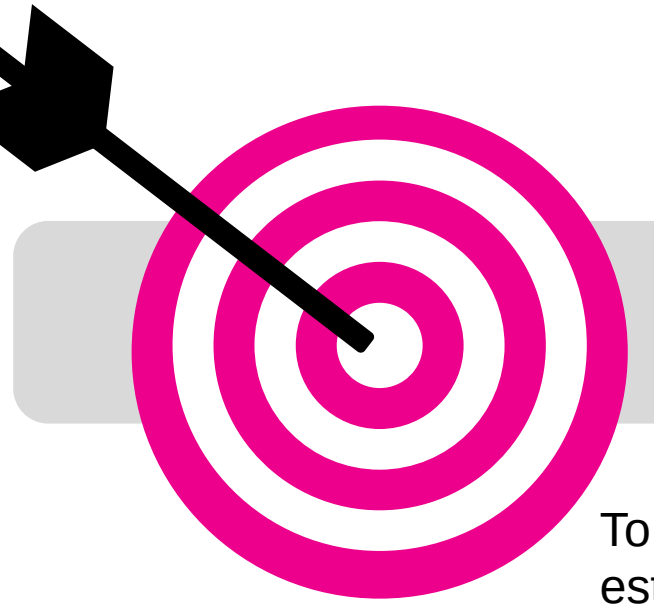
Introductions

	Presenter	Company Logo	Role in Presentation
	**Judith Anzures-Cabrera** is part of the Estimands Implementation Working Group where she leads the Training sub-team.	Roche	Moderator
	**Nikhil Kamath** is Group Medical Director and Global Development Leader within Global Product Development Immunology, Infectious Disease, and Ophthalmology	Roche	Clinician & patient
	**David Wright** is Head of Statistical Innovation at AstraZeneca, previously worked for the MHRA and led the revision of the CHMP guideline on missing data in confirmatory clinical trials.	AstraZeneca	Regulator
	**Antonia Morga** is a Global Health Economics and Outcome Research Director. She co-leads the EIWG team on HTAs and RWE studies and is part of EFPIA HTA Working Group.	astellas	Health Technology Assessor
	**Sue McKendrick** is Statistical Science Director **leading the cross-functional Estimand Working Group at PPD** and is also a member of the EIWG training team.	PPD Part of Thermo Fisher Scientific	Statistician

Agenda

Introduction: Objectives and Background	Sue and David
Case Study: Tic-Toc-PSI in Heart Failure	Nikhil
Strategies for Handling Intercurrent Events into Estimands	Antonia and Sue
Different Perspectives for Handling Intercurrent Events	All
Formulating Estimands	Sue and Antonia
Challenges and Recommendations	David
Q & A	All

Objectives



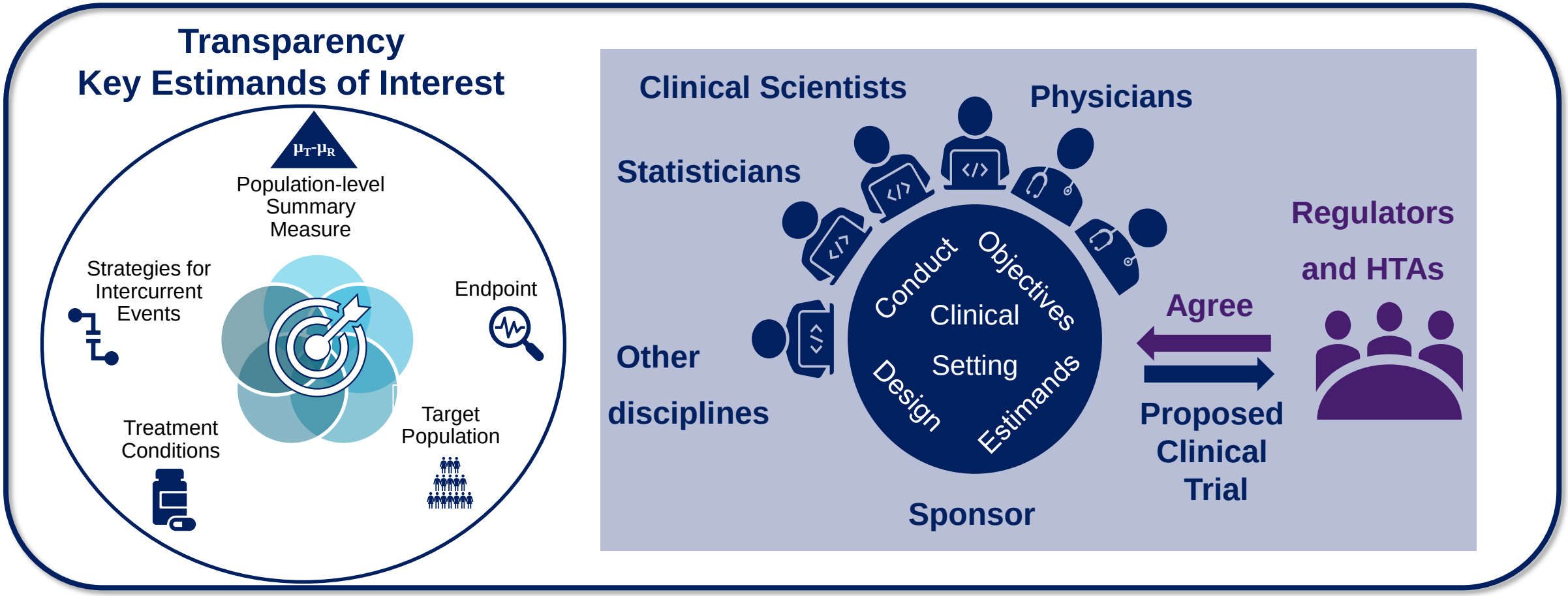
To apply the estimand framework to a challenging realistic setting

To discuss perspectives of different stakeholders when determining estimands

To understand relative merits of different strategies for intercurrent events

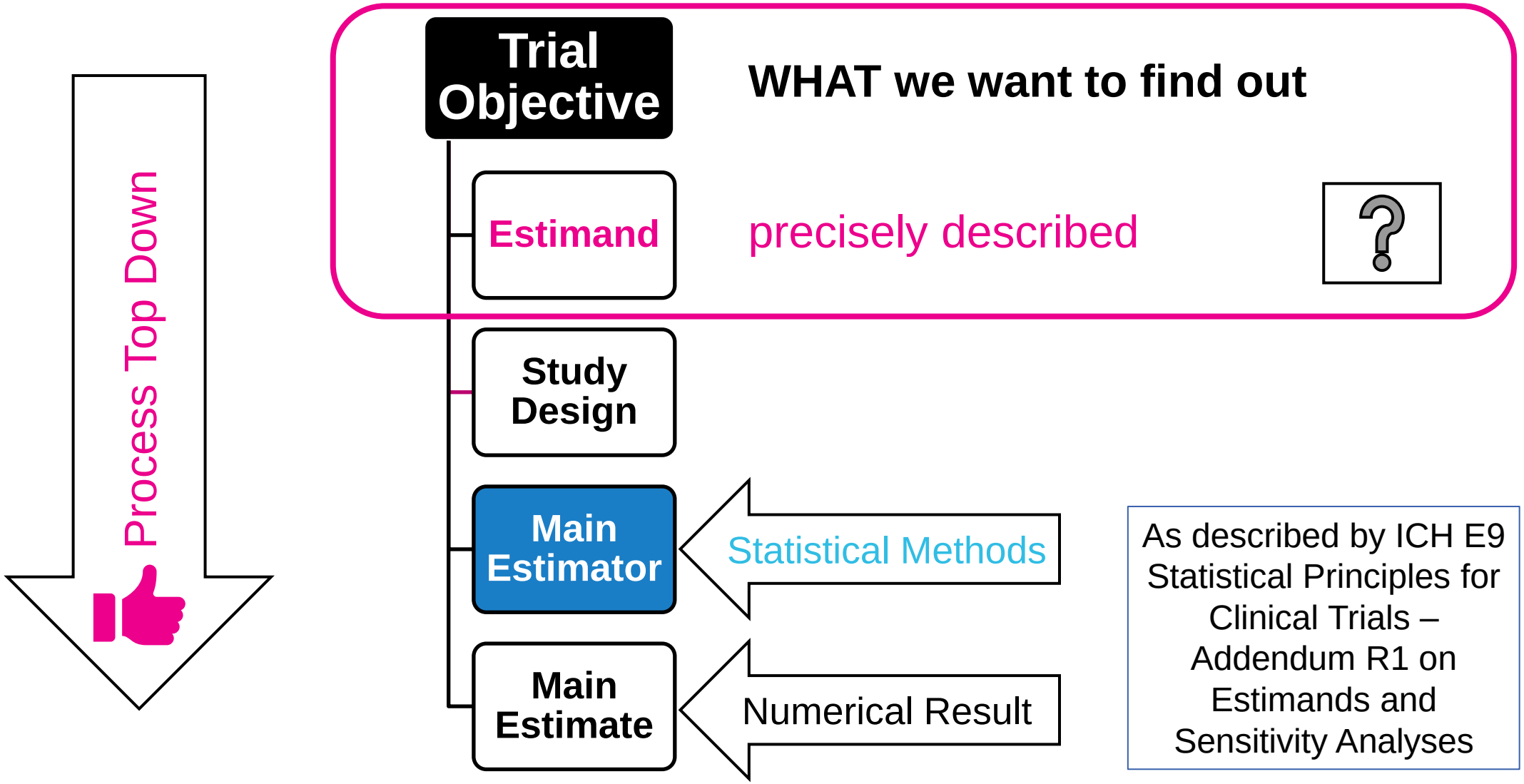
To share tips for implementation

Estimand = **What** do we want our study to find out (Estimate)?



ICH E9(R1) advocates multi-disciplinary discussions

Introduction to the Estimand Framework



Estimands should Bring Transparency to Future Product Labels

Example taken from Entresto EMA 2015 Product Label

Could the “Estimand” be more transparent on the product labels?

Product	Measure of benefit (summary + endpoint)	Relative to?	Target population	Intercurrent event strategies?
sacubitril+ valsartan (Entresto)	Hazard Ratio of heart failure hospitalizations or cardiovascular death: 0.80 (95% CI: 0.73, 0.87); relative risk reduction 20%	Enalapril =Angiotensin-converting enzyme (ACE) inhibitor	Adult patients with chronic heart failure able to tolerate treatment with Entresto (run-in)	Not stated but…. Principal stratum of those able to tolerate Entresto Were data collected and included regardless of use of other medications or treatment discontinuation?

Sacubitrilat inhibits the enzyme neprilysin, which is responsible for the degradation of atrial and brain natriuretic peptide

Valsartan is an **angiotensin II receptor blocker (ARBs)**

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Target Product Profile for Tic-Toc-PSI

Vision	Tic-Toc-PSI becomes the first choice for treating the symptoms of heart failure and would be used as add-on to standard of care (SOC) treatments
Mechanism and Rationale	Tic-Toc-PSI is a XYZ inducer which improves symptoms of breathlessness, ankle swelling and fatigue through regulating heart muscle action. Phase 2 studies showed improved • Kansas City Cardiomyopathy Questionnaire (KCCQ) • 6 Minute Walk test Distance (6MWD) (i.e. the distance walked in 6 minutes in clinical setting) • Slightly less cardiovascular hospitalisations.
Indication	Indicated to improve symptoms of heart failure (which may result in lower hospitalisations but not anticipated to significantly extend life)
Administration	Oral capsule, 50 mg twice daily
Trial Patient Population	Patients with Moderate/Severe Heart Failure (NYHA III/IV)
Primary Endpoint	Improvement in KCCQ including items on physical function, symptoms, self efficacy and social function
Secondary Endpoints	• Improvement in 6MWD • No increased risk of cardiovascular death or hospitalization
Safety	• No increased risk of stroke, bleeding events or any other SAEs

Phase III Study Overview: Tic-Toc-PSI in Heart Failure

Trial Objective

Demonstrate superiority of Tic-Toc-PSI over Placebo when added to stable standard of care (SOC) in improving quality of life (through easing heart failure related symptoms).

Estimand ?

Population

Patients with Moderate/Severe Heart Failure (NYHA III/IV)

Treatment Conditions

1. **Tic-Toc-PSI 50 mg bid + SOC**
2. **Placebo + SOC**

Primary Endpoint

Kansas City Cardiomyopathy Questionnaire at Week 52

0 to 100 KCCQ Score (high is good)

Population-level Summary ?

Strategies for Intercurrent Events ?

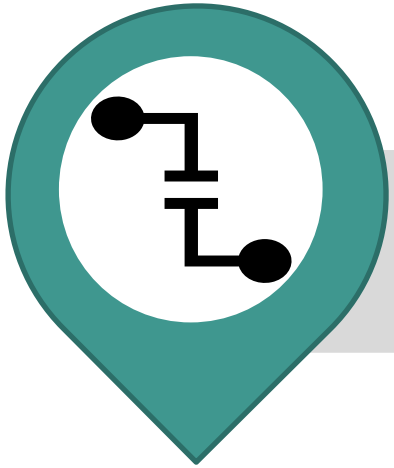
Study Design

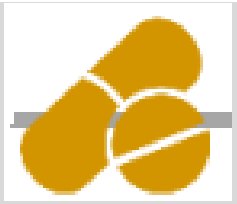
Design details should follow estimand agreement

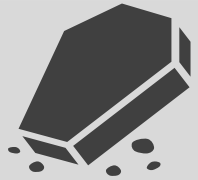
What are the Intercurrent Events (ICEs) for Tic-Toc-PSI?

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).

[List of ICEs depends on clinical setting and outcome measure]







Treatment Discontinuation

Due to
- **Tolerability issues**
- **Lack of efficacy (LOE)**
- **Logistical reasons**
  - administrative
  - unrelated medical need

Change of Background Therapy

Due to
- **Worsening symptoms**
- **Unrelated medical need**

Expected to impact QOL endpoints Including invasive surgery and additional therapy

Death

- Cardiovascular
- Any other cause

KCCQ: Kansas City Cardiomyopathy Questionnaire, LOE: Lack of Efficacy, QOL: Quality of Life, MWT: Minute Walk Test

ANSWER

Quiz Question on the Intercurrent Events

Which of the following is not an Intercurrent Event?

A. Treatment (IMP) discontinuation due to tolerability issues
B. Study withdrawal due to burden of the study
C. Taking rescue medication
D. None of the above

IMP = investigational medicinal product

Quiz Question on the Intercurrent Events

Which of the following is not an Intercurrent Event?

A. Treatment discontinuation (IMP) due to tolerability issues

B. Study withdrawal due to burden of the study

C. Taking rescue medication

D. None of the above

Study issues that result in missing data are not intercurrent events.

Discontinuation of treatment, rescue medication, treatment switching are examples of intercurrent events; they impact the outcome.

IMP = investigational medicinal product

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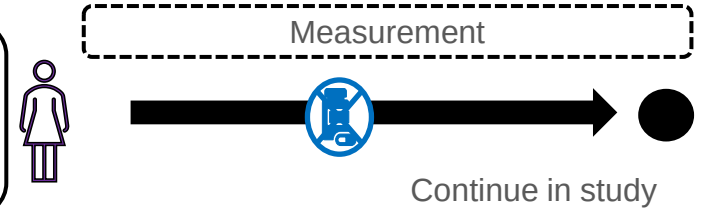
Strategies for addressing intercurrent events in the Addendum

ICE = intercurrent event

Treatment policy



Interest in the treatment effect irrespective of ICE; data collection continues until defined time of measurement

Composite variable

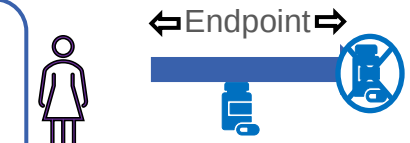
The ICE is incorporated into the definition of the composite variable

Response		No ICE	ICE
	Good	●	●
	Bad	●	●

Hypothetical strategy

Treatment effects estimated in the hypothetical situation where the ICE had not taken place (data after ICE irrelevant)

While-on-treatment



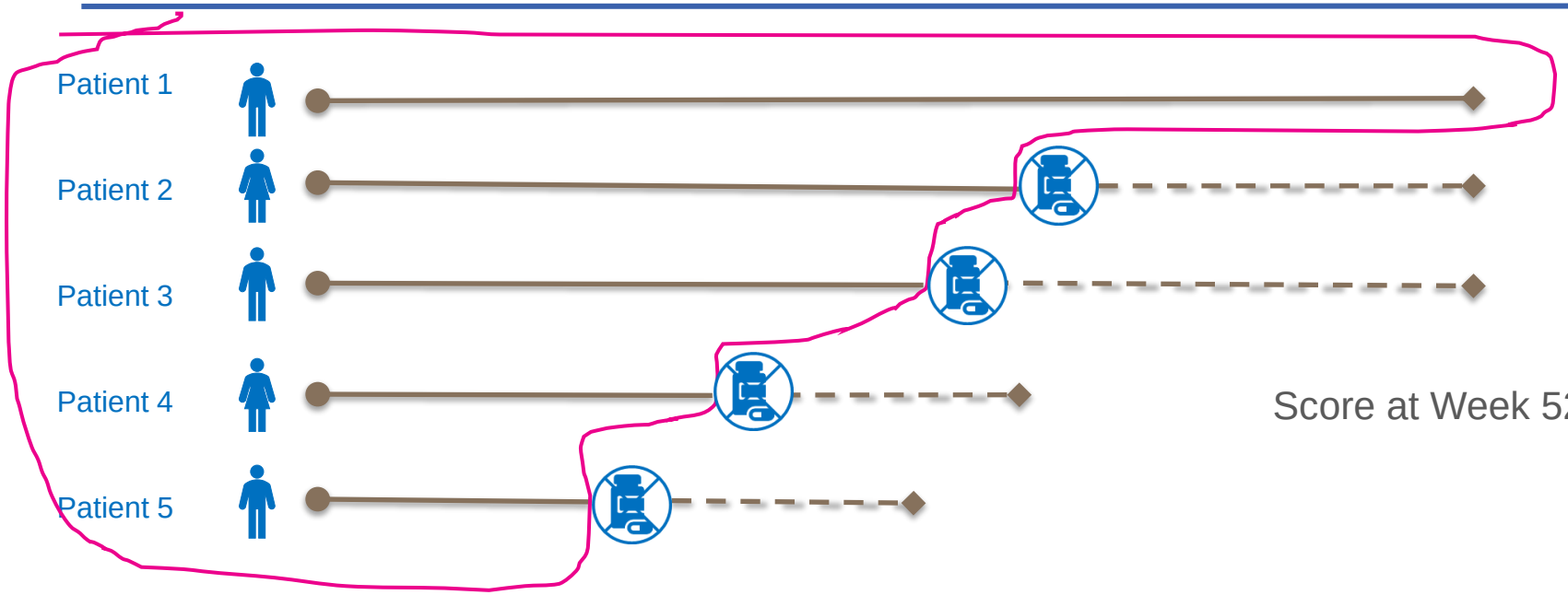
The response to treatment prior to the occurrence of the ICE is of interest

Principal stratum

The target population is the “principal stratum” in which an intercurrent event would (or would not) potentially occur

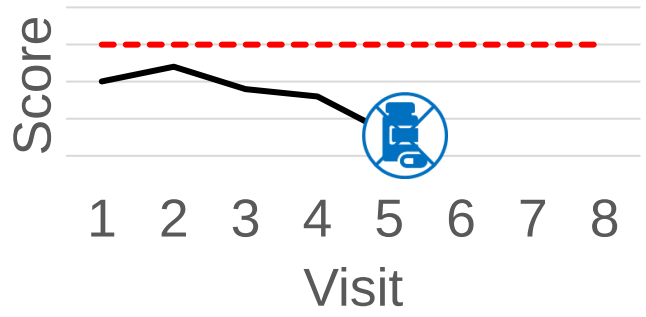
Different strata: (i) after T; (ii) after R or (iii) after T and/or R

Patient Journeys –While on Treatment versus Hypothetical

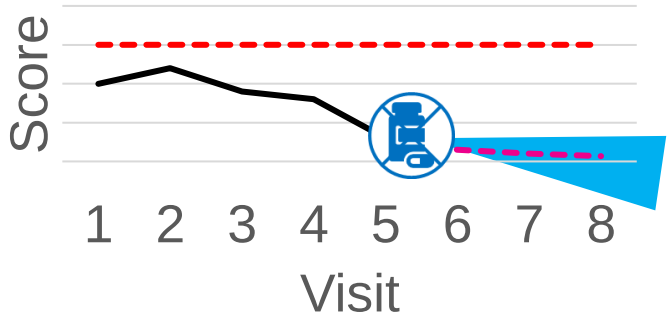


Data selected may be the same to estimate the hypothetical and while on treatment estimands

But endpoints will be different.



While on treatment => interested in the slope, rate or average prior to ICE



Hypothetical => predict/impute at Week 52 as though still on treatment

Quiz Question on the Hypothetical Strategy

A hypothetical strategy for handling an ICE means we are interested in the effect in all patients prescribed Tic-Toc-PSI:

A. irrespective of the ICE
B. as though they do not experience the ICE
C. over the period prior to ICE (when they were being treated)
D. considering the occurrence of ICE as treatment failure
E. in the subset of patients who would not experience this ICE

ICE = intercurrent event, for example, “treatment discontinuation due to logistical issues”

ANSWER

Quiz Question on the Hypothetical Strategy

A hypothetical strategy for handling an ICE means we are interested in the effect in all patients prescribed Tic-Toc-PSI:

A.	irrespective of the ICE	Treatment Policy
B.	as though they do not experience the ICE	Hypothetical
C.	over the period prior to ICE (when they were being treated)	While on treatment
D.	considering the occurrence of ICE as treatment failure	Composite
E.	in the subset of patients who would not experience this ICE	Principal Stratum

ICE = intercurrent event, for example, "treatment discontinuation due to logistical issues"

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Different Stakeholders may have Different Questions

Let's consider, these stakeholders:-

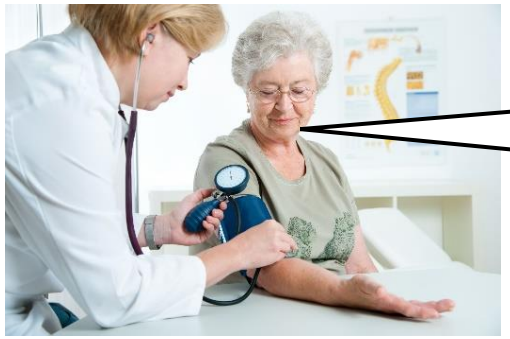
- Patient (Pat – played by Nikhil)
- Clinician (Nikhil)
- Regulator (David)
- Health Technology Assessor (Antonia)
- Statistician (Sue)

What questions do you think they have about Tic-Toc-PSI?

Pat Heart the Patient

I get tired & short of breath, can walk about 100 metres then need a rest. Sometimes I notice my ankles are swollen.

I've been in hospital a few times with difficulty breathing and fluid on my lungs.



I rattle because I take so many pills to help my heart, to get rid of the fluid and keep my cholesterol low.

My Questions about Tic-Toc-PSI:

(1) How much will **Tic-Toc-PSI** ease symptoms (tiredness, swelling and shortness of breath)?

(2) Will it reduce my risk of being admitted to hospital?

Imagine you are Pat Heart, the Patient

What do you think

Pat, should the benefit of Tic-Toc-PSI in easing symptoms be assessed:

A In patients whilst they are taking **Tic-Toc-PSI** (over up to 1 year), prior to any changes to other therapies

B In all patients, 1 year after being prescribed **Tic-Toc-PSI** (irrespective of whether able to take the full course or changes to other therapies)

C After 1 year, in the subset of patients who are able to tolerate **Tic-Toc-PSI**,

(irrespective of changes to other therapies)

25

Different Opinions

Imagine you are Pat Heart, the Patient

What do you think

Pat, should the benefit of Tic-Toc-PSI in easing symptoms be assessed:

A In patients whilst they are taking **Tic-Toc-PSI** (over up to 1 year), prior to any changes to other therapies

While on treatment = Prior to

B In all patients, 1 year after being prescribed **Tic-Toc-PSI** (irrespective of whether able to take the full course or changes to other therapies)

Treatment Policy

C After 1 year, in the subset of patients who are able to tolerate **Tic-Toc-PSI**,

(irrespective of changes to other therapies)

Principal Stratum

Treatment Policy

Clinician (Nikhil)

I am a physician who treats patients with advanced heart failure. I often prescribe ACE inhibitors, beta blockers, diuretics, and possibly anticoagulants.

If a patient worsens, I would consider adjusting their standard of care (reviewing dose levels or combinations of above medications).

KCCQ (0-100) measures symptoms (swelling, shortness of breath and fatigue), physical function (bathing, walking), social function (ability to take part in daily activities) & quality of life.

Clinically significant improvement is an increase in total KCCQ score >= 20.

My Question about Tic-Toc-PSI:

If I prescribe Tic-Toc-PSI, will the patient have an improved KCCQ >= 20 without requiring changes to other impactful background therapies?

Regulatory Perspective (David)

I am giving my personal regulatory view
as a statistician who previously worked for MHRA

My advice to the team is to justify their decisions, keep assumptions minimal, and don't over-state benefit (e.g. don't impute missing data as though patients are still taking a treatment they can't tolerate).

My Questions about Tic-Toc-PSI:

Was there a clinically meaningful improvement in KCCQ scores, and how much better is that for patients prescribed Tic-Toc-PSI on top of standard of care?

(Assume that if they don't tolerate Tic-Toc-PSI, have a change to background therapies or die, they are a "treatment failure")

Quiz Question about Regulatory Concerns

Regulator is concerned we might overstate benefit of a drug when we:-

A. Define a **composite binary endpoint*** so an improvement in KCCQ without any undesirable ICEs is defined as success (all other outcomes are failures)

B. Define a hypothetical estimand **as though they do not discontinue Tic-Toc-PSI due to tolerability issues**

C. Both A and B

D. Neither of these

*** Composite binary endpoint** defined as
[0] treatment failure: Low improvement < 20 in KCCQ or occurrence of undesirable ICEs
(i.e. needs other therapies or discontinues treatment due to lack of efficacy or tolerability issues or death)

[1] treatment success: Good improvement >= 20 in KCCQ and **no** occurrence of undesirable ICEs
(i.e. did not require adjusting other therapies and no tolerability issues/death)

ANSWER

Quiz Question Answer about Regulatory Concerns

Regulator is concerned we might overstate benefit of a drug when we:-

A. Define a **composite binary endpoint*** so an improvement in KCCQ without any undesirable ICEs is defined as success (all other outcomes are failures)

B. Define a hypothetical estimand **as though they do not discontinue Tic-Toc-PSI due to tolerability issues**

C. Both A and B

D. Neither of these

It is not clinically relevant to estimate effects as if "on-treatment" when a drug was not tolerated

*** Composite binary endpoint** defined as
[0] treatment failure: Low improvement < 20 in KCCQ or occurrence of undesirable ICEs
[1] treatment success: Good improvement >= 20 in KCCQ and **no** occurrence of undesirable ICEs

Health Technology Assessor (Antonia)

I am playing the role of an assessor from health technology agencies (HTA) such as NICE and IQWiG, that recommends which treatments to reimburse within their health care system.

HTA Agencies are interested in understating how a new treatment compares to standard of care in clinical practice.

The benefits of a new intervention are assessed with respect to *patient-relevant outcomes*, reflecting how patients feel, function or survive.

My Question about Tic-Toc-PSI:

What is the added benefit of Tic-Toc-PSI versus standard of care in KCCQ scores, irrespective of changes to other therapies or discontinuation of treatment?

(Need to be mindful that standard of cares can vary over time and be different in different regions, and may also want to look at cardiovascular mortality, hospitalization due to cardiac failure)

Quiz Question: the Health Technology Assessor's Viewpoint

A Health Technology Assessor is interested in effects *"Irrespective of Changes to Background Therapies or Discontinuation of Treatment"*, what strategy is aligned to that thinking?

A. Hypothetical
B. Principal Stratum
C. Treatment Policy
D. Composite Variable
E. While on Treatment/Prior to Change in Background Therapy

ANSWER

Quiz Question Answer: the Health Technology Assessor

A Health Technology Assessor is interested in effects *"Irrespective of Changes to Background Therapies or Discontinuation of Treatment"*, what strategy is aligned to that thinking?

A. Hypothetical
B. Principal Stratum
C. Treatment Policy
D. Composite Variable
E. While on Treatment/Prior to Change in Background Therapy

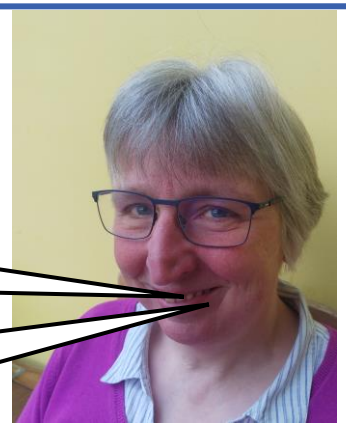
Treatment policy defined as "The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest".

Thus, the value for the variable of interest is used regardless of whether or not there are changes to background medication or discontinuation of treatment.

Statistician (Sue)

I provide input into the protocol and can help facilitate discussion.
First, understand the clinical setting, e.g. what happens when there is
(a) lack of efficacy or (b) discontinuation due to tolerability?

e.g. for lack of efficacy , other medications would be changed.



I help define suitable estimand(s) which are ideally:

(i) easy to understand
(ii) stand up to scrutiny from FDA and EMA (don't over state benefit)
(iii) Estimable (without bias)
(iv) able to pick up a "signal" (good precision)

My Question about Tic-Toc-PSI:

What is the median difference in KCCQ (taking a worst value for treatment failures)?

What is the difference in proportion (Tic-Toc-PSI-placebo) of patients who will have a successful outcome, defined as improvement in KCCQ >=20 without increase to other therapies, treatment discontinuation or death.

Different Viewpoints => Preferred Strategy for each Intercurrent Event?

- Tolerability Issues
- Lack of Efficacy
- Logistical/ Unrelated Medical
- Worsening Symptoms
- Unrelated Medical
- Death

Hypothetical	Principal Stratum	Treatment Policy	Composite (trt effect)	While on treatment
		NA		

Pat

Clinical

Regulator

HTA Assessor

Statistician

Primary endpoint: KCCQ Total Score at 1 year

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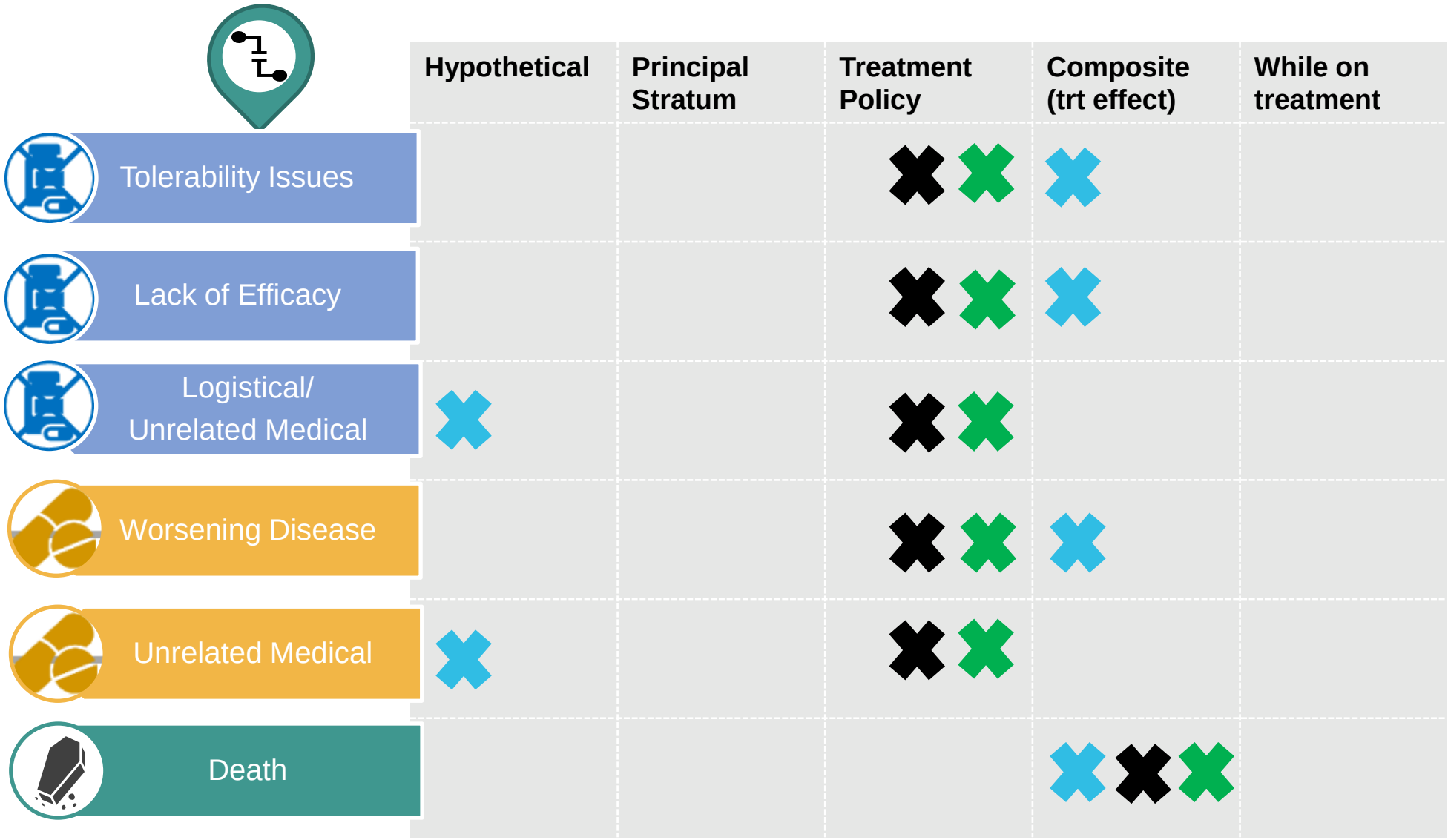
Proceed with 2 or 3 Estimands to satisfy different stakeholders



Primary Estimand 1a

Endpoint: KCCQ Total Score at 1 year

Estimand 1b

Endpoint: KCCQ Total Score at 1 year

Estimand 2

Endpoint: heart failure hospitalisations or cardiovascular deaths during 1 year

Estimand 1a: Primary Composite Responder

Estimand Attributes	
Target Population	In patients with Moderate/Severe Heart Failure (NYHA III/IV)
Treatment Conditions	treated with Tic-Toc-PSI 50 mg bid versus Placebo on top of Standard of care (SOC) for up to 1 year as though no treatment discontinuation due to logistical or unrelated medical issues and no initiation of other therapies due to unrelated medical issues [1]
Population-Level Summary	what is the difference in proportions of composite responders where
Variable	composite responder defined as ≥20 improvement in KCCQ at 1 year with • no lack of efficacy requiring changes to background therapies [2] • no discontinuation of treatment for tolerability issues [2]
Strategies for Intercurrent Events	[1] Hypothetical strategy [2] Composite strategy (death, discontinuation due to tolerability or LOE are taken to be treatment failures)

Estimand 1b: Treatment Policy (except for Death)

Estimand Attributes	
Target Population	In patients with Moderate/Severe Heart Failure (NYHA III/IV)
Treatment Conditions	treated with Tic-Toc-PSI 50 mg bid versus Placebo on top of Standard of care (SOC) for up to 1 year **irrespective of** treatment discontinuation and changes to background therapies for any reason [1]
Population-Level Summary	what is the difference in medians in
Variable	improvement in KCCQ Total Score after 1 year taking the worst observed value from baseline to death for anyone who dies [2]
Strategies for Intercurrent Events	[1] Treatment policy strategy [2] Composite strategy for death

Estimand 2: CV Hospitalisations Estimand

Estimand Attributes	
Target Population	In patients with Moderate/Severe Heart Failure (NYHA III/IV)
Treatment Conditions	treated with Tic-Toc-PSI 50 mg bid versus Placebo on top of Standard of care (SOC) for up to 1 year **irrespective of** treatment discontinuation and changes to background therapies for any reason [1]
Population-Level Summary	what is the relative risk (ratio) in
Variable	rate of heart failure hospitalisations or cardiovascular deaths [2] during 1 year
Strategies for Intercurrent Events	as though no deaths from other causes [3] [1] Treatment policy strategy [2] Composite strategy for cardiovascular deaths [3] Hypothetical strategy for death from other causes

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Challenges Arising when Specifying Estimands in Protocols

Estimands should:

(1) Be meaningful to the stakeholders you are addressing

(2) Be transparent in the handling of ICEs

Discontinuation of study drug and/or changes to standard of care

(3) Address the handling of death

Particularly for continuous endpoint (not survival time) in elderly populations and serious diseases

(4) Address an appropriate summary measure

Meaningful to clinicians and statistically appropriate

(5) Ensure estimands can be reliably estimated

Particularly for principal stratum and treatment policy strategy in the presence of missing data

(6) Deal with impact on study assessments in the protocol

Handling discontinuing study treatment versus discontinuing trial

Schedule of assessments and clarity on what data should be collected after ICEs

Suggestions to Support Successful Implementation

Estimands should:

(1) Early clinical team awareness of estimand framework

Collaborative discussion at concept/synopsis stage

(2) Prior discussion with stakeholders on estimands

Review of proposed estimands by Regulatory Authorities and HTA Agencies

(3) Clarity on high priority data to collect

Follow up after ICEs when treatment policy strategy is employed

Potential for partial withdrawal from study returning for the key end of study assessments

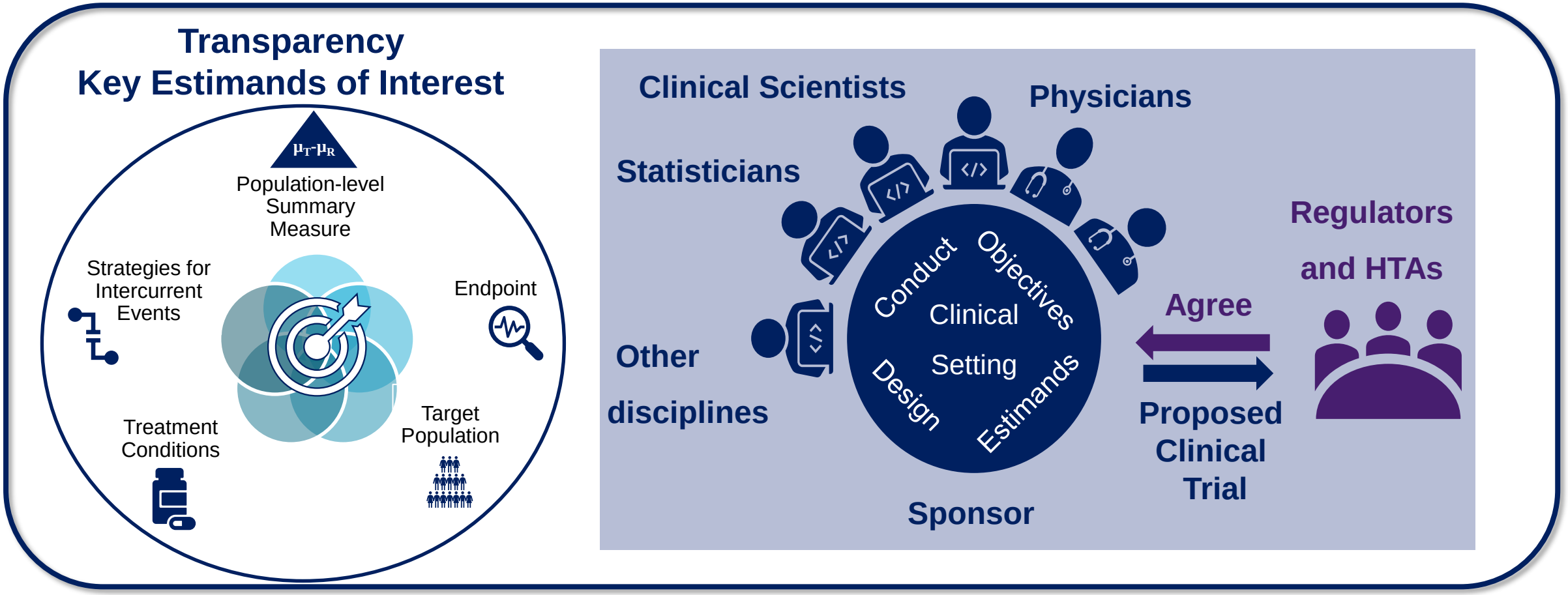
(4) CRF page(s) that collects relevant ICE data:

Capture and summarise type and time to intercurrent events

Capture reasons for discontinuing study treatment: “Investigator decision” insufficient

Distinguish discontinuation from study treatment from withdrawal from study

Final Remarks on the Estimand Framework
Powerful Tool to Encourage Deep Thinking and Transparency



Framing questions of interest to different stakeholders (regulators, payers, prescriber and patient!)

Note: when regulators are not aligned on the primary estimand, we may need Estimand 1-EMA and Estimand 1-FDA

References

- 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)
- ICH E9(R1) Training Material (December 2021): https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf
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- Callegari F, et al. Estimands in a chronic pain trial: challenges and opportunities. Statistics in Biopharmaceutical Research. 2020 Jan 2;12(1):39-44.
- Qualification of the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score and its Component Scores (fda.gov)
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- Morga A, Latimer NR, Scott M, Hawkins N, Schlichting M, Wang J. Is Intention to Treat Still the Gold Standard or Should Health Technology Assessment Agencies Embrace a Broader Estimands Framework?: Insights and Perspectives From NICE and IQWiG on the ICH E9(R1) Addendum. Value Health. 2023 Feb;26(2):234-242. doi: 10.1016/j.jval.2022.08.008. Epub 2022 Sep 21. PMID: 36150999.

Agenda

Introduction: Objectives and Background	Sue and David
Case Study: Tic-Toc-PSI in Heart Failure	Nikhil
Strategies for Handling Intercurrent Events into Estimands	Antonia and Sue
Different Perspectives for Handling Intercurrent Events	All
Formulating Estimands	Sue and Antonia
Challenges and Recommendations	David
Q & A	**All**

Back up Slides

12-item Kansas City Cardiomyopathy (KCCQ-12)

Q1. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Showering/Bathing; walking 1 block; hurrying <3 items, 5 pt scale + NA>

Q2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Q3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

12-item Kansas City Cardiomyopathy (KCCQ-12)

Q4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

Q5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

12-item Kansas City Cardiomyopathy (KCCQ-12)

Q6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

Q7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Q8. Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

- Hobbies, recreational activities;
- Working or doing household chores;
- Visiting family or friends out of your home <3 items>