

ICH E9(R1) Implementation in Study Protocols

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Acknowledgements

- For co-authoring estimand implementation recommendations
 - James Bell, Elderbrook Solutions
 - Amel Besseghir, UCB
 - Vivian Lanius, Bayer
 - Christian Lösch, UCB
 - Khadija Rantell, MHRA
 - Volker Schoder, Metronomia
- Rest of Estimand Implementation Working Group (EIWG) for valuable comments

Disclaimer

- Both presenters are members of the TransCelerate authoring team on Common Protocol Template (CPT) statistical section and Statistical Analysis Plan Template, and HL is member of the EIWG sub-team on estimand implementation recommendations
- Opinions are those of the presenters and are not necessarily the views of our respective companies and/or of TransCelerate

Outline

- Background
 - The estimand journey
 - Available templates
- Challenges
 - EIWG recommendations vs the TransCelerate Common Protocol Template
- Summary

Introduction: The Estimand Implementation Journey

Draft ICH E9 (R1) addendum available

Q1: TransCelerate statistics working group kick-off

Q3: TransCelerate Protocol template updated embracing estimands framework

Q3 Final ICH E9(R1) addendum available

Q3: EFPIA Estimands Implementation Working Group (EIWG) Kick off

Final ICH E9 (R1) addendum on estimands adopted in July by EMA

Q1: ICH M11 protocol template available for party review

Final ICH E9 (R1) addendum on estimands adopted in May by FDA

(EIWG) reflections on challenges & recommendations

2017

2018

2019

2020

2021

TransCelerate:

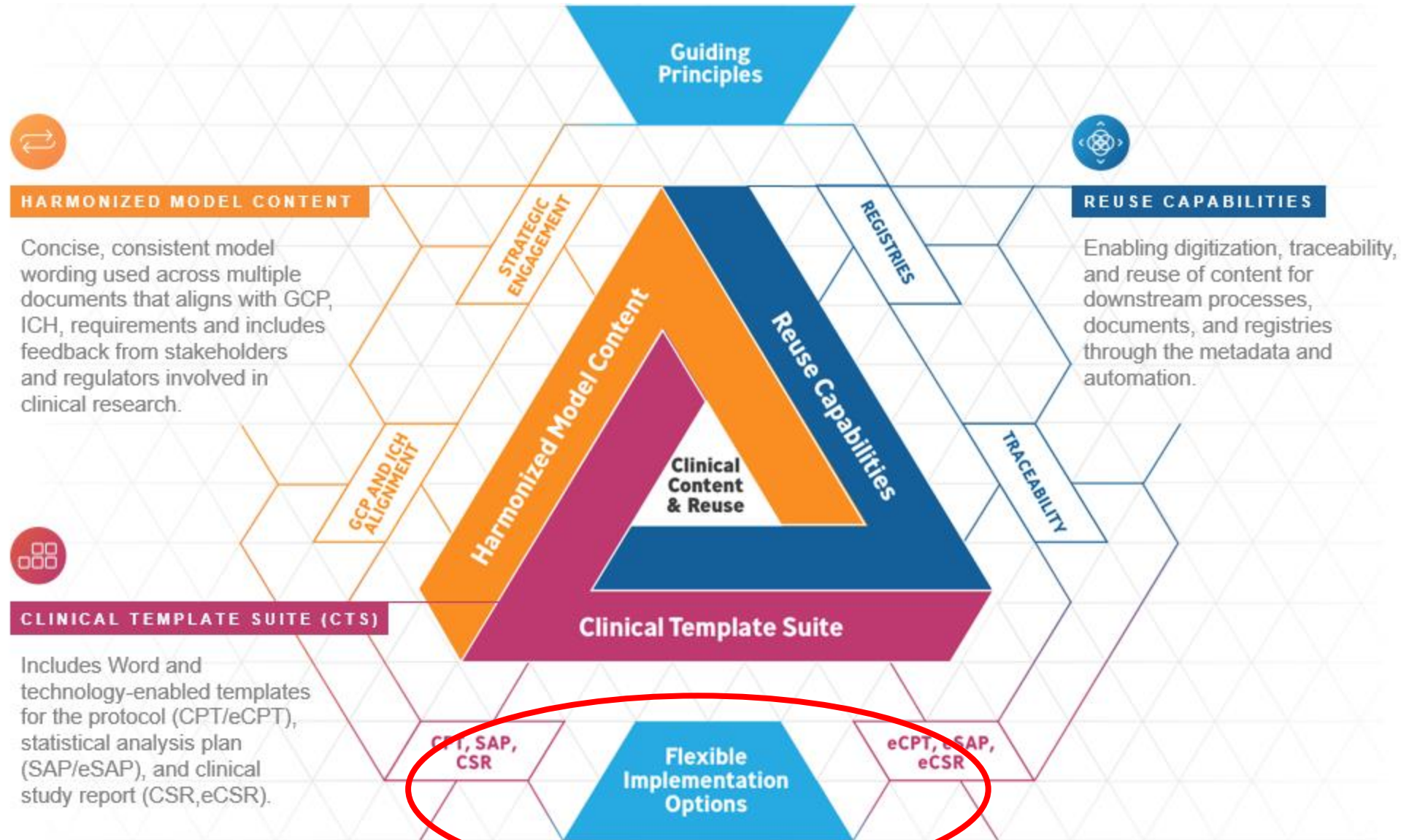
A Not-for-Profit Entity Created to Foster Collaboration

Our Shared Vision:

To improve the health of people around the world by accelerating and simplifying the research and development of innovative new therapies.



TransCelerate Templates



In Summary, What is Publicly Available?

TransCelerate Clinical Template Suite*

- Estimands in V6 (2018)
- Releases every year including learnings & improvements
- **Not a standard!**

ICH M11 Protocol Template

- Expected by 2023
- **A standard!**

Clinical template suite includes Protocol, SAP and Clinical Study report Templates

Initial Considerations

Detail in the study objective

- Detailed clinical objective¹
 - Estimand attributes addressed in objective
- Less detailed
 - Clinical question of interest/estimand attributes need to be specified

Details in Objectives

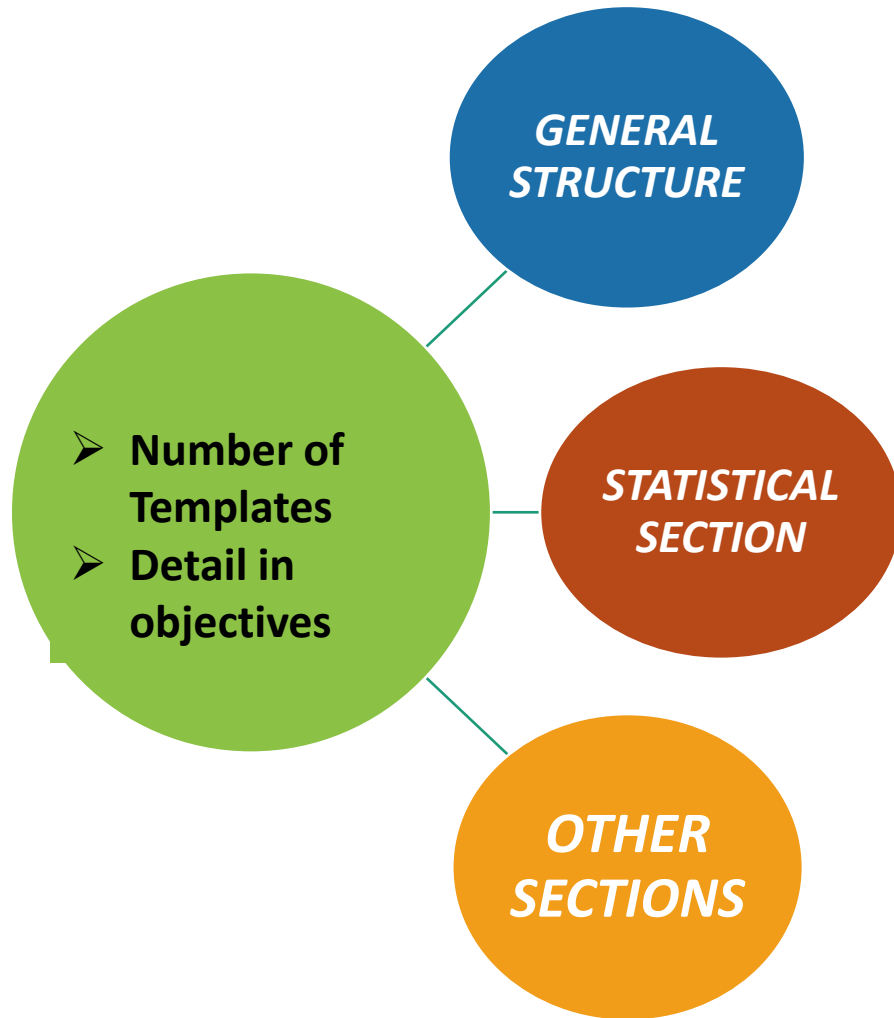
Number of Templates

Estimands not mandatory for all type of trials

- One template fits all versus
- Separate templates for studies with or without estimands

¹Bell J, Hamilton A, Sailer MO and Voss F. The detailed clinical objectives approach to designing clinical trials and choosing estimands. *Pharmaceutical Statistics*. 2021;1-13.

Initial Considerations, Downstream Challenges

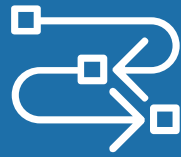


- Where to describe estimands?
- Structure around objectives or estimands versus structure around endpoints

- Align main analysis with estimand or objective
- Distinguish between intercurrent events & missing data
- Data points selection & implementation of intercurrent events strategies
- Distinction between sensitivity & supplementary analyses
- Sample Size estimation

- Design
- Conduct
- Study intervention
- Discontinuation of intervention
- Withdrawal from study

General Structure

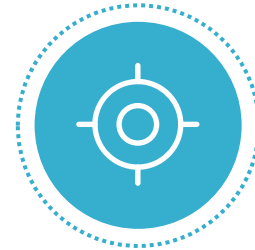


- Pre-ICH E9(R1):
 - Structure endpoint-centred
 - Estimand attributes were scattered across different sections and intercurrent events never explicitly mentioned



IMPACT

**Change of mindset:
Focus on all
estimand attributes**



RECOMMENDATIONS

- Estimands described early on with all attributes
- Analysis sections structured around objectives or estimands



TRANSCCELERATE EXAMPLE

- Estimands described in objectives section
- Statistical Considerations sections focussed on estimands/endpoints

How to Write Estimands?

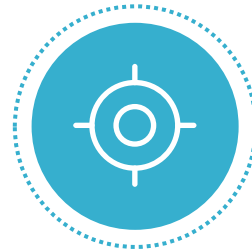


- Pre-ICH E9(R1):
 - Objectives most often unspecific
 - Focus on linking objectives and endpoints



IMPACT

Change of mindset:
Focus on clarity



RECOMMENDATIONS

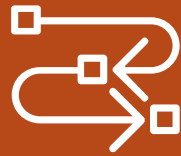
- Detailed clinical objective
- Less detailed objective – various alternatives:
 - Layman – easier for stakeholders
 - Bullet list of attributes – more transparent, but “technical”
 - Table - Linking objective & estimand OR textual
- Rationale



TRANSCCELERATE EXAMPLE

- Objectives & endpoints table, estimands described below ~~GO~~
- Clinical question of interest (“layman”)
- Estimand attributes in bullet format (“technical”)
- Rationale

Statistical Section

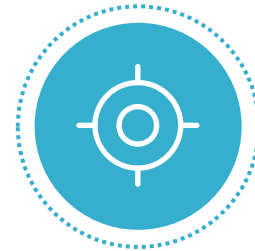


- Pre-ICH E9(R1):
 - Unclear which question the main analysis addressed
 - Sensitivity analyses a mixture of unrelated competing analyses
 - Intercurrent events were not separated from missing data



IMPACT

Change of mindset:
Transparency



RECOMMENDATIONS

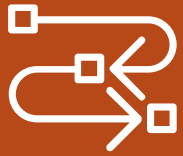
- Main analysis with subsections for sensitivity and supplementary analyses
- Distinguish between intercurrent events and missing data



TRANSCCELERATE EXAMPLE

- Separated – additional estimands to be described together with supplementary analyses
- Not clearly distinguished

Statistical Section: Supplementary Analyses



- Pre-ICH E9(R1):
 - No distinction between sensitivity and supplementary analyses



IMPACT
Change of mindset:
Transparency



RECOMMENDATIONS

Different understanding on what supplementary analyses encompasses:

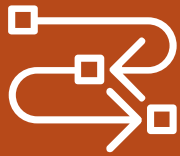
- Compared to main, supplementary analysis targets:
 - The same estimand?
 - A different estimand?
 - Either of the above (reflected in draft ICH E9(R1))



TRANSCCELERATE EXAMPLE

- No explicit specification:
 - Placeholder for supplementary analyses

Statistical Section: Participants & Data Points



- Pre-ICH E9(R1):
 - Data points selection usually not described
 - In ICH E9, “Analysis Set” refers to the set of participants whose data are to be included in an analysis



IMPACT

Change of mindset
Participant level
versus data level



RECOMMENDATIONS

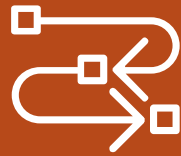
- Specification of data points (and participants) per estimand
- **No consensus on best implementation approach:**
 - Analysis Sets section
 - Separate section on statistical implications of intercurrent events and their strategies
 - In relevant analysis section



TRANSCCELERATE EXAMPLE

- Examples proposed in Analysis Sets section:
 - Participant Analysis Set
 - Defined Data Points Set

Statistical Section: Sample size



- Pre-ICH E9(R1):
 - Sample size adjusted according to expected extent of missing data



IMPACT

**Change of mindset:
Intercurrent events
should be considered**



RECOMMENDATIONS

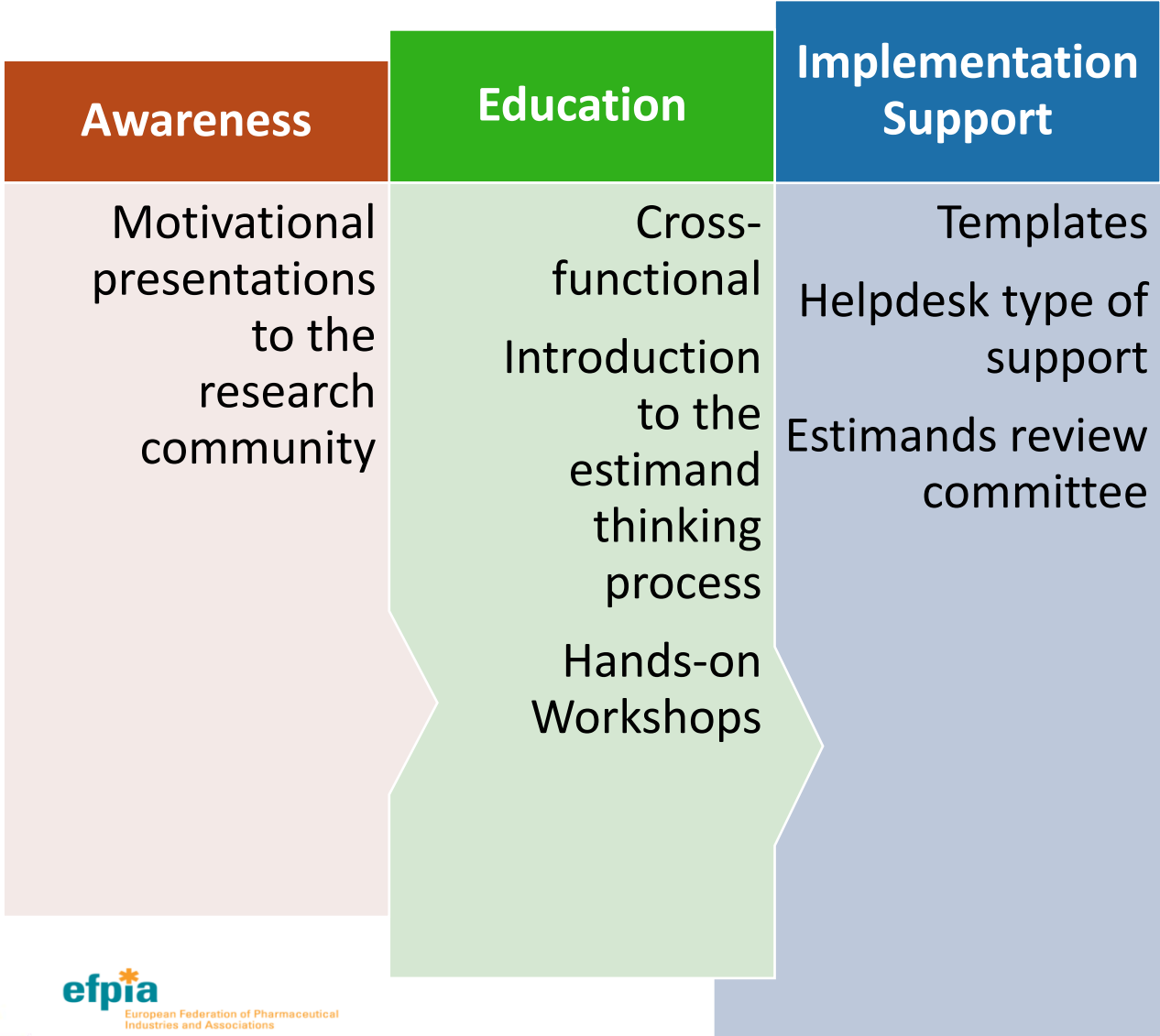
- Specification of expected frequency of each intercurrent event by intervention arm and expected impact on effect size and precision
- Estimands in reference studies to be mentioned



TRANSCCELERATE EXAMPLE

- Partly reflected in instructional text

Training & Support within Companies



Summary



TransCelerate Common Protocol Template is the only publicly available template today including estimand framework



ICH M11 Clinical electronic Structured Harmonised Protocol (CeSHarP) is expected to be released in 2023



Estimands Implementation is challenging



Estimands and objectives are the backbone of the study



Strategy for implementation within companies is key

Thank you!