Implementation of the estimand framework in the regulatory assessment: How it started and how it's going

Laura Rodwell, Statistical assessor

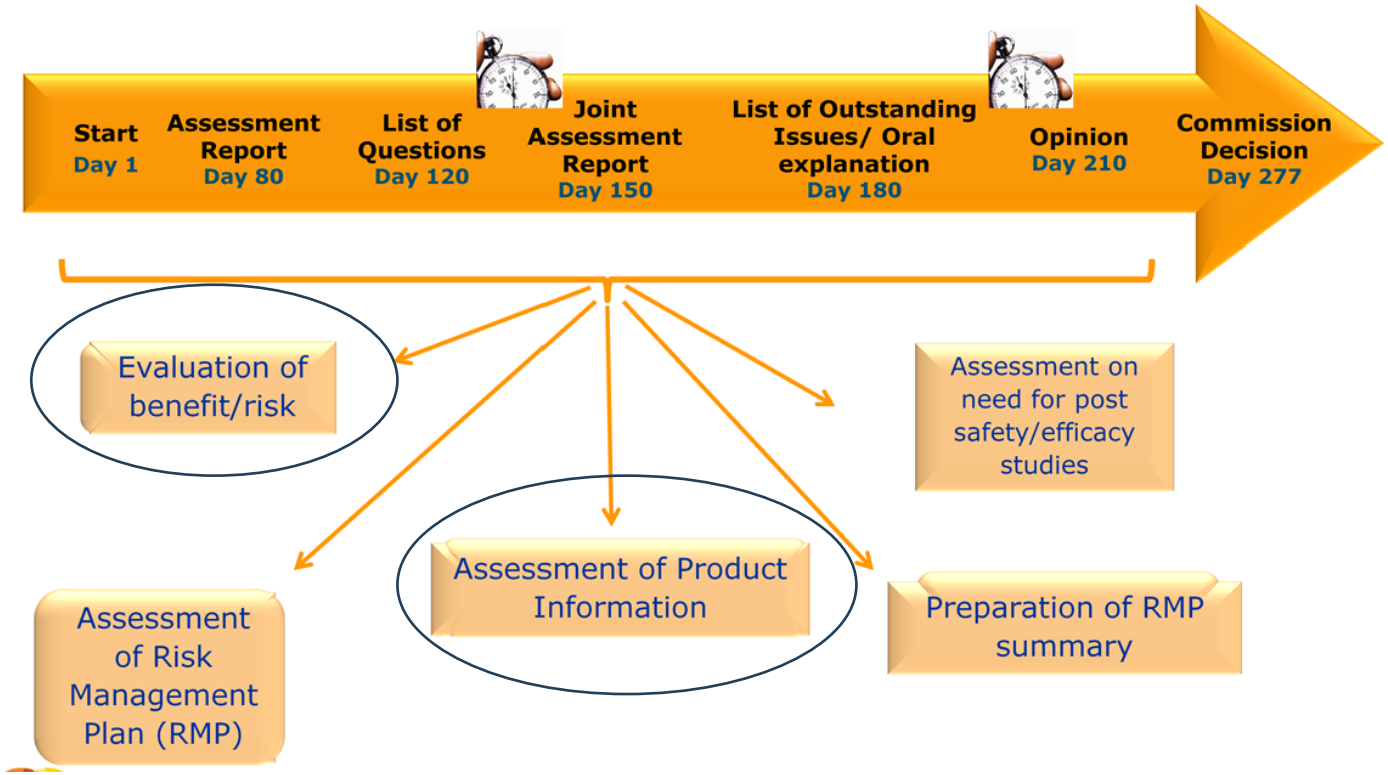
Medicines Evaluation Board

GOOD MEDICINES USED BETTER

Disclaimer

The views expressed in this presentation are the presenter‘s personal views and not necessarily the views of the MEB or EMA

Centralised procedure



At the MEB

As Rapporteur or Co-rapporteur:
Two clinical assessors (efficacy and safety)
One statistical/methodology assessor

Other assessors (PK, quality, non-clinical..).

Important reports and documents
for the clinical/stats assessment:

Day 80 Clinical Assessment Report
(Draft) overview and list of questions
Joint assessment reports
European public assessment report (EPAR)
Product information/SmPC

How it started

Estimand

Intercurrent events

Sensitivity analysis

Supplementary analysis

Estimator

Treatment policy strategy

Composite

Hypothetical strategy

While on treatment

Principal stratum strategy

Artist's impression. Any resemblance to real clinicians is purely coincidental.

How it's going…

Still some apprehension and confusion but clinical assessors recognise the importance of the estimands framework and are becoming more engaged in discussions.

Challenges and sources of confusion for the assessment:

- Comparisons with previous procedures
  - Assessors have a good memory (and access to previous assessments) and aim for fairness and consistency
- The role of the statistical assessor vs clinical assessor
  - Are statistical assessors reducing learning opportunities for the clinical assessors by doing the work?
  - Statistical assessor needs to also act as translator and facilitator to support the clinical assessor's thinking
- Sensitivity analyses vs supplementary analyses/estimands

Reducing the barriers for clinicians

- Training and education
  - Workshops within the NCAs and network-wide training
  - Including in university education (teach them young)

- Exposure to scientific advice discussions and examples in assessments
  - Include the clinicians in the “fun” discussions

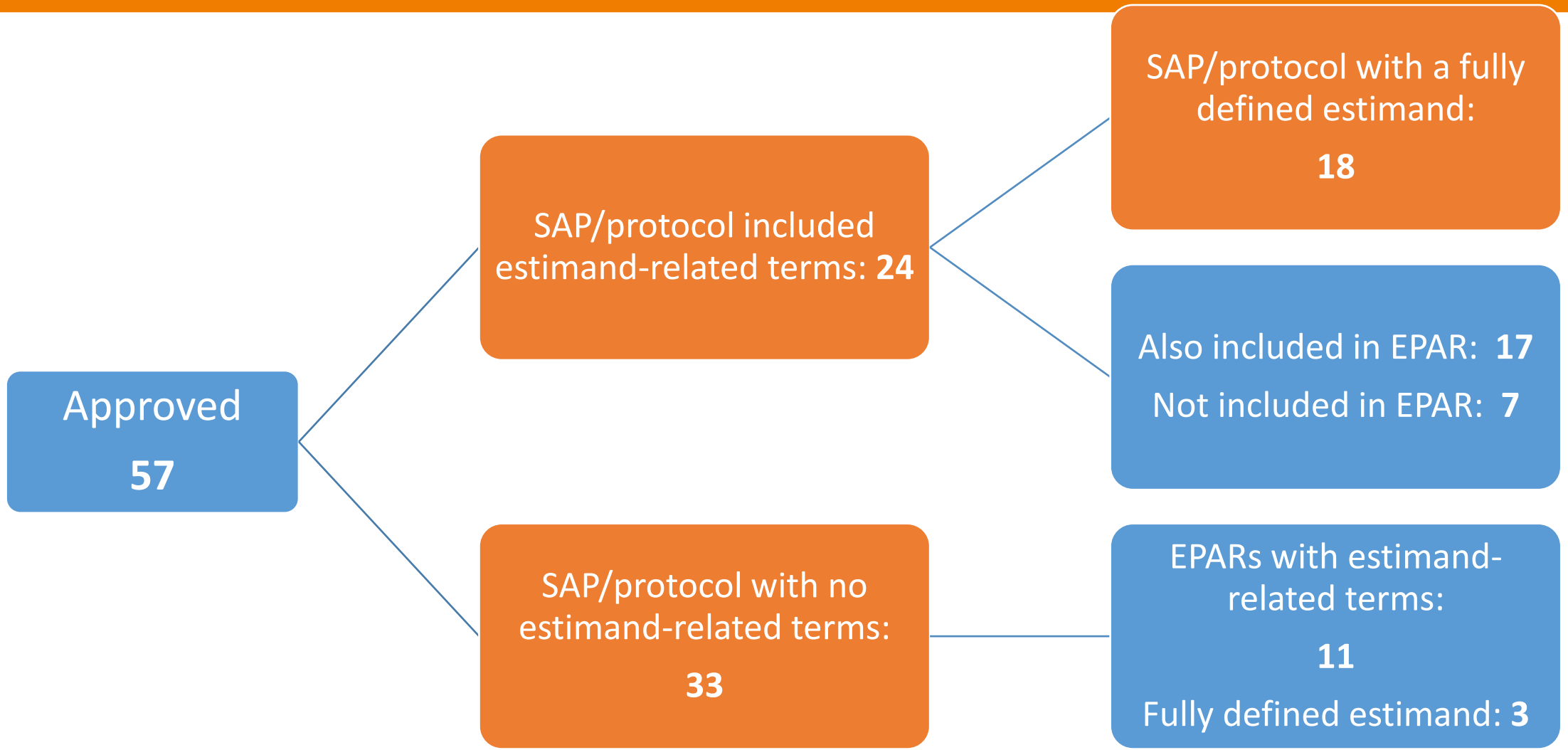
- Make it more relevant for the clinicians – bring the WHY into the discussions

How it’s going with the assessments

Let the numbers do the talking…

- Approved medicines between January 2023 – May 2024 (based on marketing authorisation date)
- Excluded biosimilars, generics, extensions of indication, hybrid applications, diagnostics
- Searched in the European Public Assessment Reports (EPARs) and the SAP/Protocol using the following terms: “estimand”, “intercurrent”, “treatment policy”, “hypothetical”, “composite”, “while on”, and “treatment effect of interest”
- For both the EPAR and the SAP(s)/Protocol(s) for the approved medicines I noted 1) if there was any reference to the estimand based on the terms above, and 2) if the estimand was defined in full, either in a table or words

Let the numbers do the talking…



New Estimand table in the Clinical AR (AR REVAMP project)

Population	E.g., <Patients with [condition and applicable specifiers] <who would encounter the Intercurrent Event of [intercurrent event] if assigned to [treatmentName].>>
Treatment condition<s>	E.g., <Assignment to [treatmentName], regardless of discontinuation, compared to assignment to [comparatorName], regardless of discontinuation.>
Endpoint (variable)	[name of the variable or outcome to be observed from every participant] at [timepoint] <or before the occurrent of the [intercurrent event]>
Population-level summary	[Population-level summary, e.g. difference in means]
Intercurrent events and strategy to handle them	
<IE n>	<Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum>

Also includes a request to include a “plain language” statement of the estimand and guidance for the rapporteur’s assessment:

Are the estimands justified? Is the strategy for intercurrent events also justified?

Assessment scenario 1: Everything is clear

At time of study design:

- Scientific advice sought, which included a comprehensive discussion on the estimand attributes (especially intercurrent events and proposed strategies)
- Disease-specific EMA guidance with a discussion on the estimand was available

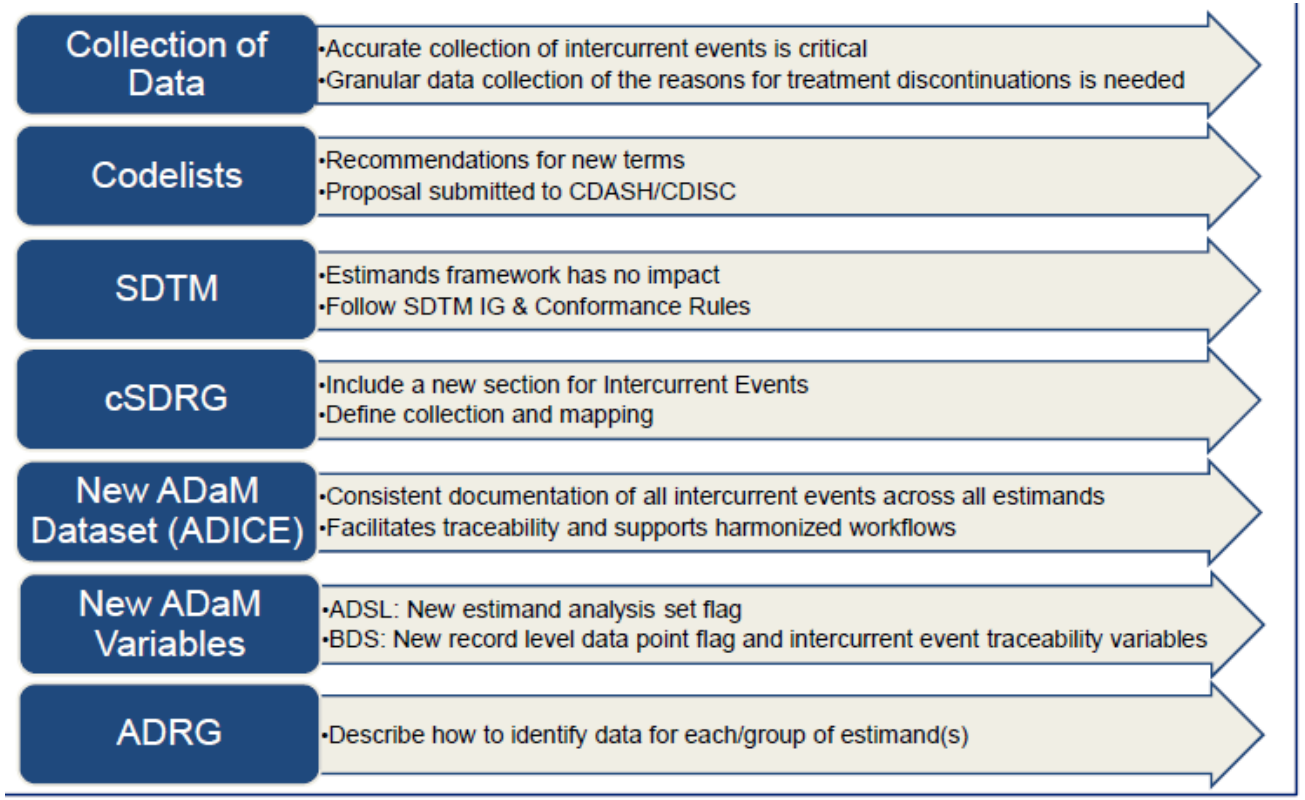
For the assessment:

- Estimand specified, aligns with “our” scientific question of interest
- Method of estimation aligned with estimand
- Well-summarised intercurrent events and Listing of intercurrent events by patient (where relevant with date and specific rescue therapy used)

ICE collection and reporting: Easily said, not so easily done…

PP10: Implementation of the ICH E9(R1) Estimands Framework Using Data Standards

Lori Van Meter, Chris Price, PHUSE Estimands Project Team



From: PowerPoint Presentation (lexjansen.com)
https://advance.phuse.global/display/WEL/Implementation+of+Estimands+%28ICH+E9+%28R1%29%29+using+Data+Standards

Assessment scenario 2: When the estimand has been pre-specified and "new" challenges arise

Estimand pre-specified with two intercurrent events identified: treatment discontinuation and use of rescue therapy

Primary estimand: treatment policy strategy for both ICEs, Supplementary estimand: hypothetical for both ICEs

Interest in treatment effect at week 12, measurements also taken at baseline, and weeks 4 and 8

Analysis approach: "Standard" MMRM assuming MAR for the primary and supplementary analyses

Number of patients with available/included data at each visit				
Visit	Treatment policy		Hypothetical	
	Treatment	Control	Treatment	Control
Baseline	100	100	100	100
Week 4	99	98	99	98
Week 8	96	93	93	90
Week 12	90	89	83	80

Assessment scenario 2

Questions that might arise during assessment:

- What do we know about the patients who do not have complete visit data?
- Which (if any) intercurrent events are recorded for these patients and when did they occur?

Is this information already available or does it need to be requested as part of the LoQ?

- Is the “standard” MMRM model unbiased for treatment policy strategy given missing data? What are the alternative analysis options that could be requested?

Estimation methods for estimands using the treatment policy strategy; a simulation study based on the PIONEER 1 Trial

Authors: James Bell[1], Thomas Drury[2], Tobias Mütze[3], Christian Bressen Pipper[4], Lorenzo Guizzaro[5], Marian Mitroiu[6], Khadija Rerhou Rantell[7], Marcel Wolbers[8], David Wright[9]

Assessment scenario 3: When the estimand hasn't been pre-specified

Progression free survival in oncology (time to centrally-determined progressive disease or death)

(Typically) Primary analysis: If new anticancer therapy is received before centrally-determined progression, patient is to be censored at the time of the previous assessment
Discontinuation of allocated treatment alone is not a reason to censor

"Sensitivity analysis": no censoring for new anticancer therapy (EMA/CHMP-preferred approach)

Assessment scenario 3

Challenges for assessment:

- Should we translate the “censoring rules” to the estimand language?

- Can “we” get an answer to our question of interest?
  - Did the assessment schedule continue for patients who received new anticancer therapy?
  - What happened before the use of new anticancer therapy?

- Very quickly end with requests for sensitivity analyses (including tipping point analyses)
  - Challenging to formulate questions, likely just as challenging to answer them, and an evaluation of the responses requires an evaluation of the plausibility of assumptions etc.

Importance of early interactions and discussions

Guidelines

Scientific advice

THINGS GOT REALLY INTERESTING WHEN THE STATISTICIAN STARTED DOING WARD ROUNDS.

Thank you