



Shaping the Future of
Drug Development

ESTIMANDS - PICOT – EEG-SPIDER

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EFPSI: Latest Trends in Health Technology Assessments (HTA)

Berlin, February 15th 2019

Agenda

- Estimands:
 - Timelines for ICH E9 (R1)
 - The four attributes of estimands
 - The five strategies to account for intercurrent events
- HTA-relevant criticism on the ICH E9(R2) addendum (selection)
 - Some estimand strategies are irrelevant (for HTA?)
 - Lack of guidance on how to decide among the five strategies
 - Not (yet) a good guidance for a multidisciplinary approach to decide on the estimand partly because communication is hampered by introducing new and confusing terminology (estimand, intercurrent events)
- What do PICOT and PRECIS have to offer to address these issues
 - PICOT for Estimand description
 - PRECIS → EEG-Spider to assess the expected efficacy-effectiveness gap of estimand choices

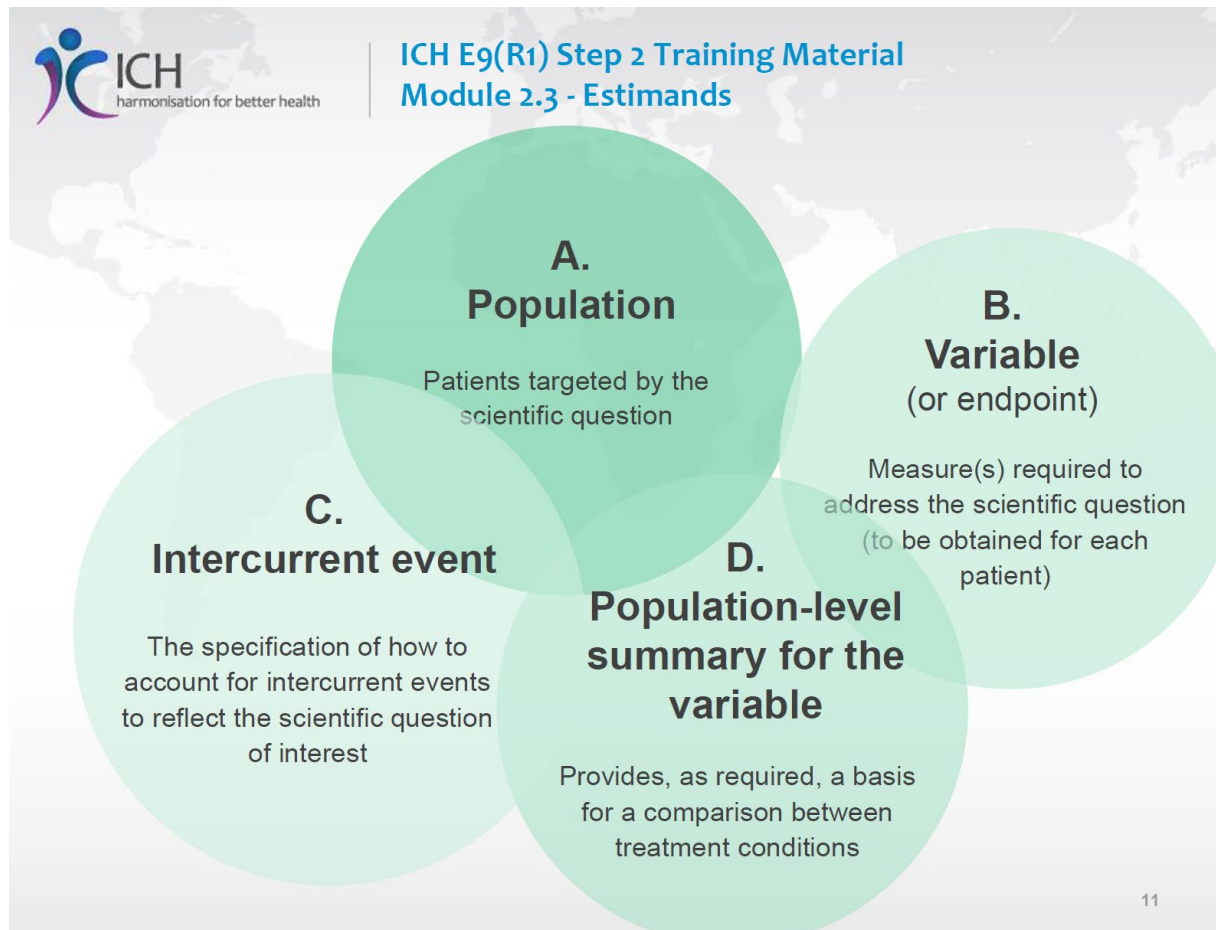
ICH E9(R1) EWG Workplan: Implementation phase starts soon!

Beginning date	End Date	Task / Activity	Details
Dec. 2017	Early 2019	Step 3	Organise or participate at meetings at a global or regional level to promote awareness and comments on the addendum. Discuss regional consultation comments and modify the addendum and accompanying documents, based on comments received. Outline plans for further progress towards finalisation.
Jan. 2018	Early 2019	In parallel with Step 3	Discuss methodological issues related with estimands and sensitivity analysis in clinical trials. Consider the relationship of ICH E9(R1) with other ICH documents.
Jun. 2019		Step 3 and Step 4	Finalise the addendum and accompanying documents. Organise an ICH training. Once all documents are finalised, engage the sign-off process. Step 3: Sign-off by topics leaders of Regulatory ICH Parties. Step 4: Sign-off by all ICH Regulatory Parties.

For the implementation of the guidance the HTA community can give valuable input to improve upon the readability and practicality of estimands in clinical trial practise.

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1_EWG_WorkPlan_2018_0731.pdf, 09JAN2019

Reminder: The four attributes of an estimand



http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Modules1-3_Step2_COMPILATION_TrainingMaterial_2018_0703.pdf, 09JAN 2019

Reminder: The five strategies for ICEs – HTA view

J. Wang, C. Fletcher, N. Hawkins 2018 Sense and sensibility of estimands for HTA

Strategy	Pros	Cons
Treatment policy	HTA typically evaluates effectiveness of a policy rather than a treatment.	- Hard/impossible to replicate feasible policies for multiple payers in a single trial. - Effects of test treatment may be diluted.
Composite endpoint	- A good composite endpoint (e.g., QALY) may fit to HTA well - Meaningful for BRA and HTA if it reflects benefit-risk balancing	- Only work well for some events (e.g., death) - May have to categorize continuous measures, which may not be good for HTA.
Hypothetical	Comparisons between randomized treatments	The hypothetical scenario is meaningful only under some situations
Principal stratum	- Randomization may still be useful - Extensive researches have been done	- Principal strata may not be identifiable - They may not be of interest.
While on treatment	May construct meaningful estimands, e.g., together with the composite approach	May only measure short-term effects for some patients.

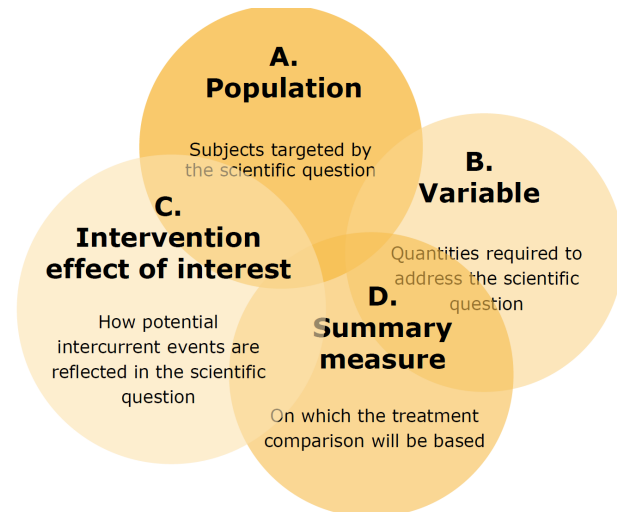
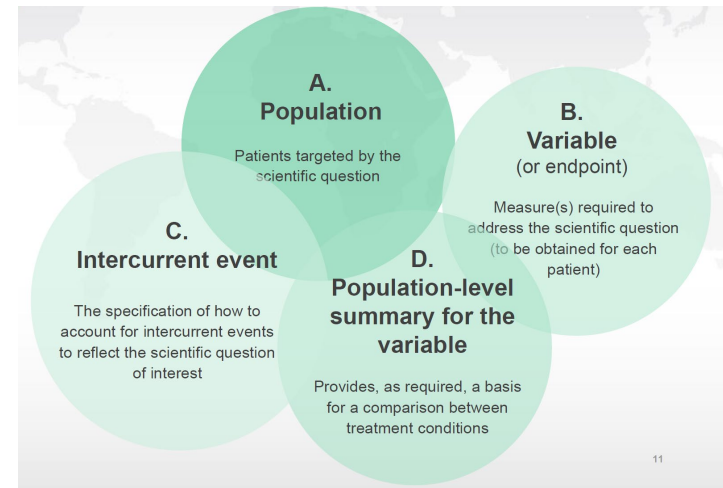
IQWiG

Criticism and suggestion on how it can be addressed

- Not (yet) a good guidance for a multidisciplinary approach to decide on the estimand partly because communication is hampered by introducing new and confusing terminology (estimand, intercurrent events)
- Lack of guidance on how to decide among the five strategies
- Some estimand strategies are irrelevant (for HTA?)
- PICOT can be used to describe an estimand within a familiar terminology framework (EBM)
- Like with PRECIS-2, an EEG-Spider can be used to score estimands of choice for their risk of generating an efficacy-effectiveness gap

PICOT side to side with Estimand

P	–	Population	Population
I	–	Intervention	ICE := Precise definition of intervention and control
C	–	Control	
O	–	Outcome	Variable
T	–	Time frame	Variable



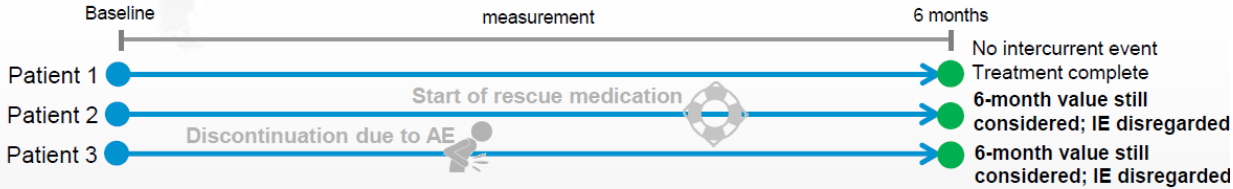
ICH E9(R1) training example in PICOT

 ICH
harmonisation for better health

ICH E9(R1) Step 2 Training Material
Module 2.3 - Estimands

Multiple intercurrent events – example

- **Treatment-policy strategy to account for both intercurrent events:**
- **Estimand:** Difference in means between treatment conditions in the change from baseline to month 6 in the targeted patient population, regardless of whether or not rescue medication had been used and regardless of treatment discontinuation due any adverse events.
- **Applying treatment-policy x treatment-policy strategy...**



Baseline measurement 6 months

Patient 1: No intercurrent event
Treatment complete
6-month value still considered; IE disregarded

Patient 2: Start of rescue medication
6-month value still considered; IE disregarded

Patient 3: Discontinuation due to AE
6-month value still considered; IE disregarded

Legend:

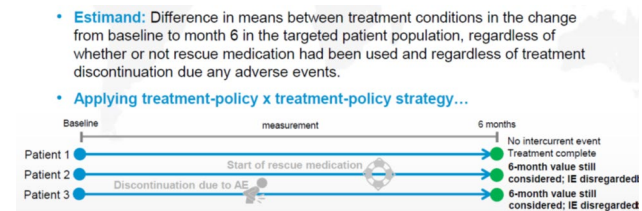
- 6-month value has been collected
- Part of patient time course considered
-  Intercurrent events (in grey when disregarded)
- IE Intercurrent event

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PICOT used to describe an Estimand

Example – Treatment policy for two ICEs

- Population: ~~Targeted treatment population~~ Patients with disease A & In/Ex
- Intervention:
 - Patient starts being treated with Drug X and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events
- Control:
 - Patient starts being treated with Placebo and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events
- Outcome:
 - Measurement of Y
- Timeframe:
 - 6 months after start of treatment



PICOT used to describe an Estimand

Example – Composite endpoint strategy for both ICEs

Population: Patients with disease A & In/Ex

Intervention:

- Patient starts being treated with Drug X and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Control:

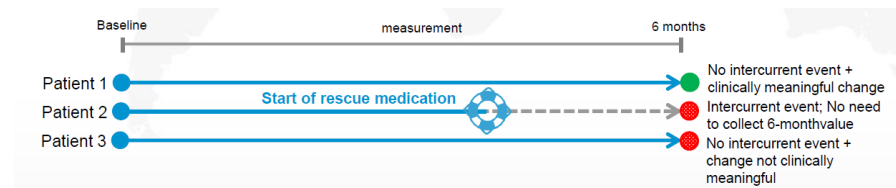
- Patient starts being treated with Placebo and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Outcome:

- Success, if no treatment discontinuation and measurement of $Y > \text{threshold}$,
- Failure, otherwise

Timeframe:

- 6 months after start of treatment



PICOT used to describe an Estimand

Example – Composite endpoint strategy for three ICEs

Population: Patients with disease A & In/Ex

Intervention:

- Patient starts being treated with Drug X and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Control:

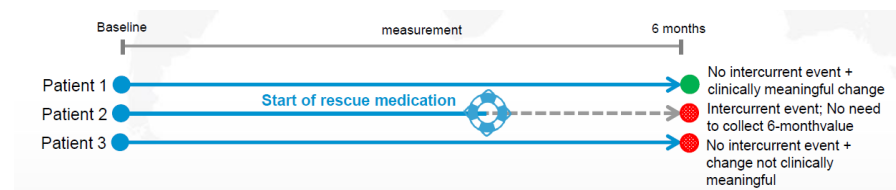
- Patient starts being treated with Placebo and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Outcome:

- Success, if no treatment discontinuation **nor death** and measurement of $Y > \text{threshold}$,
- Failure, otherwise

Timeframe:

- 6 months after start of treatment



PICOT used to describe an Estimand

Example – Treatment policy and hypothetical strategy

Population: Patients with disease A & In/Ex that have no access to rescue medication

Intervention:

- Patient starts being treated with Drug X and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Control:

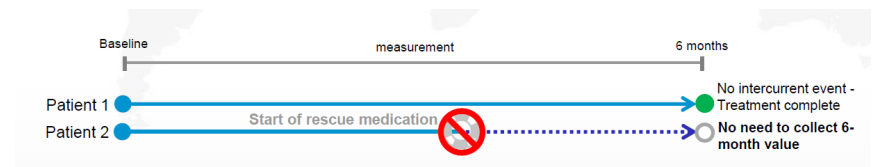
- Patient starts being treated with Placebo and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Outcome:

- If no rescue medication was taken, measurement of Y,
- otherwise a predicted value of Y

Timeframe:

- 6 months after start of treatment



PICOT used to describe an Estimand

Example – Treatment policy and principle stratum

Population: Patients with disease A & In/Ex **that do not need rescue medication**

Intervention:

- Patient starts being treated with Drug X and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Control:

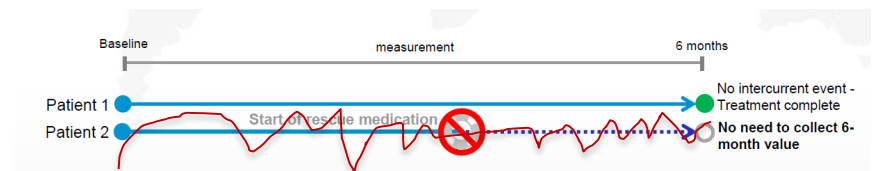
- Patient starts being treated with Placebo and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Outcome:

- **If no rescue medication was taken, measurement of Y,**
- **otherwise ignored**

Timeframe:

- 6 months after start of treatment



PICOT used to describe an Estimand

Example – While on treatment strategy for both ICEs

Population: Patients with disease A & In/Ex

Intervention:

- Patient starts being treated with Drug X and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

Control:

- Patient starts being treated with Placebo and switches to rescue medication in case of lack of efficacy or to any appropriate further treatment in case of (severe) adverse events

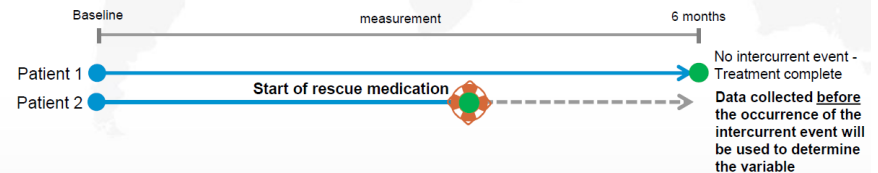
Outcome:

- Measurement of Y

Timeframe:

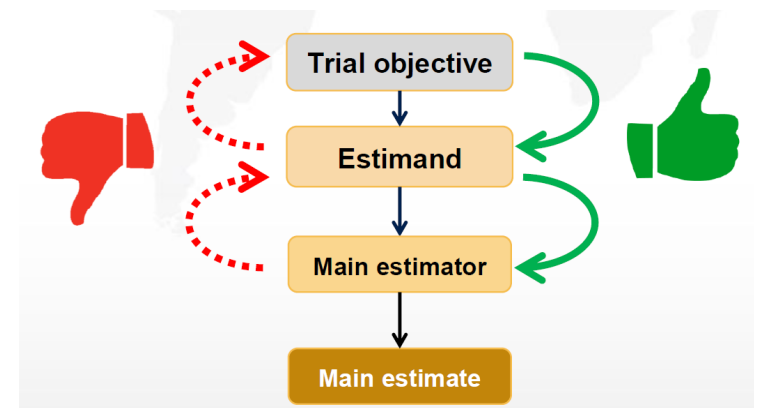
- If no treatment discontinuation, 6 months after start of treatment
- or at timepoint of treatment discontinuation

• Applying the while on treatment strategy



PICOT used to describe an Estimand

- It is not difficult to do
- It improves transparency
 - In general
 - And by being clearly differentiating different types of intercurrent events
 - Intercurrent events by design come in as intervention and control.
 - Observed intercurrent events come in outcome/timepoint only
- ? It has a tendency away from the intention that one first describes the estimand, and then tries to have a trial design with which the estimand can be assessed ?



Criticism and suggestion on how it can be addressed

- Not (yet) a good guidance for a multidisciplinary approach to decide on the estimand partly because communication is hampered by introducing new and confusing terminology (estimand, intercurrent events)
- **Lack of guidance on how to decide among the five strategies**
- **Some estimand strategies are irrelevant (for HTA?)**
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- **Like with PRECIS-2, an EEG-Spider can be used to score estimands of choice for their risk of generating an efficacy-effectiveness gap**

PRECIS-2 to assess a trial on the explanatory-pragmatic continuum

Step 1: Why are you doing your trial?

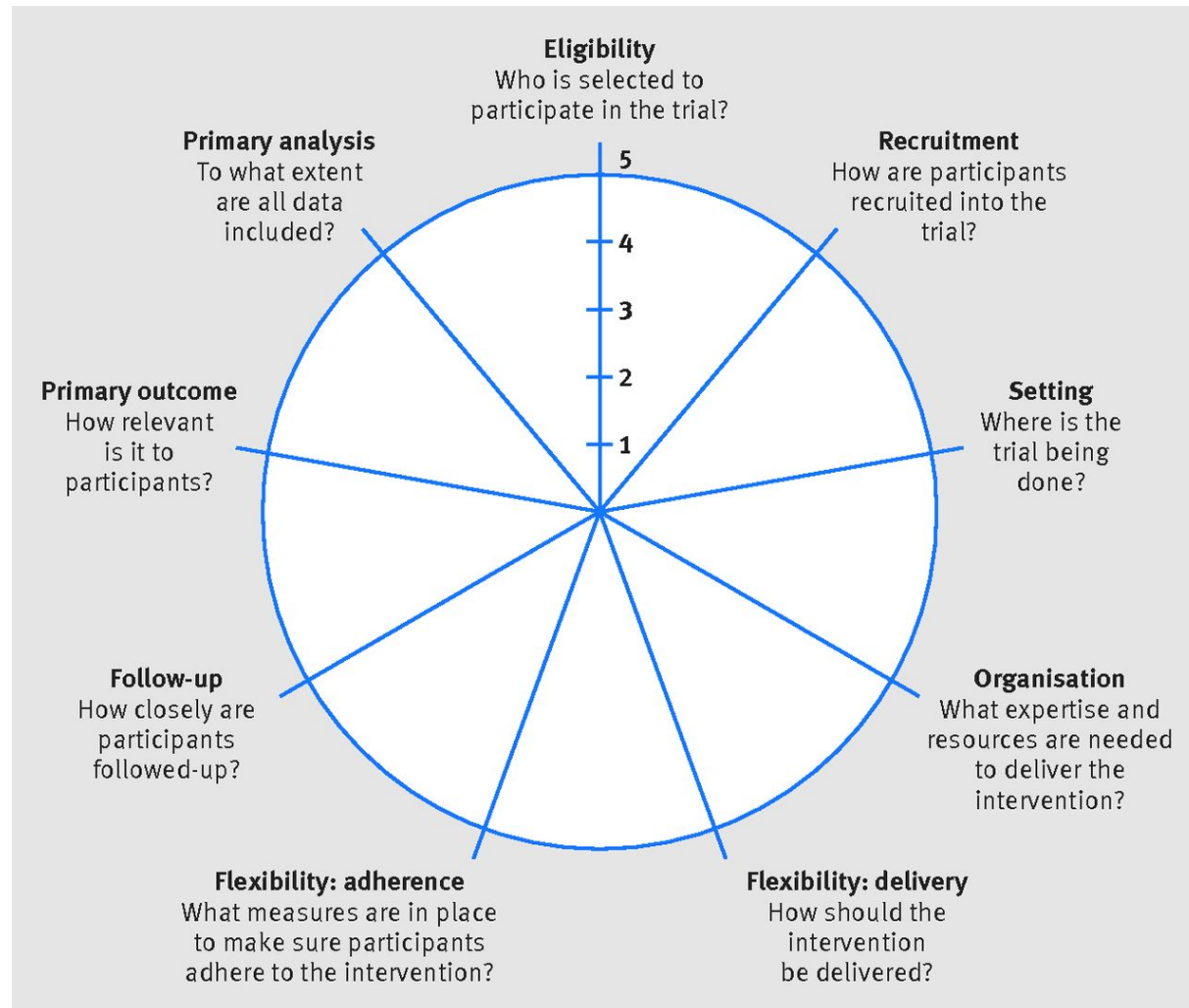
Your first step is to be clear about why you are doing your trial. Are you:

1. Aiming to take an explanatory approach to answer the question
'Can this intervention work under ideal conditions?' *"Can the medical hypotheses underlying the intervention be confirmed?"*
2. Aiming to take a pragmatic approach and answer the question
'Does this intervention work under usual conditions?'

Both approaches to trial design have their place but trialists should be clear which path they are on. As Schwartz and Lellouch pointed out, trialists have often taken the first approach by default rather than as a considered judgement.

Kirsty Loudon et al. BMJ 2015;350:bmj.h2147

The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.



Kirsty Loudon et al. *BMJ* 2015;350:bmj.h2147

PRECIS-2 to assess a trial on the explanatory-pragmatic continuum

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2. Aiming to take a pragmatic approach and answer the question
 ‘Does this intervention work under usual conditions?’

Step 1: Which decision do you want to make based on the results of the trial?

- Continue the development of the compound
- EMA/FDA: Market authorization
- HTA: should the health care system in our country/area spend any money on this HT?
- Reimbursement: How much money will we pay?

From PRECIS-2 to Efficacy-Effectiveness Gap Spider

Why not the same spider as in PRECIS-2:

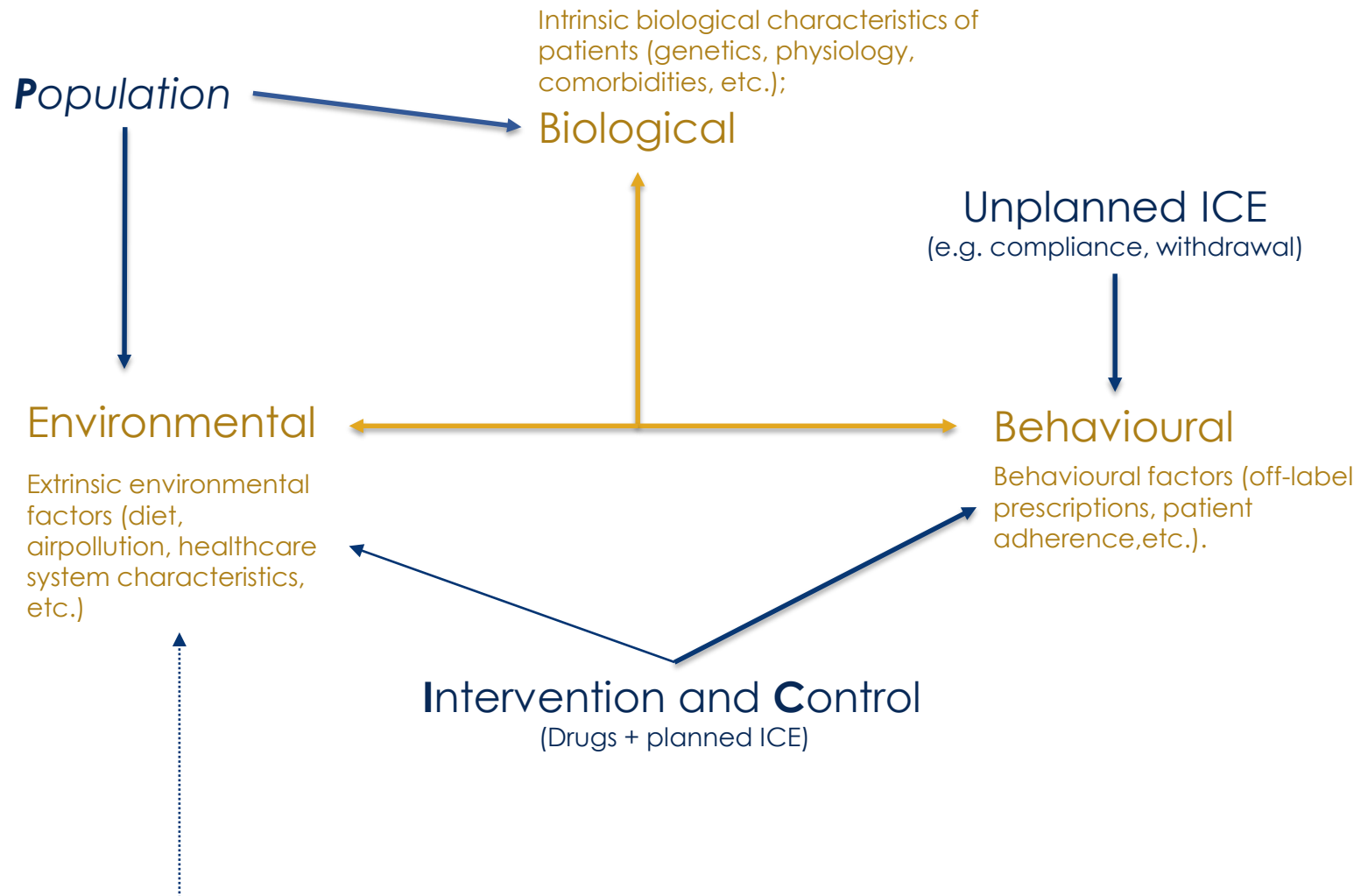
- Primary analysis judgement is mixing IIT analysis with ICE choices
- It has components beyond the estimand definition
- Not focussing on decision making needs?

What else?

- New paradigm for Efficacy-Effectiveness Gap may be useful to build another spider more suitable for estimand assessment
- Factors of potentially increasing variability in real life:
 1. Intrinsic biological characteristics of patients (genetics, physiology, comorbidities, etc.);
 2. Extrinsic environmental factors (diet, airpollution, healthcare system characteristics, etc.)
 3. Behavioural factors (off-label prescriptions, patient adherence, etc.).

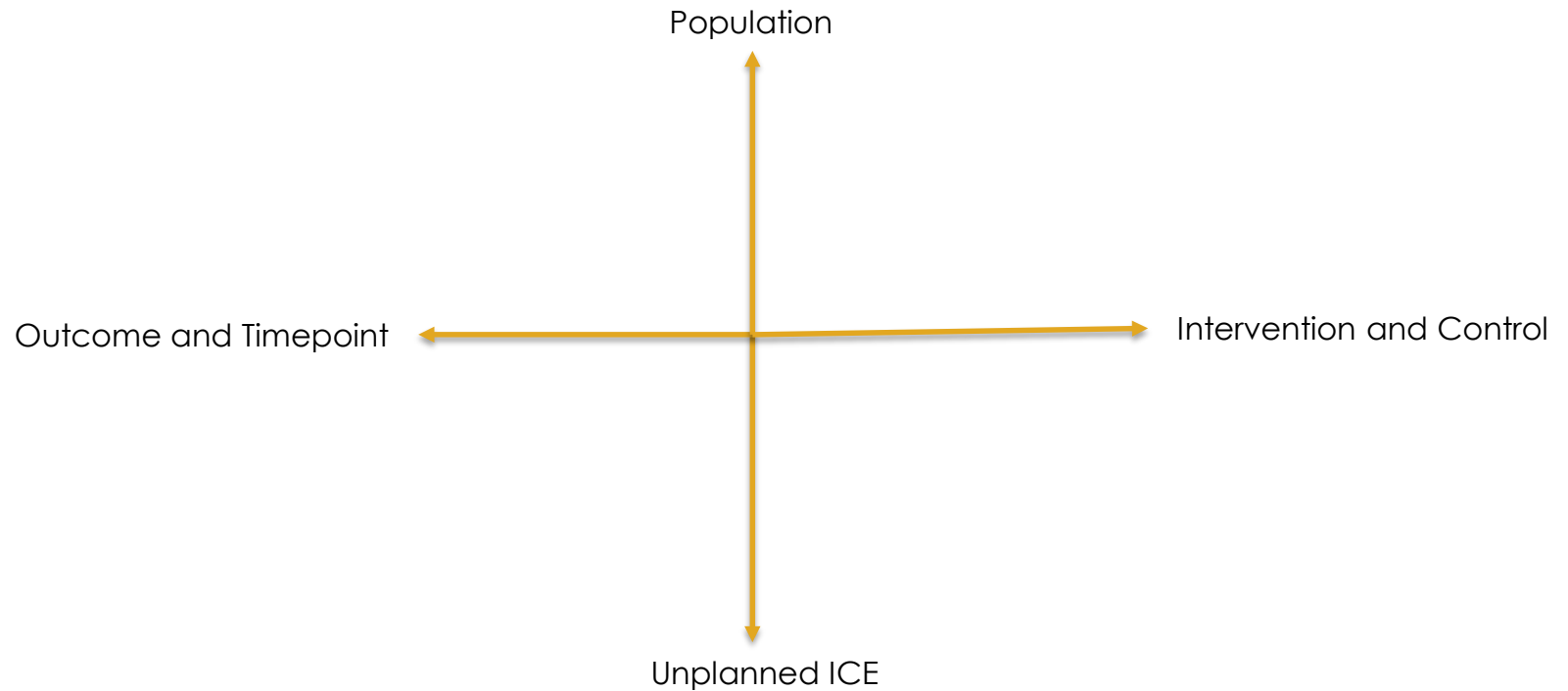
Comparative Effectiveness Research / Health Technology Assessment (HTA) 2016: The “Efficacy-Effectiveness Gap”: Historical Background and Current Conceptualization C. Nordon et al on behalf of the Get Real consortium

Building the EEG-spider

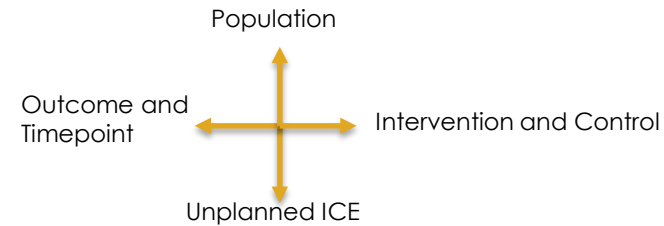


Outcome and Timeframe

EEG-spider



EEG-Spider explained



Population

- Comparison of the biological and environmental variation of the study population to the population that will be given the drug under consideration

Intervention and Control

- How much the fully described intervention and control (with planned intercurrent events) reflect the current practise and variability of interventions

Unplanned ICEs

- How much does the trial set-up match the real world setting in influencing patients and providers behaviour towards the treatment.

Outcome and timeframe

- How meaningful is this measure for the patient population – possibly a weighted average of individually perceived meaningfulness

Scale

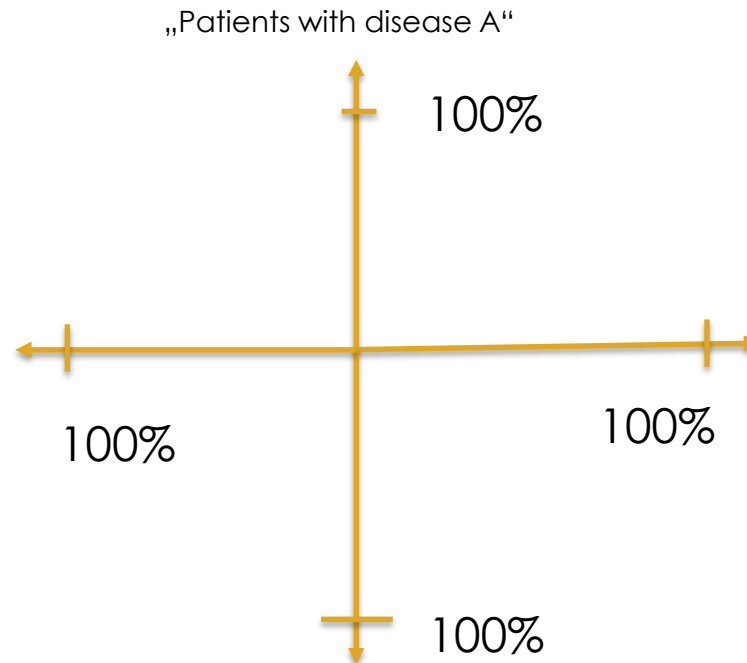
- For estimand comparison for one trial, the maximum possible match among the choices with the envisioned real world(s), is set to 100%

EEG-SPIDER to assess Estimands

Example – Treatment policy for two ICEs

Country where
rescue medication is
available

Measurement Y
At 6 months



Compliance is taken as is
by estimand, Withdrawal of consent
or loss to follow up leads to missing data

Intervention:

Patient starts being
treated with Drug X
and switches to rescue
medication in case of
lack of efficacy or to
any appropriate further
treatment in case of
(severe) adverse events

Control:

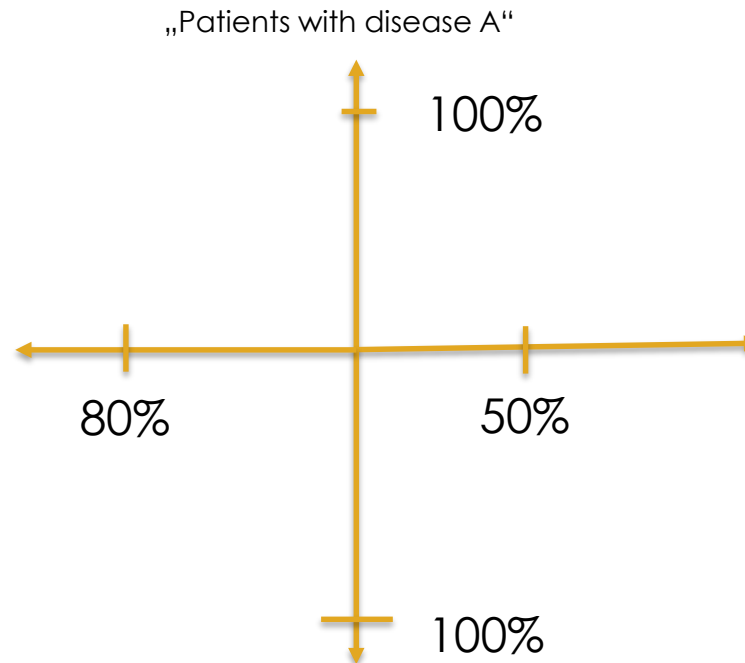
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EEG-SPIDER to assess Estimands

Example – Treatment policy for two ICEs

Country where
rescue medication
is not available

Measurement Y at 6 months
(- 20% for the expected patients
that get rescue medication)



Compliance is taken as is
by estimand, Withdrawal of consent
or loss to follow up leads to missing data

Intervention:

Patient starts being
treated with Drug X
and switches to rescue
medication in case of
lack of efficacy or to
any appropriate further
treatment in case of
(severe) adverse events

Control:

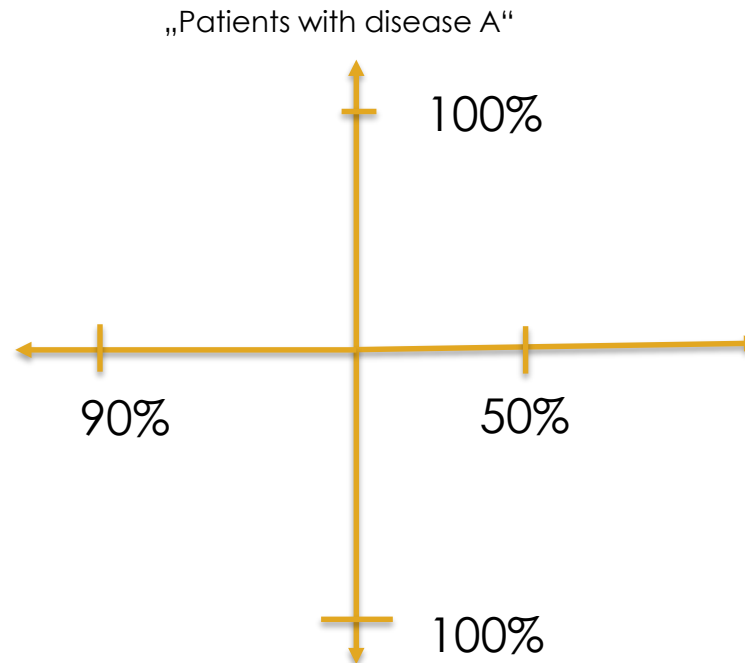
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EEG-SPIDER to assess Estimands

Treatment policy and hypothetical strategy

Country where
rescue medication
is not available

Measurement Y at 6 months or
Predicted Y at 6 months
(-20% expected + 10% for
prediction)



Compliance is taken as is
by estimand, Withdrawal of consent
or loss to follow up leads to missing data

Intervention:

Patient starts being
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Control:

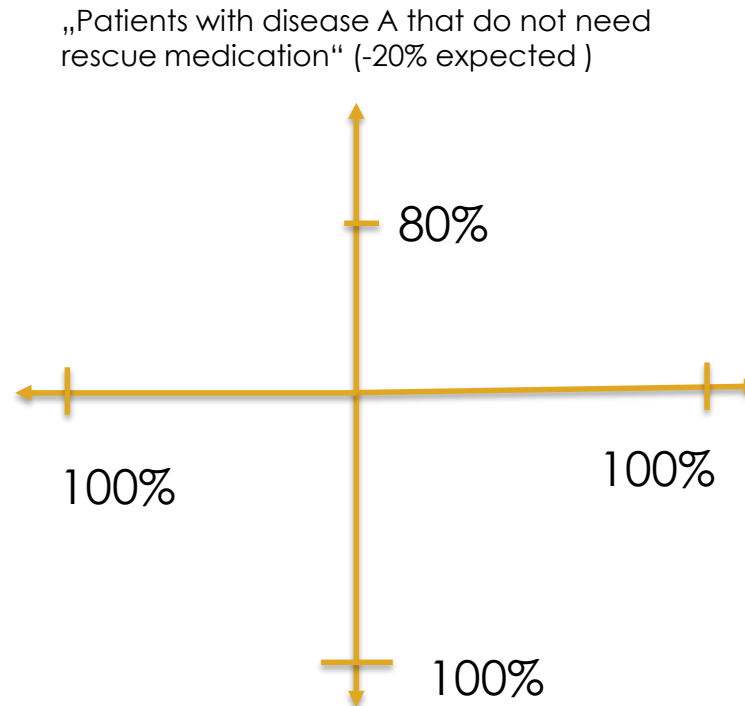
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EEG-SPIDER to assess Estimands

Example – Treatment policy and principle stratum

Country where
rescue medication is
available

Measurement Y
At 6 months



Compliance is taken as is
by estimand, Withdrawal of consent
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Intervention:

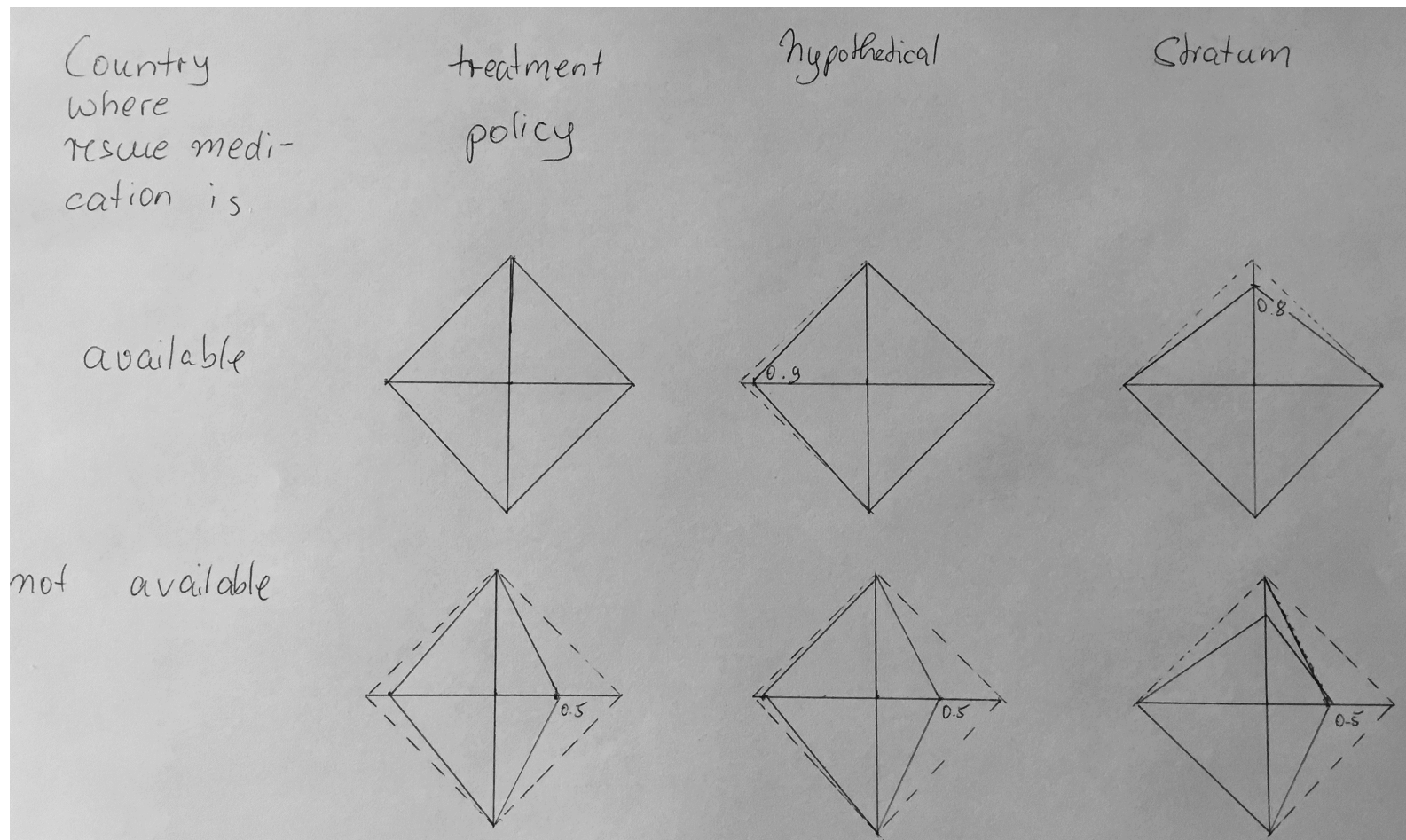
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EEG-SPIDER to assess Estimands

Example – Overview



EEG-Spider for estimand scoring

Conclusions

- It improves transparency
 - There are plentiful of reasons why RCTs may not match the real world setting
 - Spiders can give an overview among ethical choices how to keep the EEG small
- Choices of arms in the spider to be discussed

Conclusions

- Estimands:
 - How to discuss them in multi-disciplinary teams is a challenge for implementation
- HTA-relevant criticism on the ICH E9(R2) addendum (selection)
 - Some estimand strategies are irrelevant (for HTA?)
 - Lack of guidance on how to decide among the five strategies
 - Not (yet) a good guidance for a multidisciplinary approach to decide on the estimand partly because communication is hampered by introducing new and confusing terminology (estimand, intercurrent events)
- What do PICOT and PRECIS have to offer to address these issues
 - PICOT can improve communication about estimands in multidisciplinary teams
 - EEG-Spider can help making choices among estimands