The hypothetical strategy: why, how, when?

Mouna Akacha, Frank Bretz

Joint EFSPI & BBS virtual event:
Addressing intercurrent events - Treatment policy and hypothetical strategies

December 15th, 2022

NOVARTIS | Reimagining Medicine

Disclaimer

The slides reflect our current thinking rather than offering specific solutions or advice at this point. They are meant to facilitate discussions and exchange of experience.

Outline

- Hypothetical strategies and the need for precise definitions
- Examples of hypothetical scenarios
- Conclusions

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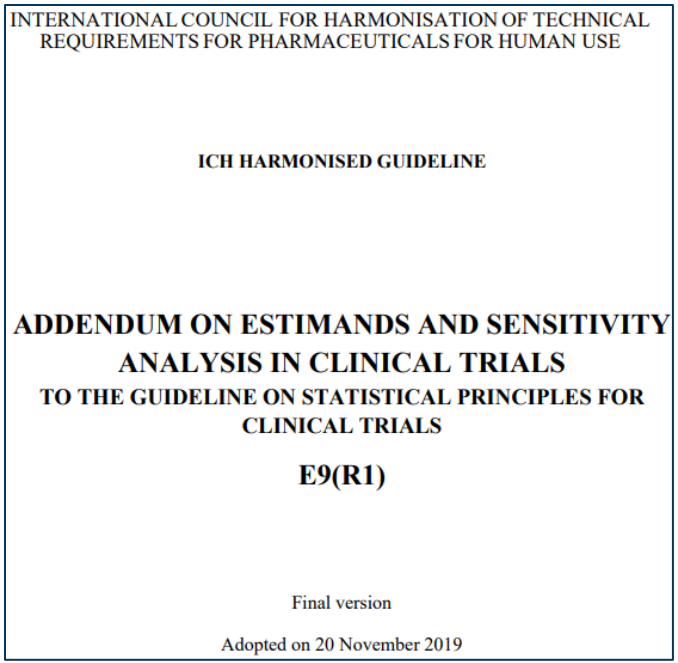
ICH E9(R1)



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

Estimand

A precise description of the treatment effect reflecting the clinical question posed by the trial objective.

ICH E9(R1) highlights the importance of intercurrent events and introduces five strategies to address them

- Hypothetical strategy is one of them

Hypothetical estimands under discussion...


STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2022, VOL. 00, NO. 0, 1–12
https://doi.org/10.1080/19466315.2022.2081599

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Hypothetical Estimands in Clinical Trials: A Unification of Causal Inference and Missing Data Methods

Camila Olarte Parra[a], Rhian M. Daniel[b], and Jonathan W. Bartlett[a]


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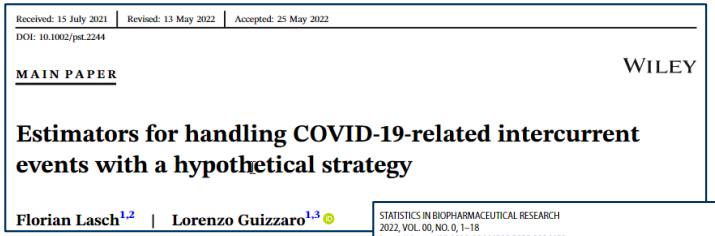
Bayesian Approaches for Handling Hypothetical Estimands in Longitudinal Clinical Trials With Gaussian Outcomes

G. Frank Liu[a], Jiajun Liu[b], Fang Chen[c], Roee Gutman[d], and Kaifeng Lu[e]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DOI: 10.1002/pst.2244

MAIN PAPER

WILEY

Estimators for handling COVID-19-related intercurrent events with a hypothetical strategy

Florian Lasch[1,2] | Lorenzo Guizzaro[1,3]


STATISTICS IN BIOPHARMACEUTICAL RESEARCH
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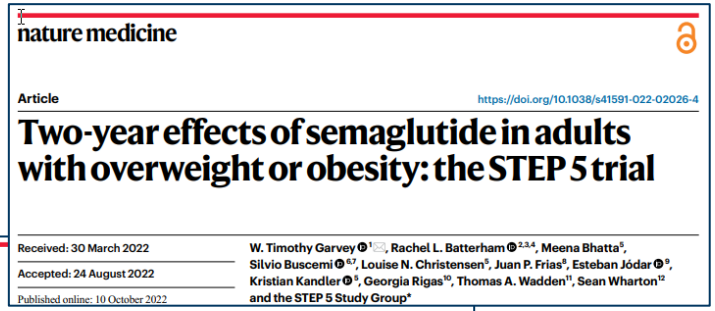
Estimands and their Estimators for Clinical Trials Impacted by the COVID-19 Pandemic: A Report from the NISS Ingram Olkin Forum Series on Unplanned Clinical Trial Disruptions

Kelly Van Lancker[a,b], Sergey Tarima[c], Jonathan Bartlett[d], Madeline Bauer[e], Bharani Bharani-Dharan[f], Frank Bretz[g,h], Nancy Flournoy[i], Hege Michiels[b], Camila Olarte Parra[d], James L. Rosenberger[j], and Suzie Cro[k]


nature medicine

Article

https://doi.org/10.1038/s41591-022-02026-4

Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial

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W. Timothy Garvey[1], Rachel L. Batterham[2,3,4], Meena Bhatta[5], Silvio Buscemi[6,7], Louise N. Christensen[5], Juan P. Frias[8], Esteban Jódar[9], Kristian Kandler[9], Georgia Rigas[10], Thomas A. Wadden[11], Sean Wharton[12] and the STEP 5 Study Group*


News & views

Clinical trials

https://doi.org/10.1038/s41591-022-02032-6

Endpoints and estimands: understanding trials of weight-loss drugs

Amanda I. Adler

Check for updates


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 February 2018
CPMP/EWP/553/95 Rev.2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease


29 January 2018
CPMP/EWP/1080/00 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

Draft

Some regulatory feedback

"…. As COVID-19 will likely be endemic …., we recommend handling any intercurrent events that may be related to operational complications caused by COVID-19 with treatment policy strategy."

*"We **do not agree with** using hypothetical strategy for handling use of [XYZ]. All the observed periods prior to the trial cut-off date should be included in the efficacy analyses regardless of use of [XYZ]."*

Hypothetical strategies – 'What if…'

According to ICH E9(R1):

"*A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.*

A wide variety of hypothetical scenarios can be envisaged, but some scenarios are likely to be of more clinical or regulatory interest than others."

Broad range of hypothetical scenarios can be considered

The hypothetical scenario ‘if additional medication had not been taken’ is not precise enough

- What would the treatment effect be, had additional medication not been made available?
  - May be plausible to ask this question if additional medication was optional
  - Presumably patients would have more severe symptoms if additional medication was withheld
- What would the treatment effect be, had patients not needed additional medication and *behaved* like other patients who did not take additional medication?
  - Not clear what plausible scenario would lead to ‘patients not needing additional medication’
  - Not clear why patients who needed additional medication would behave like patients not needing additional medication
- What would the treatment effect be, had patients not needed additional medication and *behaved* like placebo patients?
  - Not clear what plausible scenario would lead to ‘patients not needing additional medication’
  - Not clear why patients who needed additional medication would behave like placebo patients thereafter

Broad range hypothetical scenarios can be considered

The hypothetical scenario 'if additional medication had not been taken?' is not precise enough

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  -
  - Not clear why patients who needed additional medication would behave like placebo patients thereafter

Importantly, speaking of 'THE hypothetical' leaves too much room for ambiguity → a precise language is required to explain how the hypothetical scenario is realized

Numerous hypothetical estimands can be formulated – some are more useful and clinically plausible than others

Outline

- Hypothetical strategies and the need for precise definitions
- Examples of hypothetical scenarios
- Conclusions

How to ensure the relevance of a hypothetical scenario?

In the following, we use several examples to delineate different hypothetical scenarios

1. Chronic rhinosinusitis with nasal polyps (NP)
2. Rare and progressive renal indication, no approved therapies
3. Treatment switching in a placebo-controlled trial
4. COVID-19 pandemic

Disclaimer: Examples have been simplified for the purpose of this presentation

1. Chronic rhinosinusitis w/ nasal polyps

- Chronic rhinosinusitis with nasal polyps (CRSwNP) affects 2.5% of adults
- Commonly used endpoint is a NP score measuring the level of obstruction (via endoscopy, total score: 0-8)
- NP surgery is an intercurrent event and the question is whether a hypothetical estimand ('if surgery had not been made available') is clinically meaningful
- While surgery is common clinical practice, arguing that a hypothetical estimand is neither of clinical nor of regulatory interest leaves room for ambiguity
- What if the decision to perform surgery is optional, for example:
  - at the discretion of the investigator?
  - comorbidities limit some patients to have the surgery?
  - decision to undergo surgery may be driven by subjective factors, e.g., fear from surgery?
  - out of two patients presenting with exactly the same clinical symptoms, one may to decide to undergo a surgery while the other one won't

1. Chronic rhinosinusitis w/ nasal polyps

Need for surgery may indicate that the drug is ineffective, in which case it should be part of the outcome definition

Use of a composite strategy could then be reasonable (e.g., by assigning surgery the worst NP score). Importantly, it is reasonable for clinical reasons, not because a hypothetical strategy is unreasonable

Note that changing the endpoint needs discussion by entire clinical community, may lead to new clinical standards, etc.

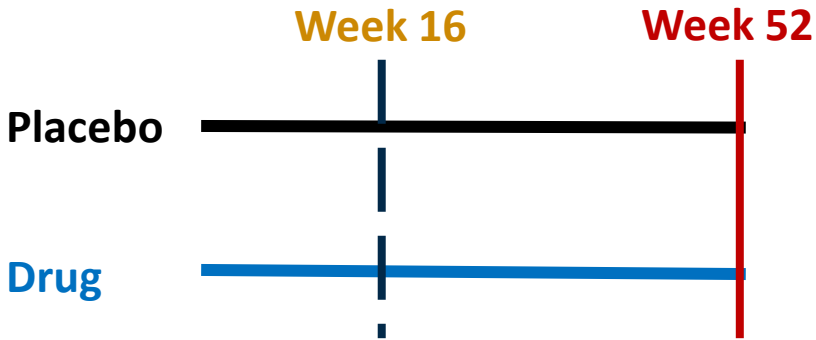
– out of two patients presenting with exactly the same clinical symptoms, one may to decide to undergo a surgery while the other one won't

2. Rare and progressive renal indication, no approved therapies

- Rare renal disease leading to ~50% patients progressing to kidney failure
- Primary endpoint of proteinuria assessed in a placebo-controlled trial
- Due to lack of approved treatments and despite increased infection risk, patients are often treated with immunosuppressants to reduce proteinuria with the hope to improve kidney function
  - In a placebo-controlled setting, immunosuppressants may be prescribed as rescue medication during the trial
  - However, such therapies are not desired as part of a future treatment strategy, if the new treatment is shown to be beneficial
- Conclusion: It seems reasonable to evaluate the treatment effect in a hypothetical scenario where immunosuppressants were not made available

3. Treatment switching in a placebo-controlled trial

- Randomized, double-blind, placebo-controlled Phase III study
- Compare a new drug versus placebo in the treatment of an inflammatory disease
- Clinical measurement of interest: continuous symptom score at week 52



- Patients are allowed to switch to rescue therapy (essentially new drug itself) after week 16 if symptoms are not controlled
- No deterministic rule for switching to rescue
- Many placebo patients are expected to switch to new drug after week 16

3. Treatment switching in a placebo-controlled trial

What is the role of hypothetical estimands in placebo-controlled trials?

- The fact that we are conducting a placebo-controlled trial suggests that we want to tease out the ‘pure treatment effect’ of drug versus placebo
- If administration of placebo is questionable for ethical reasons, patients have to be offered the possibility to switch to an alternative treatment option or use rescue

In such settings, it is conceivable that a hypothetical estimand is of regulatory interest

If a ‘pure treatment effect’ is not of interest, then the design seems to be inappropriate → if real clinical practice was of interest, wouldn't we consider running more pragmatic trials and limit the use of placebo-controlled trials?

4. COVID-19 pandemic

- Pandemic led to various intercurrent events during the conduct of clinical trials
- Example: Treatment discontinuation due to drug supply issues during lockdown
- Treatment policy strategy: Intercurrent event as part of the 'treatment'
  - No adaptation of the original estimand implicitly suggests a treatment policy approach
  - Treatment effect is of interest regardless of lockdown
- Hypothetical strategy: Treatment effect in a post-pandemic patient population (i.e., society and the healthcare system have adapted to COVID-19), where
  - individuals can suffer from COVID-19 infections (treatment policy strategy),
  - but in the absence of administrative and operational challenges (hypothetical strategy)

Regulatory feedback on one study: "…. As COVID-19 will likely be endemic …., we recommend handling any intercurrent events that may be related to operational complications caused by COVID-19 with treatment policy strategy."

4. COVID-19 pandemic

- Pandemic led to various intercurrent events during the conduct of clinical trials
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It is reasonable to assume that

- Operational challenges caused by the pandemic do not depend on the randomized treatment or the health status of patients
- COVID-19 still exists in a post-pandemic world, but in the absence of administrative challenges caused through the pandemic

Hence, it could be of interest to ask: “What would have been the outcome of interest had the patients not discontinued treatment due to drug supply issues?”

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complications caused by COVID-19 with treatment policy strategy?

Credit to Melanie Wright

Summary of examples

Intercurrent event (IE)...	Example	Strategy
... is outcome-related (possibly even being an efficacy endpoint in its own right)	Surgery in nasal polyp indication	Composite strategy: Assign worst outcome on an existing ordinal scale
... is a medication or procedure which is necessary to offer for ethical reasons, but is not desired as part of a future treatment strategy	Off-label rescue medication in rare renal disease	Hypothetical strategy: A scenario is envisaged to assess the pure treatment effect of the new drug
	Treatment switch if symptoms are not controlled	
... due to administrative or operational challenges that are not expected to occur in future	Complicating events during COVID-19 pandemic	Hypothetical strategy: A scenario in the absence of lockdowns is envisaged

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Relevance of hypothetical scenarios

- ICH E9(R1) acknowledges that "*some scenarios are likely to be of more clinical or regulatory interest than others*"
- While it does not provide guidance on assessing the relevance of hypothetical scenarios, it suggests a two-step approach:
  - Hypothetical scenarios that cannot possibly occur in future clinical practice are likely irrelevant and should be avoided for a primary estimand in a confirmatory trial
    - For example, it may not be reasonable to hypothesize a scenario where patients fully adhere to their treatment notwithstanding serious adverse events
  - Otherwise, a hypothetical strategy might be of interest, but...
    - clinical plausibility remains to be justified in each case
    - statistically valid and robust analysis approaches must be ensured

Conclusions

We argue that

- the class of hypothetical estimands is very broad and a precise definition is crucial to enable a fruitful discussion with different stakeholders
- arguments in favor of/against hypothetical estimands are often subtle and a thorough justification is needed when engaging with different stakeholders
- it is a joint discission between clinical and statistics

Recommendations

- Early discussions with the agencies regarding the most appropriate estimand for the situation at hand
- Ensure that an analysis approach is in place that aligns with the estimand (i.e., the hypothetical scenario being envisaged)
  - Importantly, this includes sensitivity analyses to evaluate the robustness of the conclusions

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Thank you

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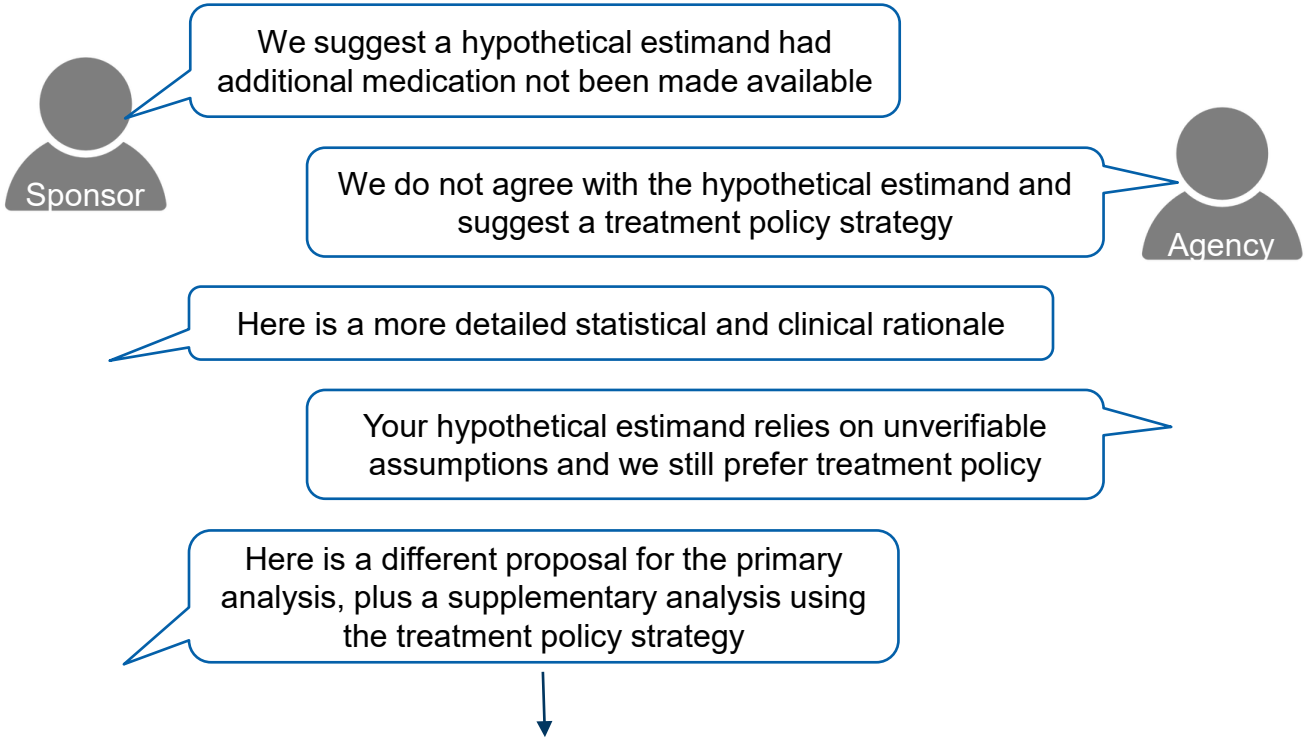
Kidney transplant in dialysis patients

- Chronic kidney disease where patients need dialysis
- Consider a two-year study to either compare two types of dialysis on morbidity and mortality or investigate the effect of a drug intended to reduce the frequency or number of dialysis sessions
- A minority of patients will be eligible for a renal transplantation during this period
  - this is neither due to treatment toxicity nor a trial endpoint
  - it would not be possible to anticipate in advance who will get a transplant and when a donor kidney will be available
- Hence a transplant can be considered a randomly occurring intercurrent event and the patient would be withdrawn from the study
- It could well be of interest to ask the question of what would have been the outcome of interest in the arms had the patients not been withdrawn for transplant

Clinical input is essential



- Fictional dialogue based on a real study

- No discussion about clinical relevance of proposed estimand, discussion was entirely driven by the analysis
- Whether a hypothetical estimand is clinically relevant, or not, requires clinical input
  - Statistical methods should be discussed after agreeing on a clinically relevant estimand