Target Trial Emulation meets clinical trial design two case studies

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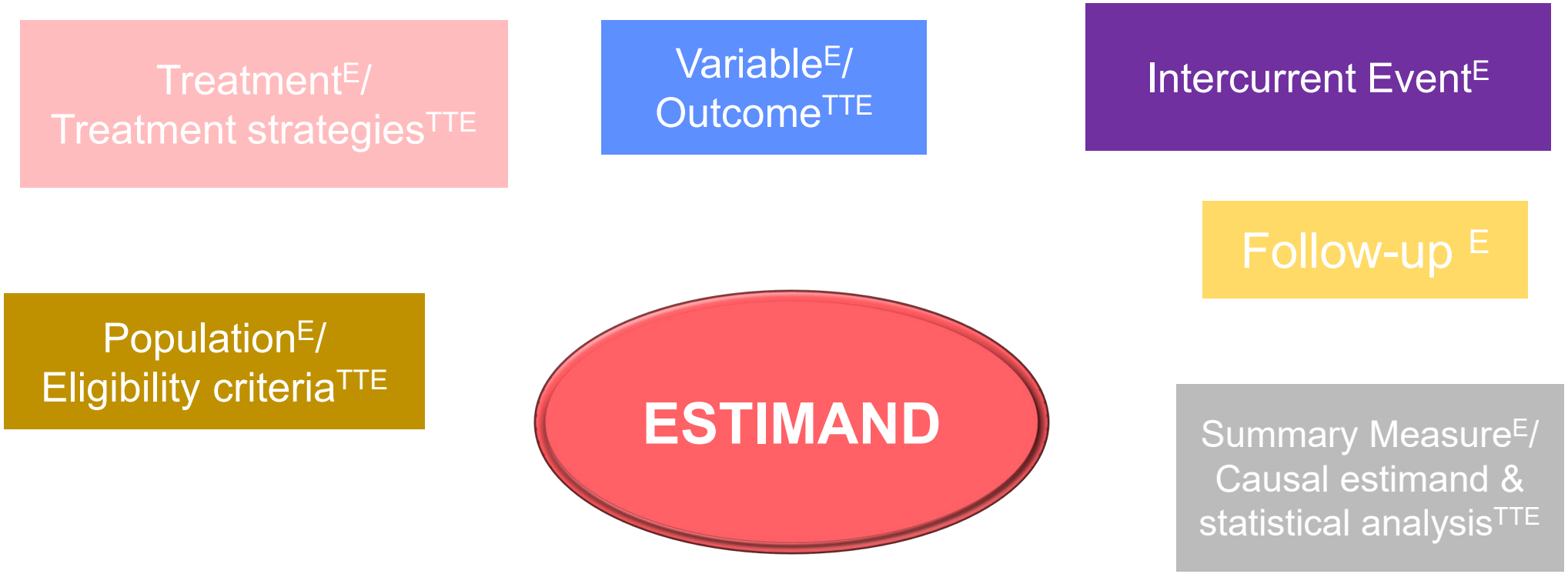
Comparisons from an RCT vs. non-randomized comparisons

When shall we design a new randomized controlled trial to answer a clinical question of interest?

How can we increase the rigor and the regulatory acceptability of non-randomized (comparative) studies?

Target trial emulation and target causal estimand

Target trial emulation: Process of designing an imaginary ***simple*** randomized trial (target trial) that would answer the comparative objective of interest, and emulating this trial with existing data



E: Estimand Framework (ICH E9 (R1))
TTE: Target Trial Emulation (Hernan and Robins 2016)
Combining E & TTE (Hampson et al 2024)

Case Study 1: Leveraging an external control to a single arm study

Acknowledging contribution of Jilles Fermont, and Soudeh Ansari from Novartis

Paroxysmal Nocturnal Hemoglobinuria (PNH), iptacopan's development program

1. APPLY-PNH (pivotal Ph3)-NCT04558918

- What is the effect of iptacopan on hematological response in adult PNH patients **on anti-C5**?
- Double-blinded randomized, active control trial (iptacopan vs. anti-C5)

2. APPOINT-PNH (pivotal Ph3) -NCT04820530

- What is the effect of iptacopan on hematological response in adult PNH patients **naive to anti-C5 treatment**?
- Single arm trial

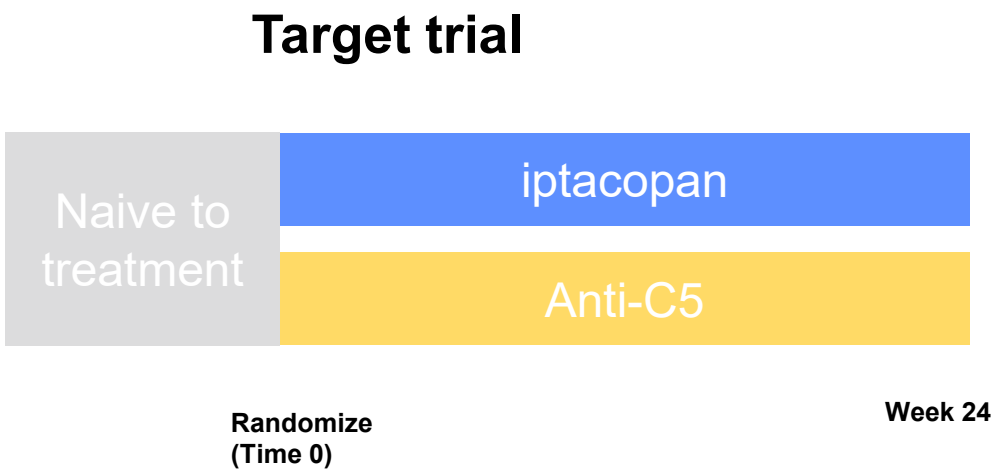
3. APPEX – NCT05842486

- What would have happened to APPOINT-PNH patients had they received anti-C5 instead of iptacopan?
- PNH longitudinal "registry" from extracted medical chart review

Source: Peffault de Latour R. et al (2024), Holt M et al (2025)

Attributes of the target trial in APPEX

Attributes	Target trial
Population	Patients with PNH naive to anti-C5, and with hemoglobin level < 10g/dL
Treatment	Iptacopan versus Anti-C5 therapy
Outcome(s) Intercurrent event	Hemoglobin Transfusion
Follow-up for outcomes (start/end)	Start of treatment until the end of study (24 weeks)



Modified from Supplementary Table S1 in Holt et al 2025

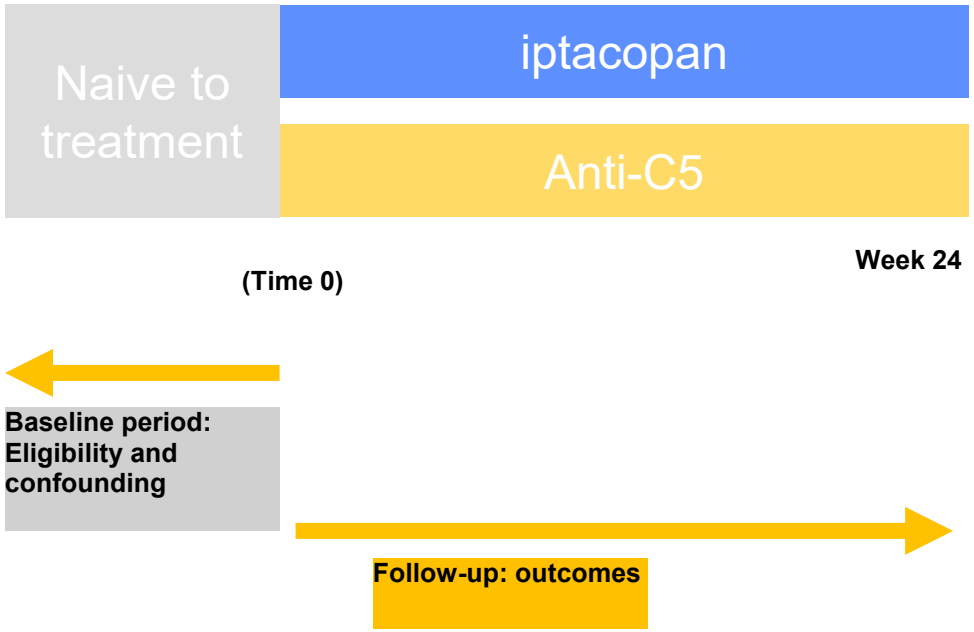
Emulation of the target trial in APPEX

Attributes	Target trial	Emulation in APPOINT (N=40)	Emulation in APPEX (N=85)
Population	Patients with PNH, naive to anti-C5, and with hemoglobin level < 10g/dL	More selection criteria than target trial **[Sites primarily in Asia 2021-2022]**	Same selection criteria as target trial & Age > 18 yrs **[France, UK, 2007-2022]**
Treatment	Iptacopan versus Anti-C5 therapy	Iptacopan	Anti-C5 therapy (eculizumab or ravulizumab)
Outcome(s) Intercurrent event	Hemoglobin Transfusion	Hemoglobin Transfusion	Hemoglobin Transfusion
Follow-up for outcomes (start/end)	Start of treatment until the end of study (24 weeks)	**Time-0: initiate iptacopan** **Visit schedule: weeks (1,2, 4, 6, 8, 12, 16, 18, 20, 22, 24)**	**Time-0: initiate anti-C5 therapy** **Visit schedule: as-needed, expected every few weeks at anti-C5 injection**

Modified from Supplementary Table S1 in Holt M et al 2025

Iptacopan development program, added value of TTE

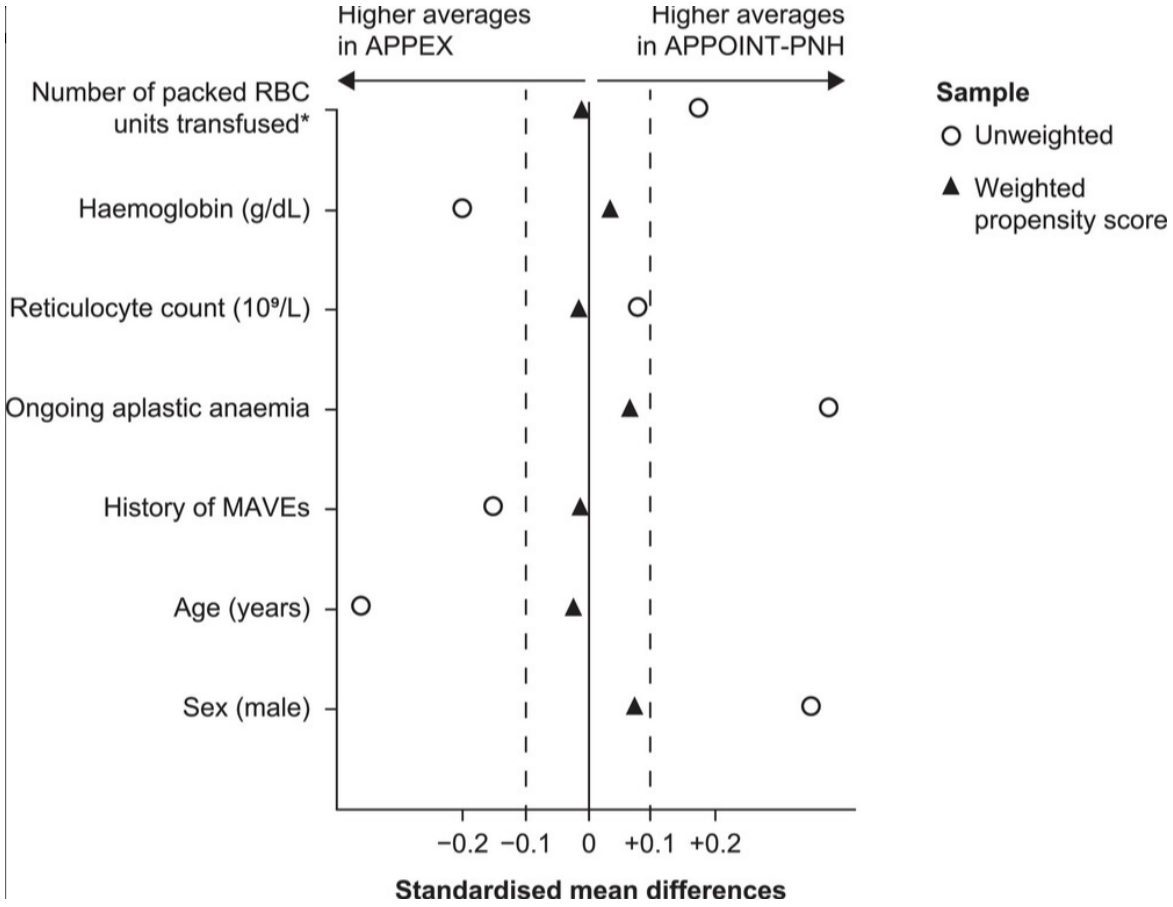
Target trial

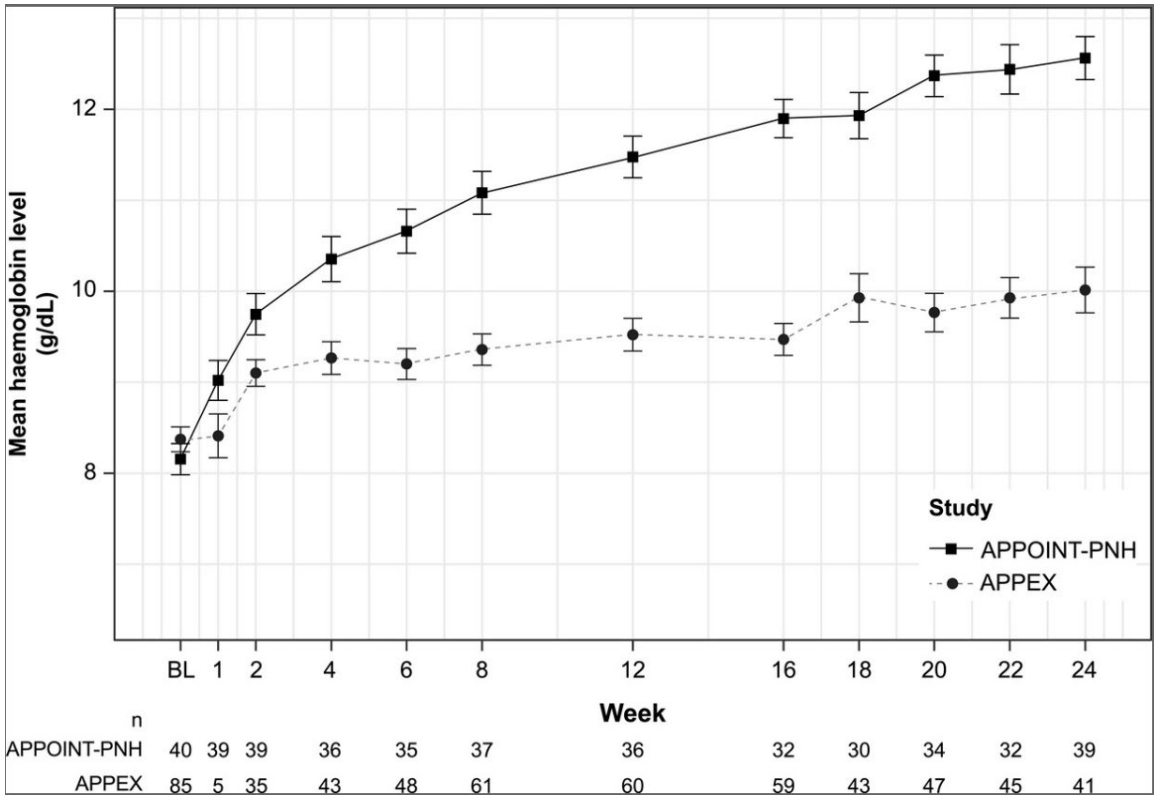


TTE as bias identification and mitigation strategy in APPEX

Sources of bias	Mitigation
Selection of patients	- Clear time-0
Confounding	- Filter registry data based on inclusion/exclusion in baseline period - Identify potential confounding at baseline & use propensity score weighting to increase APPEX similarity to APPOINT-PNH
Outcome assessment schedule	Conduct sensitivity analyses to different definitions of visit-windows, and different confounding

APPEX – some results





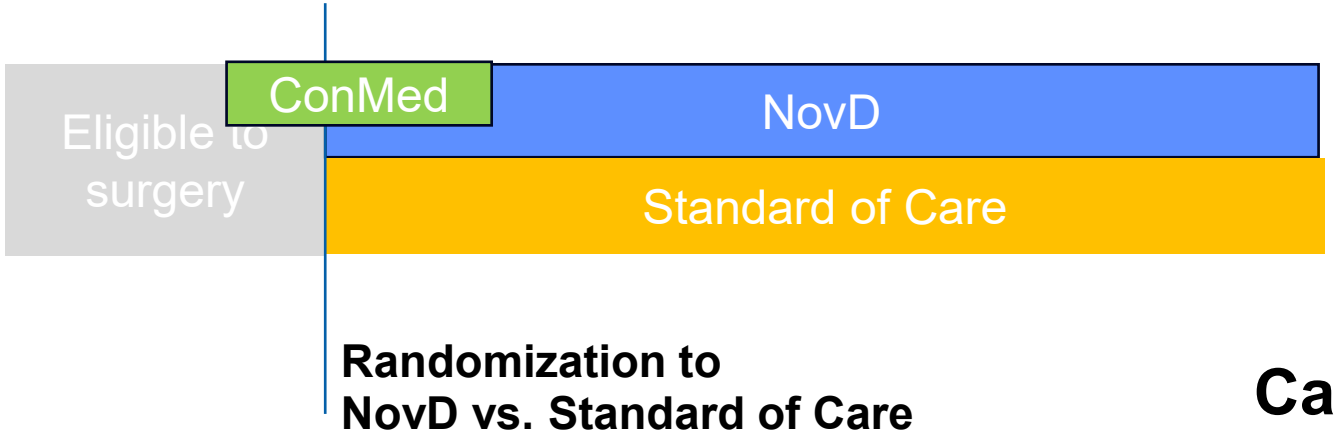
Source: Holt et al (2025)

Case study 2: Secondary use of clinical trial data to answer a new question

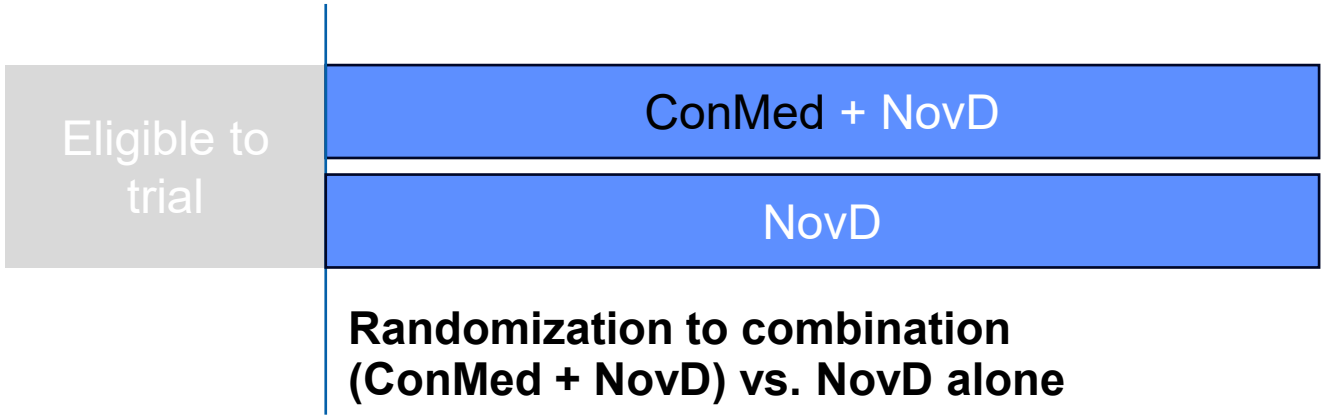
a hypothetical case

Case study 2: secondary use of clinical trial data to answer new questions

Observed randomized clinical trial



Can we emulate this target trial?



Target trial nested in the NovD arm of the RCT

Attributes	Target trial	Emulation in NovD RCT arm
Population	Patients eligible to receive NovD and ConMed	Subset of the NovD arm of the RCT that is eligible to receive ConMed
Treatments	NovD alone NovD + ConMed treatment strategy	NovD alone NovD + ConMed treatment strategy
Outcome(s) Intercurrent event	Survival Treatment discontinuation	Survival Treatment discontinuation
Follow-up for outcomes (start/end)	Start of treatment strategy until 12 months	Multiple possible estimands - Anchor time-0 at eligibility to surgery or start of therapy

Questions of interest

When shall we design a new randomized controlled trial to answer a clinical question of interest?

→ **(Rima)'s answer:** when the knowledge gap is high and all existing data is unreliable or irrelevant

How can we increase the feasibility, rigor, and trust in findings from non-randomized (comparative) studies?

→ **(Rima)'s answer:** pre-specify your estimand, use target trial emulation (to evaluate fitness-for-purpose and identify potential sources of bias), be transparent on limitations, and be pro-active on addressing sources of bias.

(e.g., Seewald et al (2024) & Hernan et al 2025 (Annals of internal medicine), Dib et al (2025) (JAMA Annals of internal medicine)

References

Hernan, M. A. & Robins, J. M., 2016. Using big data to emulate a target trial when a randomized trial is not available. *American journal of epidemiology,* 183(8), pp. 758-764.

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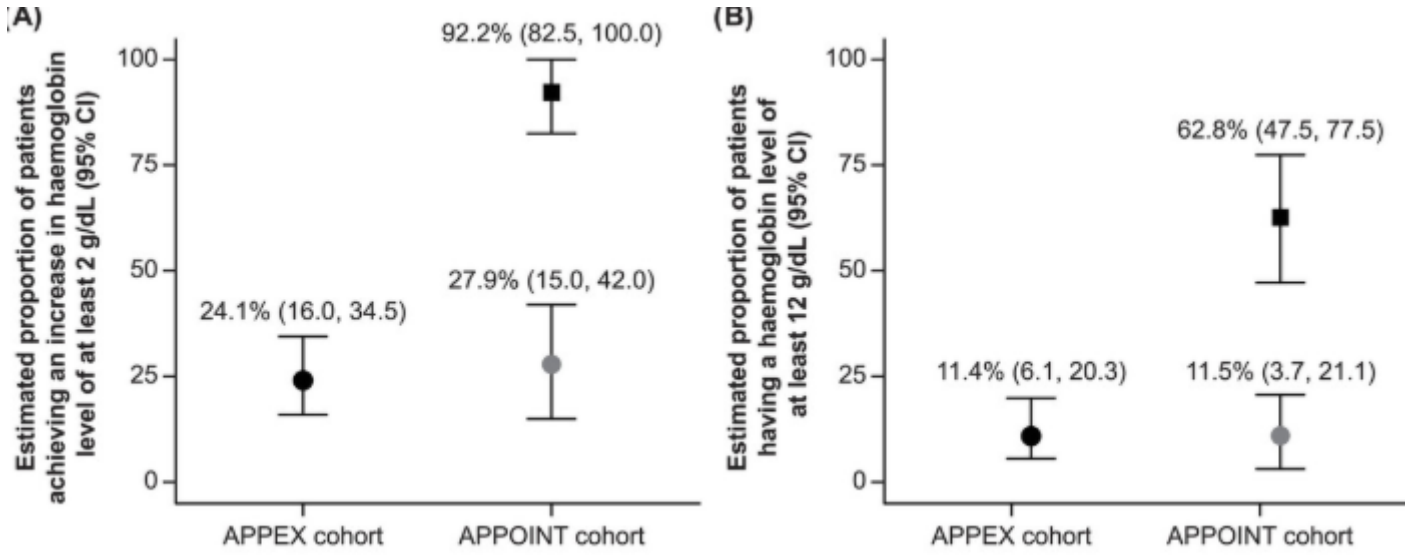
Back-up



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