Evaluating the impact of treatment discontinuation on the outcome of clinical trials for weight management: A simulation study

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Introduction

Obesity and treatment

Obesity is a major global health challenge with an expected **prevalence** of **20% by 2030**. Numerous weight management trials investigate treatments like **incretin analogues**. (**1**)

Estimands of treatment effect

Different estimands to assess trial endpoints are frequently used: The **hypothetical estimand** (treatment per protocol) and the **treatment policy estimand** (intention-to-treat principle). (**2**)

Prediction of treatment policy estimand in clinical trials simulations

Significant proportions of **treatment discontinuation** are observed in **phase 3** weight management trials (**3,4**). An impact on treatment policy estimands is expected, but its characterization is lacking. To **predict the outcome of new trials**, a **robust framework** for characterizing, understanding and integrating the effect of treatment discontinuation in **clinical trial simulations** is warranted.

Aims

- Develop a **simulation framework** to describe **treatment discontinuation** using time-to-event modelling
- Incorporate the framework in **clinical trial simulations** to characterise impact of discontinuation on **treatment policy estimand**

Methods

Hypothetical time-to-event model for treatment discontinuation

- Weibull hazard function was assumed and parameter values were chosen to match typical proportion of treatment discontinuation (**3**,**4**):

$$\lambda = \lambda_0 \times \gamma \times t^{(\gamma-1)} \text{ with } \lambda_0 = 1.207 \times 10^{-3}\ d^{-1}, \gamma = 0.800$$

Simulating population of STEP 1 trial

- Multinormal distribution of baseline covariates (**3**) without covariate correlations
- 1000 patients were simulated with covariates for PK and weight loss model (age, sex, ethnicity, race, weight, eGFR, HbA1c)
- 500 replicates were simulated to account for variability

Simulating discontinuation

- Different scenarios of discontinuation were simulated for a treatment period of 68 weeks:
  - No discontinuation
  - Reference discontinuation (λ_0)
  - Moderate increase (25% increased λ_0)
  - Strong increase (50% increased λ_0)

Simulating PK

- Published semaglutide PK model (**5**)
  - 1-compartment model
  - Dosing was stopped after treatment was discontinued
- Individual PK was simulated:
  - Individual weekly C_{avg} was calculated for each replicate and scenario

Simulating weight loss and treatment policy estimand

- Published semaglutide weight loss model (**5**)
  - Indirect response model with slow ($E_{max,S}$) and immediate ($E_{max,I}$) treatment effect
  - Mean weight loss [%] was simulated and treatment policy estimand obtained as median [95% PI]
- Treatment policy estimand was simulated at end of treatment period for hypothetical treatment arms:
  - Placebo
  - Treatment A: Reference efficacy
  - Treatment B: 25% increase in $E_{max,S}$

Results

Simulating treatment discontinuation

Figure 1: Treatment discontinuation [95% PI] over time for each scenario.

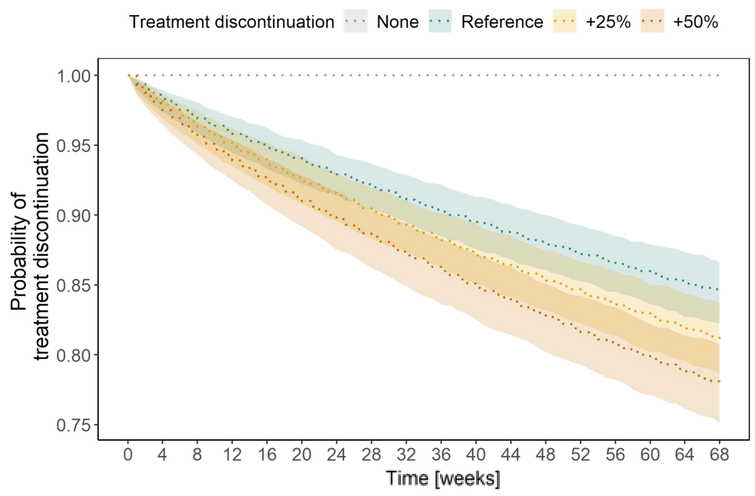

Table 1: Treatment discontinuation at end of treatment period for each scenario.

Scenario	Discontinuation [95% PI]
No discontinuation	0%
Reference	15.5% [13.3-17.8]
Moderate increase	18.9% [16.3-21.4]
Strong increase	22.1% [19.2-24.9]

Simulating weight loss and treatment policy estimand

Figure 2: Mean weight loss [95% PI] from baseline over time simulated for each scenario with treatment A.

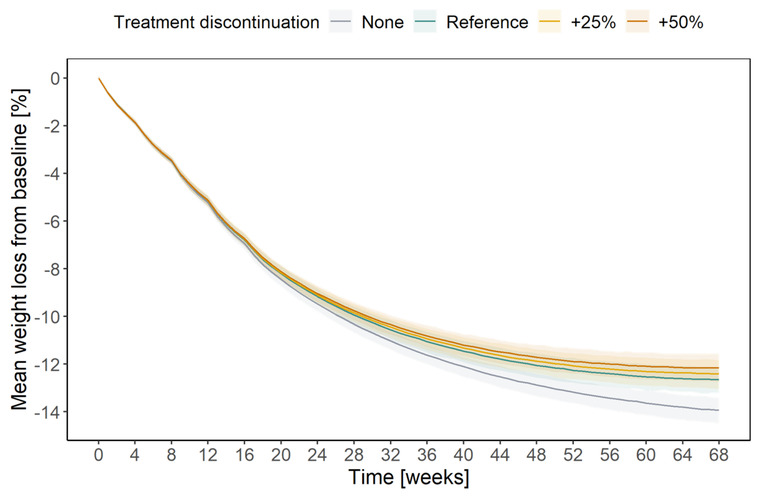

Figure 3: Treatment policy estimands [95% PI] for each scenario and treatment arm.

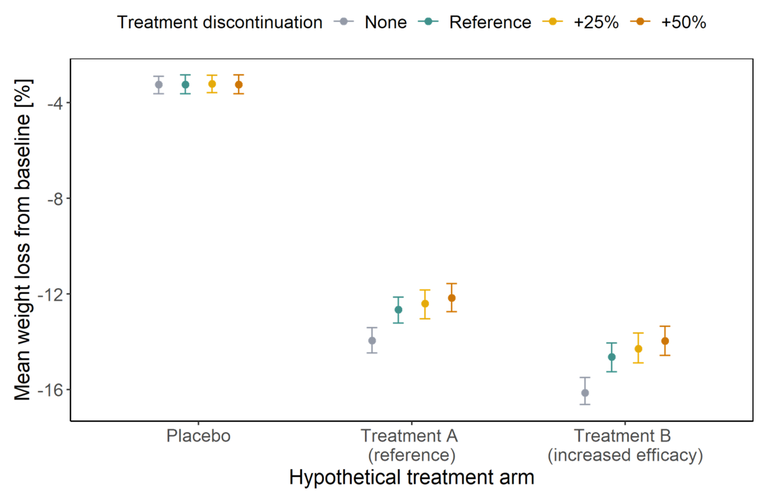

Table 2: Median treatment policy estimands [95% PI] and difference compared to full adherence for each scenario and treatment arm.

Scenario	Treatment A [95% PI]	Δ vs no discontinuation	Treatment B [95% PI]	Δ vs no discontinuation
No discontinuation	-13.9% [13.4-14.5]	-	-16.1% [15.5-16.6]	-
Reference	-12.7% [12.1-13.2]	+1.2% points	-14.6% [14.1-15.3]	+1.5% points
Moderate increase	-12.4% [11.8-13.0]	+1.5% points	-14.3% [13.6-14.9]	+1.8% points
Strong increase	-12.2% [11.6-12.7]	+1.7% points	-14.0% [13.4-14.6]	+2.1% points

Discussion

- A **time-to-event framework** was successfully developed to describe treatment discontinuation (Fig. 1, Tab. 1)
- Treatment discontinuation **reduced treatment policy estimands** (Fig. 2, 3 and Tab. 2)
- Further increasing treatment discontinuation from reference scenario had a limited effect on treatment policy estimands (Fig. 2, 3, Tab. 2)
- Treatment policy estimands of **compounds with higher efficacy** were **stronger affected** (Tab. 2)
- **Evaluation using clinical data** to extend time-to-event framework with **covariate effects**
- Integrating **impact of treatment efficacy and toxicity** on treatment discontinuation could give insights into **underlying reasons**
- **Dose reductions** need to be considered for **comprehensive prediction** of treatment policy estimands for flexible trial protocols

Conclusion

Incorporation of treatment discontinuation in clinical trial simulations may improve **prediction of treatment policy estimands** in weight management trials

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References: (**1**) World Obesity Federation. World Obesity Atlas 2022 [https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022, accessed 05 March 2025]; (**2**) Akacha et al. CPT Pharmacometrics Syst. Pharmacol. 2021;10:279-282; (**3**) Wilding et al. N. Engl. J. Med. 2021;384:989–1002; (**4**) Davies et al. Lancet. 2021;397:971-984 (**5**) Strathe et al. Diabetes. Obes. Metab. 2023;25:3171–3180