The Prevalence and Impact of Multiple Hypothesis Testing Corrections in Clinical Trials

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Intro

Medical regulators in major healthcare markets deem multiple hypothesis testing (MHT) corrections necessary when multiple outcomes are involved

- E.g., European Medicines Agency, UK Medicines and Healthcare Products Regulatory Agency
- In particular, the U.S. Food and Drug Administration deems family-wise error rate (FWER) corrections for all trials with multiple primary outcomes (FDA 2022, draft guidance in 2017)
- **Idea:** Either a trial needs stat. sig. results for all primary outcomes to be successful, or each primary outcome is a 'separate chance' at stat. sig. results

However, systemic evidence that academic clinical trials don't comply with these guidelines

- **Synthesis of 13 published systematic reviews on 3122 published clinical trials:** 1317 engage in MHT, only 16% apply corrections (Menyhárt & Győrffy 2025, *IJE*)

Two questions:

1. Do we observe the same non-compliance across regulated, non-academic trials?
2. If so, how much does this affect clinical trial conclusions?

This Project

I leverage aggregated data on 9653 clinical trials registered on ClinicalTrials.gov with multiple primary outcomes (MPOs) to assess the prevalence and impact of MHT corrections

- I use a systematic large language model (LLM) classification approach that determines whether *p*-values are adjusted based on *p*-value descriptions and statistical analysis plans (SAPs)

In 2025, over 56% of MPO trials, and over 35% of Phase 3+ MPO trials, didn't apply *any* MHT corrections

- These non-compliance rates were even higher in previous years

Applying FWER corrections to *p*-values of MPO trials that didn't adjust for MHT erases *all* statistically significant results in 11-15% of MPO trials, and in 9-12% of Phase 3+ MPO trials

- I highlight improvements in clinical trial reporting infrastructure to address these problems

Data

I use the Aggregate Analysis of ClinicalTrials.gov (AACT) database (CTTI 2026)

- Stores trial information, (primary) outcomes, SAP URLs, and submitted results (including *p*-values and their descriptions)

Two places where one can determine whether analytical strategies are adjusted for MHT are (1) *p*-value descriptions and (2) SAPs

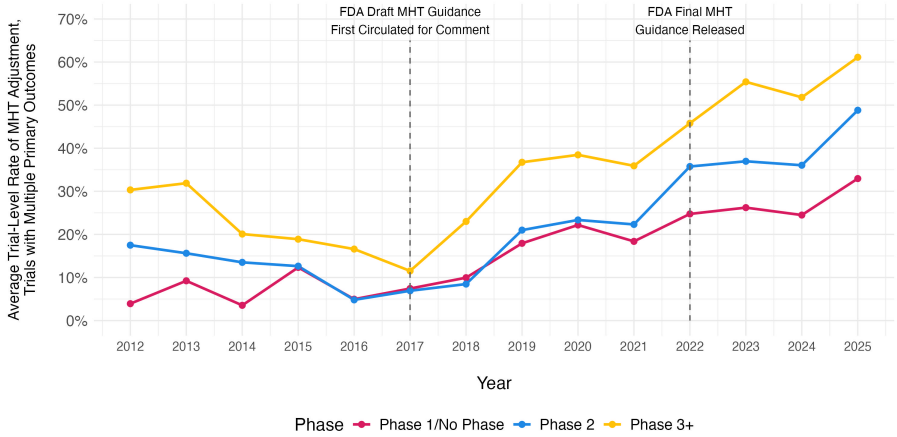
- **Challenge:** There are 9653 MPO trials in the ClinicalTrials.gov database with valid *p*-values, SAPs are typically dozens of pages long, and SAPs necessarily interact with *p*-value descriptions

LLM Classification

I use a systematic LLM classification method, passing *p*-value description text and SAP PDFs to OpenAI 6.2 Luna. To paraphrase prompts:

- ***p*-value description + SAP (27% of trials):** 'Given the SAP and this *p*-value's description, does an explicit indication make it more likely than not that this *p*-value is MHT/FWER-adjusted?'
- ***p*-value description + no SAP (30% of trials):** 'Does an explicit indication in this *p*-value description make it more likely than not that this p-value MHT/FWER-adjusted?'
- **No *p*-value description + SAP (22% of trials):** 'Does an explicit indication in the SAP make it more likely than not that a *p*-value with no description is MHT/FWER-adjusted?'
- **No *p*-value description + no SAP (21% of trials):** Automatically coded as not MHT-adjusting

Prevalence of MHT Adjustment



73% (64%) of all (Phase 3+) MPO trials do not adjust any results for MHT

What Is The Impact of FWER Adjustment?

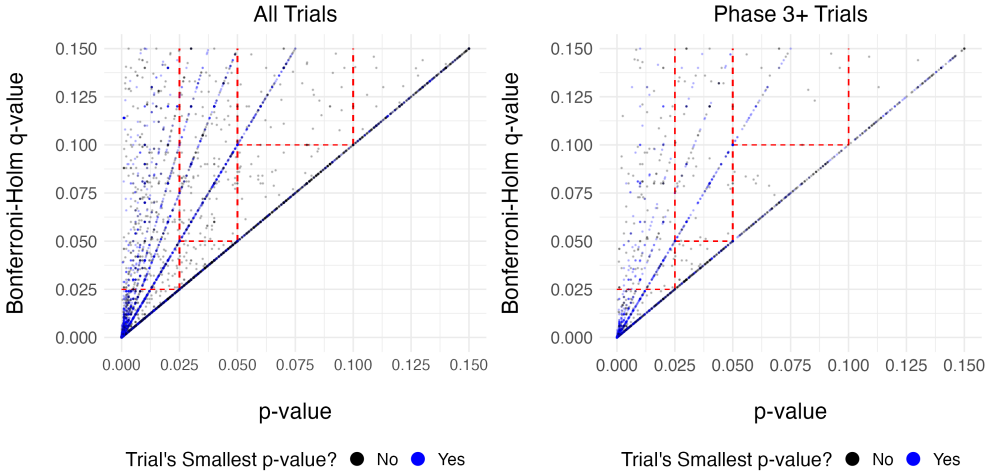
The AACT data has reported p-values for each trial arm's effect on each outcome

- For trials that don't MHT-adjust, I use Bonferroni-Holm adjustment (Holm 1979, *SJS*) to convert the family of raw, primary-outcome p-values to FWER-adjusted q-values

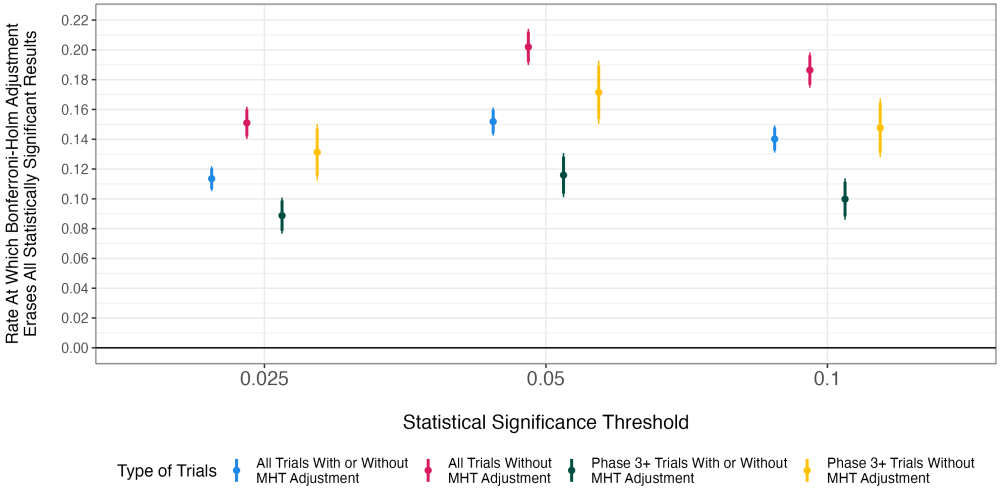
Reliable computation of Bonferroni-Holm q-values requires that I'm looking at the study's original p-values, so...

- I exclude 4095/9653 trials that threshold-report some p-values
- I do not adjust p-values for any trial that does *some* MHT adjustment for any p-value, FWER or not (minor point; 92% of trials that MHT adjust are FWER adjusting)

Visualizing Bonferroni-Holm Correction



Main Results



Implications

In Bonferroni-Holm correction, the q-value of the largest p-value is just the original p-value

- So by definition, a trial where all statistically significant results are erased by Bonferroni-Holm correction has at least one p-value above the significance threshold
- These trials are *relying on their smallest p-values* to have any statistically significant results at all
- ... but those results aren't precise enough to rule out that they arise simply due to MHT

Conclusion

This research has extremely actionable implications for medical regulators

- The FDA (2022) already has official guidelines deeming FWER adjustment necessary for all trials with multiple primary outcomes
- ... but the FDA (2022) guidelines are currently non-binding

When considering Phase 3+ trials for treatment approval, the FDA should either:

1. Require that researchers implement FWER adjustments before the trials are eligible for treatment approvals (i.e., make the guidelines binding)
2. Require that researchers report raw p-values and automatically do FWER adjustment on researchers' behalves

The FDA has considerable discretion to deem trial evidence insufficient to warrant approval (Janiaud et al. 2021, *AIM*)

- They should use this discretion to make sure that we have **precise evidence that treatments work before they're approved for public use**

Thank You For Your Attention!

These Slides

I am on the job market this year!

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