Addressing RWE Challenges in Real-Time: The 'Clean Room Committee' Approach

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OP19

Background

- Best practices for Real-world evidence (RWE) intended for regulatory decision-making are still being established
- Examining data can lead to discovery of unexpected challenges with the data that would lead to invalid estimates
- Adequately addressing these challenges can lead to deviations from pre-specified statistical analysis plan (SAP)
- Investigators can formally amend the SAP, but if the team analyzing the data and the team making decisions about amendments overlap, they know how their amendments may affect subsequent analyses, opening up the possibility of investigator bias
- Need to adapt study in a timely manner while guarding against investigator bias

Clean Room Committee approach

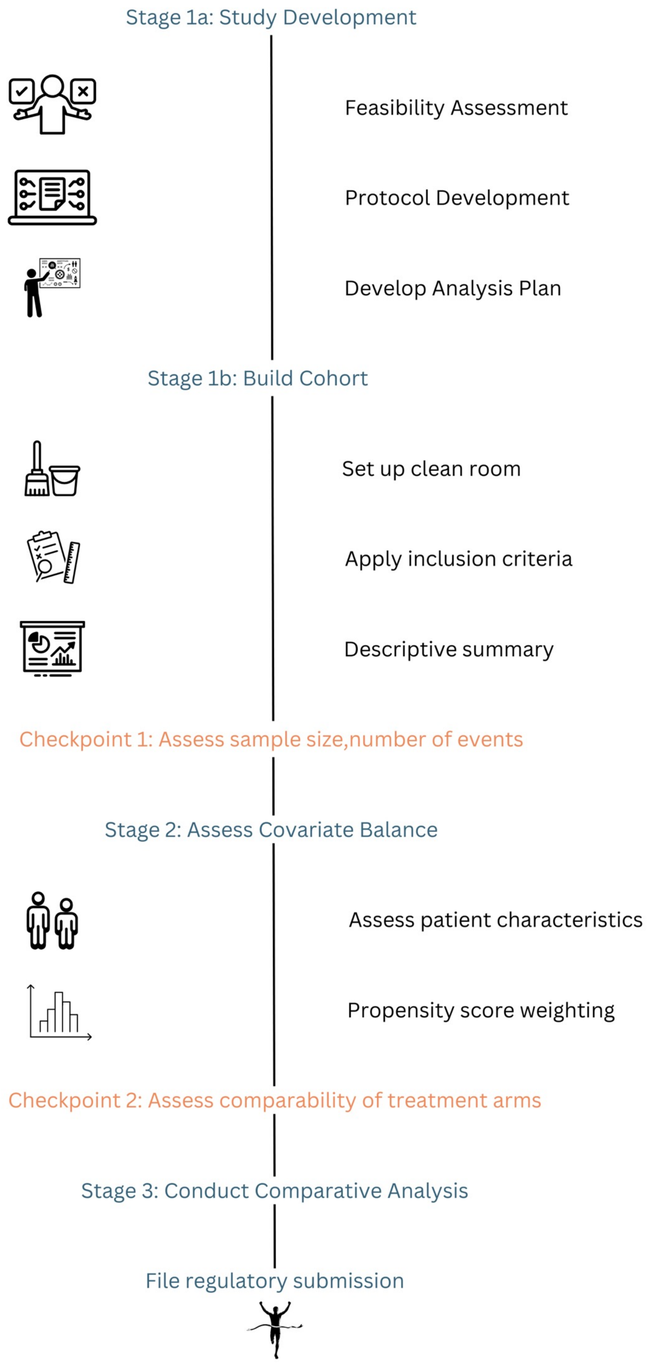
- Analytic team has unblinded access to the data to implement the SAP
- The Clean Room Committee (CRC) is a team of statisticians, epidemiologists, and clinicians distinct from the analytic team
- The CRC does not have access to the data and can only view blinded summary data provided by the analytic team
- At pre-defined stages, the CRC reviews the summary data to determine if the study can proceed to the next stage
- If the summary data highlight challenges that need to be addressed, the CRC will document the desired revisions to the SAP
- Crucially, the CRC does not know how their decisions will affect subsequent analysis, so they cannot introduce investigator bias with their decisions
- All CRC decisions are documented in the study log, which provides an audit trail for all amendments.

Case Study: Safety of Preoperative Cefazolin

Study Rationale

- Cefazolin is administered before surgery to prevent surgical site infections
- Evidence in literature that approved dose (2g) is inadequate for overweight patients (≥ 120 kg)
- Current surgical guidelines recommend 3g of cefazolin for adults weighing ≥ 120 kg.
- Study to support a singe-dose label expansion from 2g to 3g preoperatively for adults weighing ≥ 120 kg to be be consistent with guidelines

Staging for Cefazolin Safety Study



For more detail see Muntner et al. (2004) *Staging and clean room: Constructs designed to facilitate transparency and reduce bias in comparative analyses of real-world data*

Study Design

Design: Real-world retrospective observational study

Data source: Electronic health records from 95 U.S. hospitals

Treatments: Cefazolin administered by IV (2g vs. 3g) prior to surgery

Inclusion: Age ≥ 18 years, Weight between 120 and 300 kg

Patients: 2g cefazolin (N = 1579); 3g cefazolin (N = 2090)

Outcomes: Primary and exploratory safety endpoints within 12 hours of dose administration

Planned Statistical Analysis: Propensity score weighted contrasts of risk difference for safety endpoints between treatment groups (pre-specified subgroup and sensitivity analyses)

Clean Room Committee

- The CRC consisted of three investigators with extensive pharmacoepidemiology experience
- At Checkpoint 1, the CRC reviewed blinded summary statistics provided by the analytic team and noted two challenges for the planned analyses.
- For the primary safety endpoints (neurotoxicity and superficial phlebitis), the events were too rare (6 and 1, respectively) to conduct the planned IPW adjusted estimation of risk differences.
  - CRC restricted analysis to descriptive counts, percentages, patient-level safety data, and patient narratives—no risk contrasts were estimated
  - CRC dropped the planned subgroup analyses
- For the exploratory endpoints, there were enough events to proceed with comparative analyses, but there was a substantial amount of missing data for the lab values that were to be included in the propensity score models
  - CRC provided detailed recommendations on the implementation of multiple imputation to address this missing data
  - Some of the lab values had levels of missing data too high for multiple imputation, so the analyses that would have made use of those labs were dropped
- At Checkpoint 2, the CRC found adequate balance between treatment arms, so the analytic team proceeded with comparative analyses for the exploratory endpoints nephrotoxicity and thrombocytopenia.
- Propensity score weighted risk differences show no evidence of increased risk of the exploratory endpoints for patients given 3g vs. 2g of cefazolin.