COVID-19 Evidence Accelerator Collaborative

Lab Meeting #20

Thursday, October 1, 2020, 3:00-4:00 pm ET

Call Summary

Overview of Lab Meeting

The theme of this week's lab meeting was "Transparency and Quality in Real World Evidence (RWE)." First, Dr. Jan Tate from the Department of Veterans Affairs gave a presentation on the importance (and difficulty) of picking an appropriate Time Zero in observational trials. Following a short discussion on Dr. Tate's presentation, we heard about two initiatives enhancing transparency in RWE reporting to engender trust in these data:

- **Real World Evidence Transparency Initiative** - *Lucinda Orsini, The Professional Society for Health Economics & Outcomes Research (ISPOR)*
- **Structured Reporting and Template for Real-World Evidence (STaRT-RWE) Initiative** - *Shirley Wang, Brigham Women's Hospital & Harvard Medical School*

The lab meeting closed with the Data Visualization of the Week which showed a sobering trend in mortality statistics from 2018 to September 2020.

When is Time Zero?

Janet Tate, *Veteran's Affairs*

Hypothetical Trial: *Does Remdesivir and/ or Dexamethasone improve outcomes for patients hospitalized with COVID-19?*

- **Randomized Trial:** Homogenous sample, randomization, explicit treatment start-dates & follow-up dates.
    - 4 arm factorial design, patients randomized to receive:
        - Both Dexamethasone & Remdesivir
        - Remdesivir
        - Dexamethasone
        - Neither treatment
    - Outcomes measured
        - Primary – 30-day mortality
        - Secondary
    - Start designated treatment within 24 hours of randomization
- **Real World:**
    - Patients hospitalized with COVID-19 who received:
        - Both Dexamethasone & Remdesivir

        - Remdesivir
        - Dexamethasone
        - Neither treatment
    - NOT randomized
    - NOT homogenous across treatment groups
    - Variation in reporting & time treatment started
        - What is time 0?
        - What outcomes can be measured?

Time Zero Options for COVID Questions

Time 0	**Challenge/Consideration in RW**
Infection or Symptom Onset	Difficult to measure, sometimes patients are asymptomatic or don't seek care/testing immediately.
Date specimen taken or results reported to provider	Difficult because of Temporal & Regional trends in lag time – no luxury of waiting for result, physicians must operate under the presumption of a positive test result
Presentation to hospital	Is this the initial ER visit or official admittance? – A lot of variation in how these dates appear in EHR data
Admission to hospital	What about observation before hospital?
Admission to ICU	Variation in capacity and definitions of ICU

Patient Scenarios

Mr. A – *Specimen for positive test 4/13*

- EHR Timeline:
    - Admitted 4/13 (17:30) – Discharged 4/15 (18:25)
    - Admitted 4/15 (18:25) – Discharged 4/20 (17:50)
- EHR shows only date & time of admissions & discharges, looking closer at these shows:
    - 4/13 (10:58) – **Emergency Dept.**
    - 4/13 (17:30) – 4/15 (18:25) – **Observation**
    - 4/15 (18:25) – 4/20 (17:50) – **Admitted**
- Considerations
    - What if first admission after positive test is specified?
    - 30-day mortality and in-hospital death are very different
- Decision:
    - Algorithm – concatenate admissions separated by <24 hours into an episode of care.

Mr. B – *Specimen for positive test 7/30*

- EHR Timeline:
    - 7/30 (18:41) – **Emergency Dept.**
    - 7/30 (23:20) – **Remdesivir**

    - 7/31 (4:21) – **Admitted, Remdesivir continued until 8/3**
- Here, the patient received Remdesivir prior to admittance, so hospital admittance as Time 0 is not adequate:
    - What if Remdesivir stopped after first dose because of an adverse reaction?
    - Timing of second dose?
    - Total exposure?
- Depending on what time 0 is, your results may be interpreted differently or skewed.

Mr. C – *Specimen for positive test 6/29*

- EHR Timeline:
    - 6/29 (16:07) – **Emergency Dept.**
    - 7/3 (14:43) – **Emergency Dept.**
    - 7/5 (21:14) – **Emergency Dept.**
    - 7/7 (20:37) – **Emergency Dept.**
    - 7/8 (1:13) – **Admittance**
- Looking closer:
    - Between ER visits patient was having phone follow-ups
- Decision:
    - Using algorithm – determined the episode of care relevant to study began 7/7 with ER Visit preceding admittance

Implications of Time Zero

- Concerns
    - Exposures
    - Covariates – severity of illness
    - What is meant by "time of presentation"?
    - Outcomes
- Best choice of time 0 depends on the research question you are asking
- Time 0 always deserves careful consideration and exploration
    - The more you can specify about what you are asking, the better the research will be.
    - Also important to take into consideration the totality of evidence, rather than just a test result or symptoms (i.e. negative test result but patient has all symptoms)

<u>Real-World Evidence Transparency Initiative</u>

Lucinda Orsini, *The Professional Society for Health Economics & Outcomes Research (ISPOR)*

ISPOR/ISPE Joint Task Force on RWE in Healthcare Decision Making

- Recommendations on:
    - Transparency of Study Processes
    - Reproducibility of Study Implementation

Challenges to Using RWE for Decision-making

- Underlying data quality
- Perceptions of data dredging/p-hacking/cherry picking

- Lack of transparency in:
    - Research questions/ objectives
    - Data set choice
    - A priori analysis plans
- Lack of results reporting:
    - RWE studies are NOT published at the same rate as clinical trial evidence
    - **Study Registers –** Allow for transparency in reporting of clinical trials, but due to requirements for a defined start of study non-clinical trials are often unable to be shared here.
    - Limited reporting of results → decreased visibility of studies & their results, "blind-spot" for assessing comparative effectiveness
- Need to have planning and results put in plain view like with clinical trials.

RWE Transparency Initiative

- To prove quality in RWE, there needs to be transparency in processes used:
    - Posting protocols, research questions, study plans, etc. so people can access and use them.
    - Information on how much the data is touched before hypothesis/data questions generated.
    - Information about why and what changes are made to the data or study design – since RWE trials are sometimes adjusted based on what is learned along the way.
- What the Initiative is doing:
    - Study register tailored towards secondary & observational data research & studies.
        - A platform for a "trail of versioning" – eventually make public the actions & changes made during pre-publication.
- Mitigating the bad PR of RWE
    - Retracted articles are highlighted, but pros of RWE are not.
    - Some pros to highlight:
        - Cannot replace clinical trial data but can be used as tools in research.
        - Context of research occurring is important information.

<u>Structured Reporting and Template for Real-World Evidence (STaRT-RWE) Initiative</u>

Shirley Wang, *Brigham Women's Hospital and Harvard Medical School*

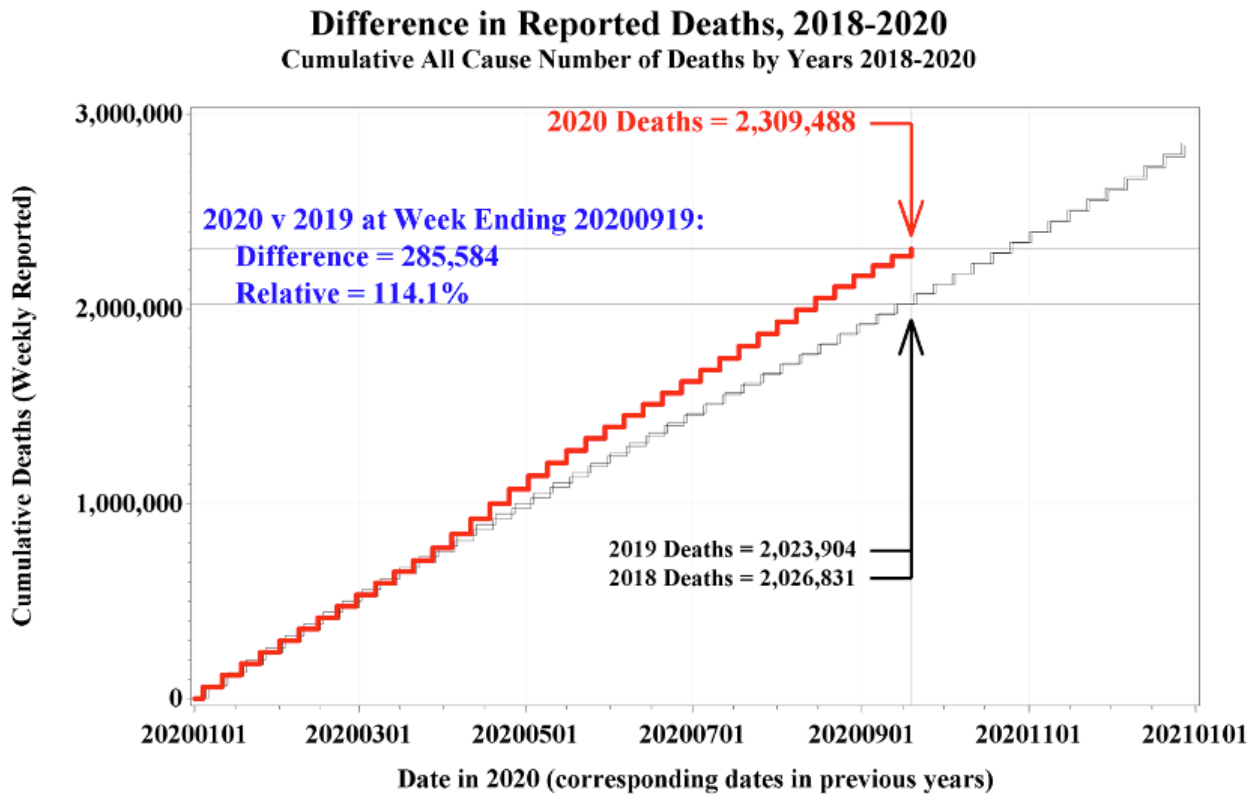
Transparency in RWE

- ISPOR/ISPE Task Force
    - Specify what decisions are being made through enhancing clarity in communicating data decisions.
- REPEAT Initiative
    - Reproducing RWE studies requires unambiguous communication of processes.
    - End users need this information to translate validity of trial results.
    - While trying to reproduce RWE studies, found there is inadequate reporting of some information making the studies hard to reproduce:
        - Incomplete info on design/analysis implementation

        - Incomplete info on data version/ETL
            - i.e. Changing how death was calculated
        - Internally inconsistent information
            - Had to make decisions about what was actually implemented
- STaRT RWE
    - Creating a technical and detailed study implementation template for RWE researchers to use during planning, implementation, and reporting of studies.
        - Common structure for communication on research
        - Minimizes potential for miscommunication or ambiguity in reporting
    - Elements of the template:
        - Tables to guide reporting on:
            - Administrative Information
            - Version History
            - Design Diagram
            - Summary of Study Population Parameters
            - Primary, Secondary, & Subgroup Analysis Specification
            - Sensitivity Analyses
            - Attrition Table
            - Power Calculation
            - Glossary of Terminology
            - Appendices
        - Example of Details included:
            - Table 3. Summary of Study Population Parameters
                - Details of Inclusion/Exclusion
                - Section detailing time 0 & # of entries into cohort
                - Operationalization of inclusion/exclusion criteria
                - Performance & validation of outcome measures
                - What is used & not used to end follow-up
- Study transparency does not = study quality, there is a need for both in RWE research.

Data Visualization of the Week

NOTE: Includes all reported deaths for the designated time periods.



Note 1: 2018 and 2019 are essentially indistiguishable, an illustration of year-to-year consistency in non-pandemic times.
Note 2: Data from https://data.cdc.gov/NCHS/Excess-Deaths-Associated-with-COVID-19/xkkf-xrst/
Note 3: Graph by Brent A. Blumenstein, PhD (www.TriArcConsulting.com)
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