Generating Actionable Insights from RWD during COVID-19 Pandemic

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The opinions presented are that of the speaker and not of FDA

Outline

- FDA definitions of RWD and RWE
  - Some regulatory statistical considerations
- RWD in COVID-19 Pandemic: Call to Action
  - Use Case I : Evidence Accelerator
  - Use Case II: Rapid Query Model with UCSF
- International Collaborations
- Concluding Remarks

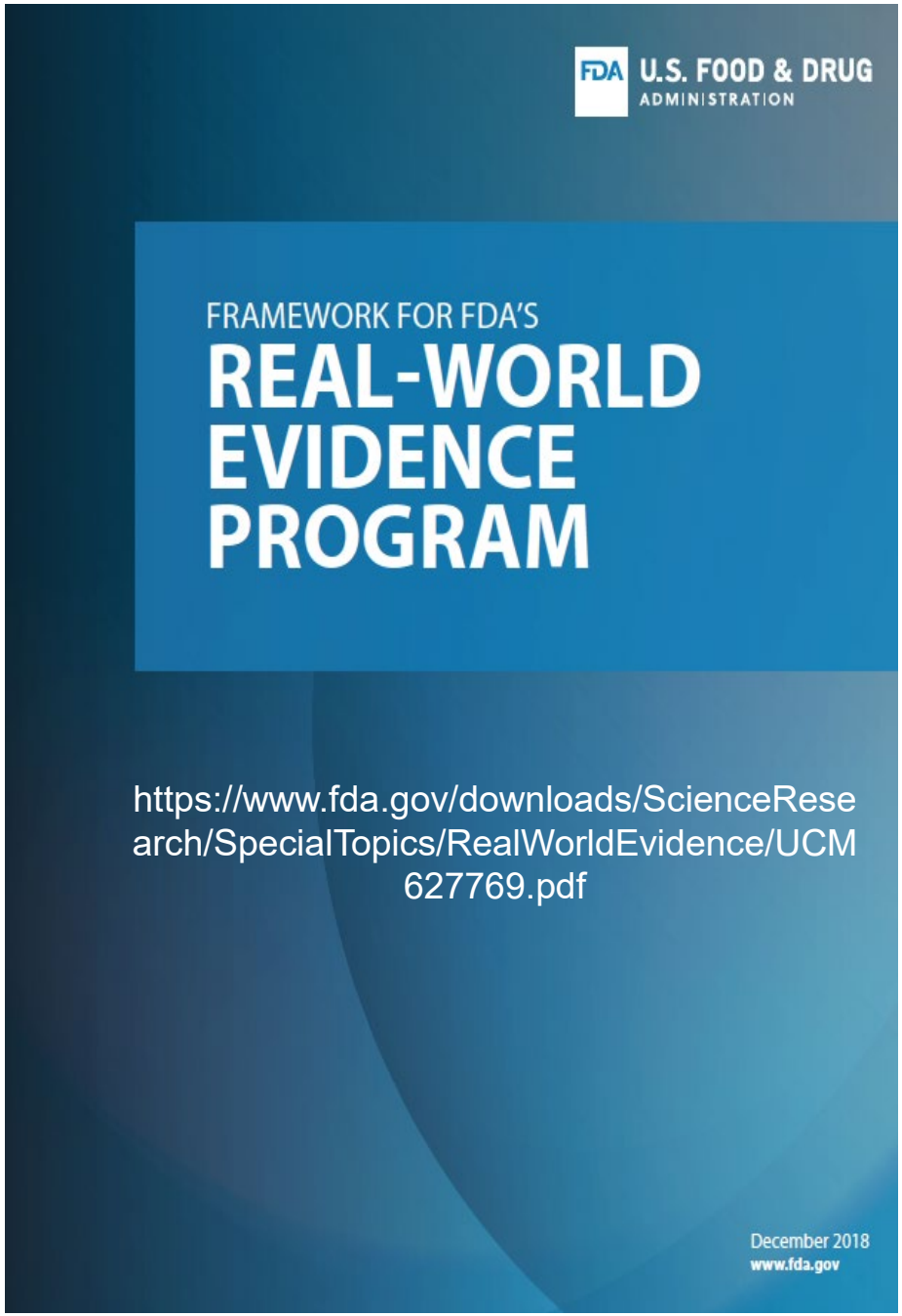
FDA Definitions of RWD/RWE

Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- electronic health records (EHRs)
- claims and billing data
- data from product and disease registries
- patient-generated data including in home-use settings
- data gathered from other sources on health status, e.g. mobile devices

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from analysis of RWD.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.



- Reflect the diversity of patients and actual health-care practices
- Improve efficiency by making use of existing data and infrastructure
- Flexible, yet maintain evidentiary standards
- **21st Century Cures (2016)** : Established a program to evaluate the potential use of RWD/RWE
  - to help to support the approval of a new indication for an approved drug
  - to help to support or satisfy post-approval study needs
  - No change in evidentiary standards

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

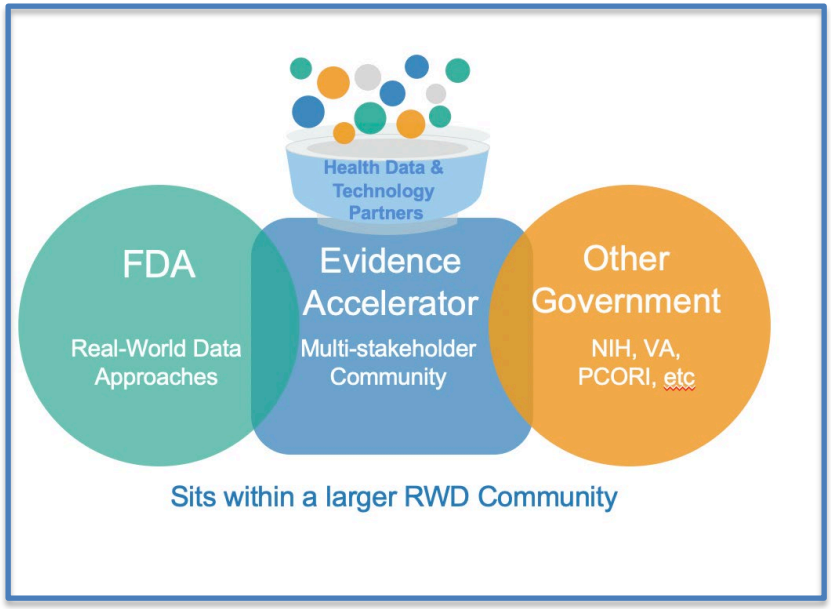
Fitness for Use	RWE Study Design	Regulatory Considerations

• Data uses
  • Population selection
  • Outcome ascertainment
  • Safety and study monitoring
• Data reliability, validity, relevance
• Multiple data sources may be needed
	• Population selection
	• Comparator groups
	• Outcome ascertainment and blinding
	• Exposures patterns, dropouts
	• Treatment definition (estimand)
	• Hypothesis (e.g., non-inferiority)
		• Human subject protection
		• Data traceability, auditing, and record keeping
		• Safety reporting
		• Study integrity and responsibility

COVID-19 Pandemic: RWD Call to Action

- Public Health Emergency
  - little historical data
  - dearth of traditional sources of information
  - required learning about the disease in real-time, from disparate data sources
  - needed multi-pronged approach
- Bring together diverse stakeholders to the (virtual) table
  - “all-hands” approach was one of the important mechanisms for advancing real-time understanding of COVID-19

COVID-19 Evidence Accelerator (EA)



- Launched April 2020 under a MOU by the Reagan-Udall Foundation (RUF) for the FDA
  - in collaboration with Friends of Cancer Research (FOCR)
- FDA active participant and provides input on prioritized research questions
  - Find areas where RWD may provide a fuller picture
- Over 200 representative organizations comprise the EA community
  - diverse contributions to broader RWD community

Two workstreams – Therapeutics (drugs/vaccines) and Diagnostics (testing)

www.evidenceaccelerator.org

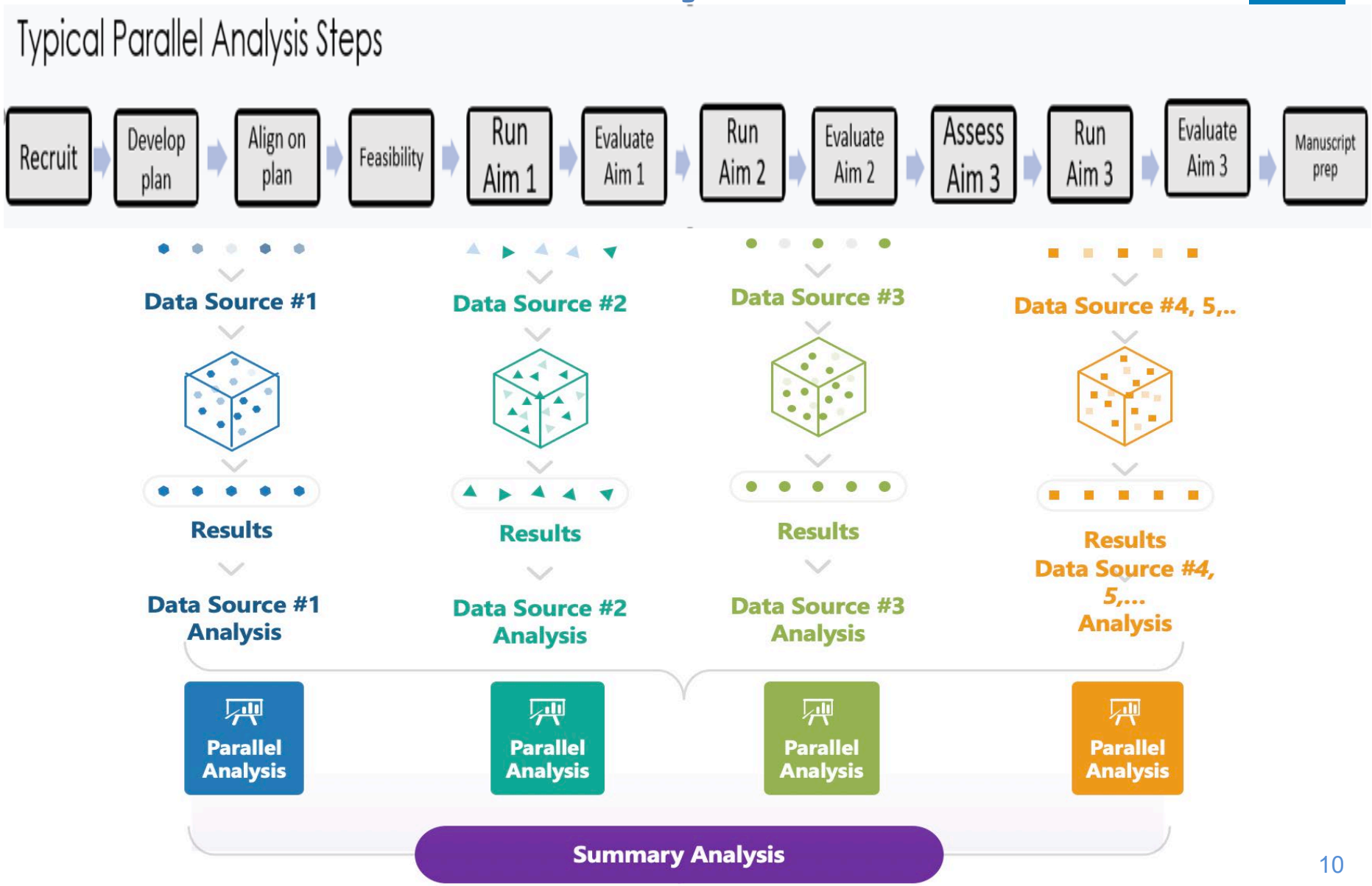
COVID-19 EA Work Model

- The COVID-19 EA brings together leading experts in health data aggregation and analytics
  - unified, collaborative effort to share insights, compare results and answer key questions to inform the collective COVID-19 response
- In Parallel Analysis work, convene a set of data partners to
  - work collaboratively with FDA to develop study protocols and analysis plans
  - execute a common analytic plan against their unique data set
  - results are reported to the Accelerator and 'in parallel'
- RWE may help regulators and scientists augment information received in RCT by shared insight, common research questions, innovative use of parallel analysis, rapid queries and lab meetings
- Creates a strong foundation for rapid collection and rigorous analysis of RWD to answer urgent questions about COVID-19

Parallel Analysis Model

- Appreciation for different capabilities of electronic health records (EHR) vs. claims as the dataset
- Allow heterogeneity in approaches for EHR vs. claims, align within the data sources
- Balance the need for alignment and model-building approaches driven by specific datasets
- Rigor across Accelerators and the need for expediency
  - a more prescriptive approach to study design and model selection
- Dedicated "Parallel Analysis" workstreams focus on therapeutics and diagnostics use, exploring discrete research questions according to a common analytic plan
- Initial activities include
  - rapidly revising a list of core data elements;
  - identifying elements critical to answering the primary question;
  - establishing uniform collection parameters.
- This Parallel Analysis approach is being deployed to address
  - 3 therapeutics-focused research questions
  - 1 diagnostics-focused question
- Results of analyses, rather than raw data, are shared among participants

Parallel Analysis Model



Research Questions analyzed in EA

Therapeutics

- Natural History/HCQ Use (complete)
  - **Citation:** Stewart M, Rodriguez-Watson C, Albayrak A, Asubonteng J, Belli A, Brown T, et al. (2021) COVID-19 Evidence Accelerator: A parallel analysis to describe the use of Hydroxychloroquine with or without Azithromycin among hospitalized COVID-19 patients.
  - PLoS ONE 16(3): e0248128. https://doi.org/10.1371/journal.pone.0248128
- Remdesivir in Hospitalized patients (ongoing)
  - Manuscript undergoing clearance
- Natural history of coagulopathy (ongoing)
  - Finalizing manuscript

Diagnostics

- Real-World test performance of serology for recent infections (ongoing)
  - Manuscript undergoing clearance

Evidence Accelerator: Overall Learnings

- Characterization of the natural clinical history of COVID-19 in hospitalized patients
  - foundational to ensuring testing performance, identifying treatment, predicting immunity, detecting potential for future waves of infection, and tracking mutation
- Insight into population and demographic subsets for an improved understanding of treatment patterns and accessibility
- Longitudinal monitoring of pandemic response across different geographies to assess changes in practice patterns over time
- Evaluation of diagnostic and serologic testing strategies to assess utilization patterns and performance across numerous health systems
- Exposure of a critical absence of data flow of the type of diagnostic test administered (test results routinely appear in RWD; the actual test used often does not)

Rapid Query Model – UCSF

- New approach to answer critical medical and operational questions quickly using RWD
- UC Health
  - 19 health professional schools, 5 academic medical centers, and 12 hospitals,
  - secure central EHR based data warehouse
- The rapid-query model is a multi-step framework
  - computational pipeline to rapidly query the data warehouse
  - refine the question further with follow-up statistical analysis
- The rapid-query model will enable RWE in a statistically rigorous manner to help inform clinical, regulatory, and operational decision making

Rapid Query Model - UCSF

daily prescription of corticosteroids

- Question: Within 28 days of a COVID-19 diagnosis, describe treatment patterns among patients who initiated one of four corticosteroids of interest in both inpatient and outpatient settings of the care
- Feb-Aug 2020
- n on meds= 789; total hospitalized since Feb 2020 = 1852)
- Temporal pattern shifts
- Gradual increases March-May
- Significantly higher in June-July

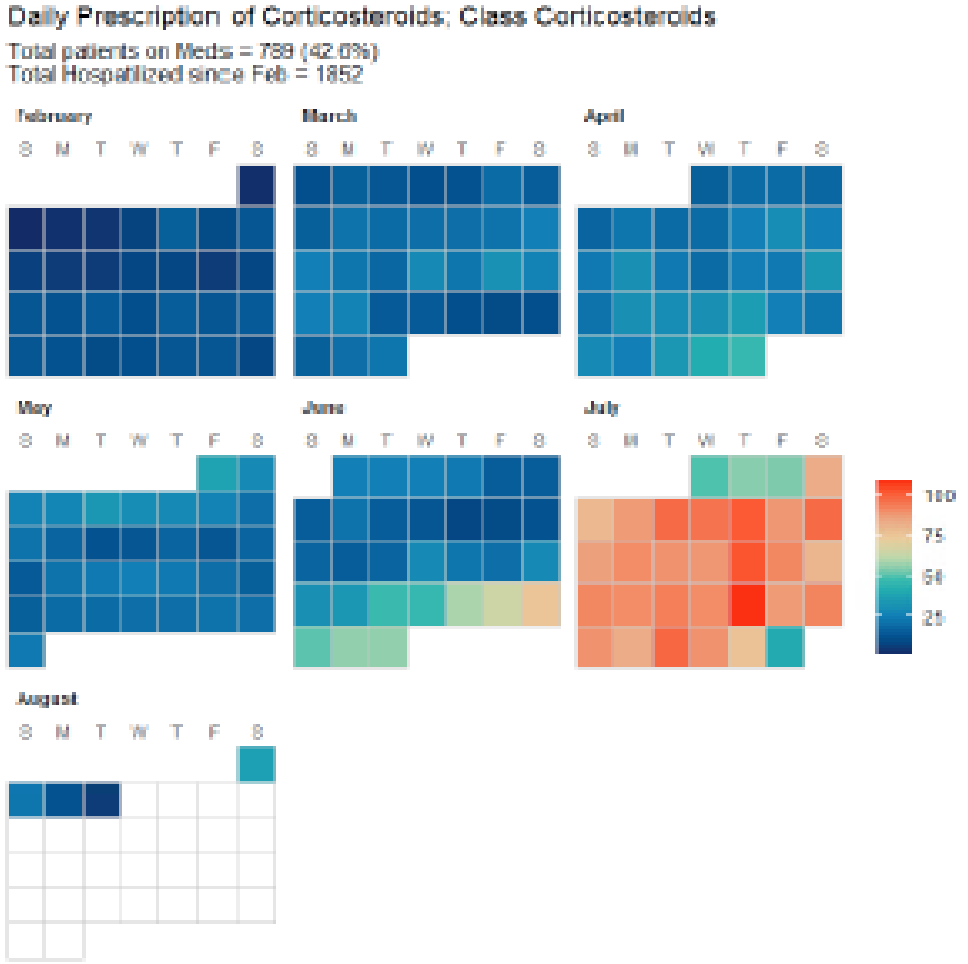
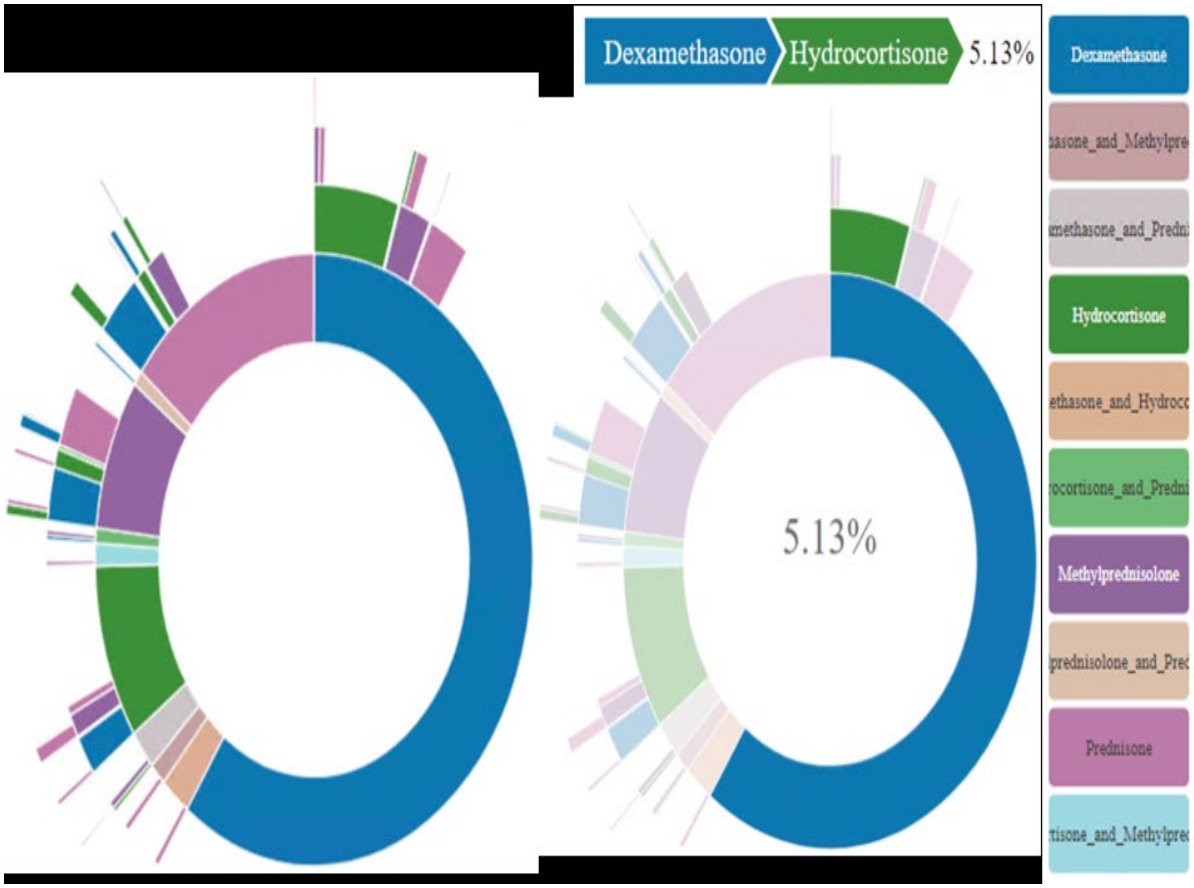


Figure 1. Daily Orders: Patterns of daily orders of the Corticosteroids during inpatient care of the patients hospitalized due to SARS-CoV-2 infection from Feb 2020 to August 2020.

Rapid Query Model - UCSF: Treatment Courses

- The majority of the inpatients were prescribed dexamethasone as their initial treatment
  - followed by prednisone, hydrocortisone and methylprednisolone
- The innermost circle represent number of patients on a given type of corticosteroid.
- Each subsequent circle represents order of other another corticosteroid e.g., 5.13% of the patients who started on dexamethasone required hydrocortisone



Rapid Query Model - UCSF: Time to Medication Order

- Time to First Order of dexamethasone vs hydrocortisone
  - Kaplan Meier plots were used to represent time to treatment initiation
  - Log-rank test was conducted to compare the curve and calculate p value
  - Shows a clear separation

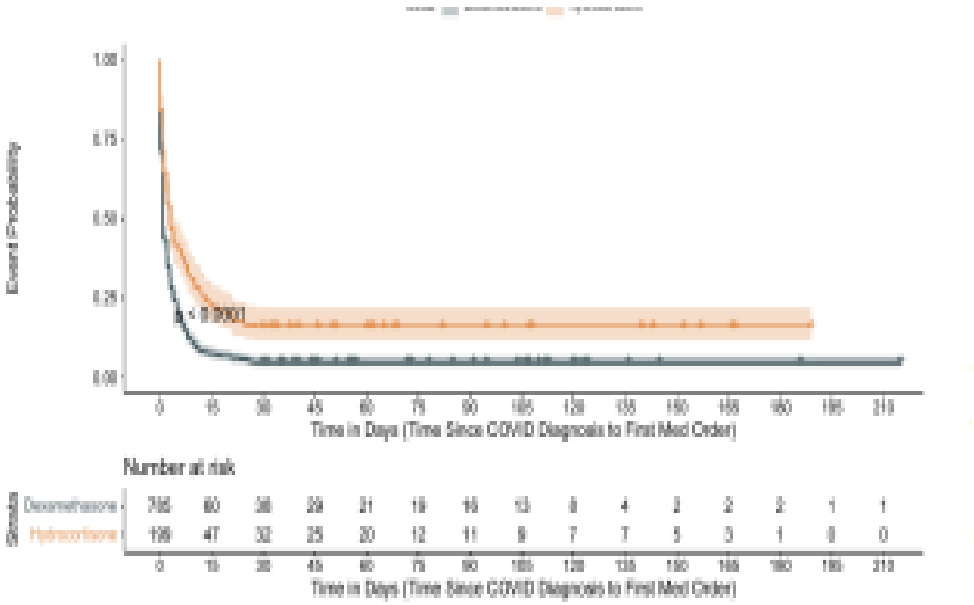


Figure 3. Time to Medication Order: Time to First Order of Dexamethasone vs Hydrocortisone.
Kaplan Meier plots were used to represent time to treatment initiation. Log-rank test was conducted to compare the curve and calculate p value using R statistical software.

Rapid Analytics: Overall learnings

- Illuminated the benefit of RWD to complement clinical trials
- Created a roadmap for efforts to leverage RWD for productive analyses
  - Help guide confirmatory trials
  - Quick visualization
- Began developing a common language for discussing FDA issues of relevance
- Created the ability to identify the types of questions that can be answered by RWD

International Collaborations in COVID-19

- ICMRA regular meetings
  - FDA participates via Sentinel
  - FDA COVID-19 initiatives presentation
- ICMRA Conference June 29-30, 2022
  - RWE Terminologies
  - From RWD to RWE
  - Data Sources and Metadata
  - Federated Data Networks
  - Landscape Analysis
  - Issues and Challenges

Concluding Remarks (1)

- RWE may help regulators and scientists augment information received in RCTs by
  - shared insight, common research questions, innovative use of parallel analysis, rapid queries, and collaborative discussion.
- The Evidence Accelerator created a strong foundation for rapid collection and rigorous analysis of RWD to answer urgent questions about COVID-19
- Rapid Query Model helped iterative decision making with constant feedback mechanism

Concluding Remarks (2)

- Application of rigorous analytic methods and a facility with real-world datasets offers
  - quick evaluation of fitness for purpose of RWD
  - opportunity to rapidly evaluate changes in practice
  - uptake of new therapies
  - understanding of the natural history of COVID and related sequalae
- This work model can be adapted for other public health and regulatory use cases, such as substance use disorders
- Provides a forum for active discussion and engagement can energize participants and stimulate stakeholder collaboration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