COVID-19 Vaccine Safety

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Safety is not the absence of risk…. it is an acceptable balance of benefits and risks.

2 Independent Advisory Committees Review Safety

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

- To provide advice to the Commissioner of FDA
- To evaluate data concerning ***safety***, effectiveness and appropriate use of vaccines…for which the FDA has *regulatory* responsibility.

Advisory Committee on Immunization Practices

- To provide advice and guidance to the Director of the CDC
- To provide recommendations on *use* of vaccines in the U.S. civilian population based on disease epidemiology, ***vaccine safety***, vaccine efficacy and effectiveness, quality of evidence reviewed, economic analyses, and implementation issues.

ACIP - Vaccine Safety

- Vaccine safety data is *routinely* considered by ACIP workgroups and full ACIP deliberations about benefit-risk balance and recommendations for use
- ACIP is *routinely* updated on post-market safety and effectiveness data for vaccines, and modifies recommendations, if needed.
- For COVID-19 vaccines, a separate safety group was assembled in Jun 2020 to support the COVID-19 Vaccine Workgroup and the full ACIP on the safety of COVID-19 vaccines in development and post-approval.

COVID-19 Vaccine Safety Technical (VaST) Subgroup

- ACIP members
  - Grace Lee
  - Beth Bell
  - Keipp Talbot
- Consultants
  - Ed Belongia
  - Matthew Daley
  - Kathy Edwards
  - Martin Kulldorff
  - Laura Riley Stanley Perlman
  - Vish Viswanath
- CDC Lead
  - Tom Shimabukuro
- Ex Officio Members
  - CDC
  - FDA
  - DoD
  - VA
  - IHS
  - HRSA
  - HHS
  - NIH
  - BARDA

VaST - Terms of Reference

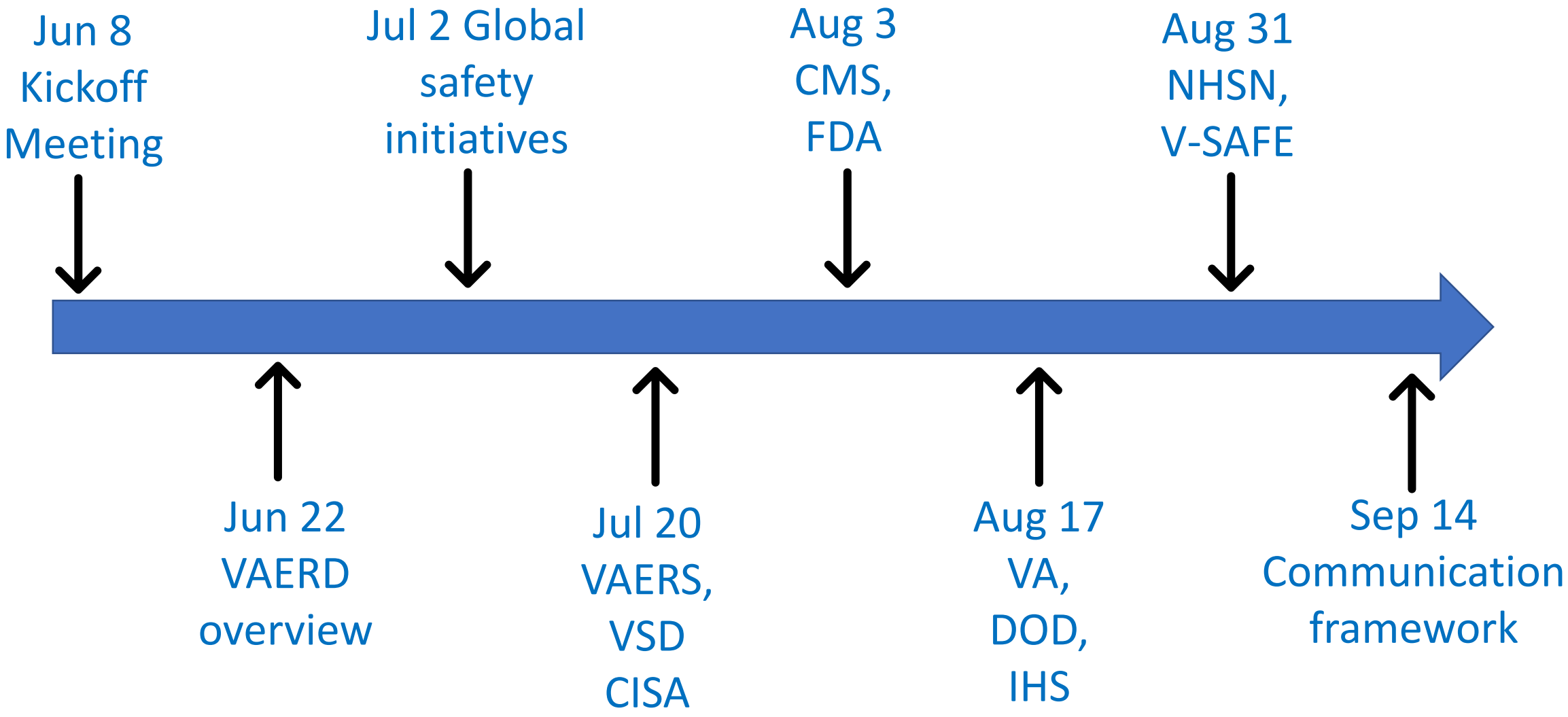
-As of May 2020

Serve as the central hub for technical subject matter experts to:

1) Review and interpret pre-authorization /pre-licensure SARS-CoV-2 vaccine candidate safety data
2) Review and interpret post-authorization/post-licensure SARS-CoV-2 vaccine safety data
3) Provide advice and guidance on presenting post-authorization/post-licensure SARS-CoV-2 vaccine safety data to the COVID-19 Vaccines Work Group, the full ACIP, and the general public

COVID-19 Vaccine Safety Planning

VaST Meetings



Key Statements

1. Should safety monitoring for **Phase III clinical trials** be harmonized (e.g. definitions for AESIs, duration of follow-up)?

   YES, critical for timely evaluation

   - Can *combine* data, if appropriate; maximizes sample size for any given adverse event of special interest (AESI)
   - Can *compare* safety across different vaccine platforms and trials, if appropriate; enables dynamic assessment of benefit-risk balance
   - Harmonizing with international standards (e.g. Brighton) is preferred

Similar to FDA guidance on COVID-19 vaccine efficacy, FDA guidance needed on vaccine safety standards

COVID-19 Clinical Trials and Vaccine Safety

- COVID-19 clinical trials in progress or planned include 30,000-50,000 participants per trial
  - Trials are designed for efficacy, but can also be designed for safety, if sufficient follow-up is allowed (e.g. rotavirus vaccine trials*)

- Minimum amount of follow-up needed to assess safety (i.e. benefit-risk balance) will depend on the types of adverse events and associated risk intervals

*Heyse et al., Clin Trials 2008;

Key Statements

2. Should safety monitoring for **post-authorization or post-licensure safety surveillance systems** be harmonized?

   YES, critical for timely evaluation

   - Common protocols, outcome definitions, risk windows, and approaches to severity grading needed for rapid evaluation of statistical signals
   - However, different systems have different capabilities; may need to align, rather than harmonize

Capability for timely evaluation of statistical signals is crucial for vaccine confidence

Coordination across post-market safety surveillance systems is recommended*

*Salmon et al., Pediatrics, 2011

Near real-time safety surveillance systems – designed for sensitivity

Syndromic Surveillance in 4 states

- 62 alerts corresponding to 17 distinct signals
- 2 true clusters of illness detected

Vaccine Safety Datalink experience

- 5 vaccines monitored for 5-7 AESIs each
- 10 *statistical* signals occurred
  - 9 were spurious
  - 1 was a true signal that led to a revised ACIP rec for MMRV vaccine

Statistical signals are expected in a robust monitoring program; timely and thorough signal investigation is needed to distinguish true associations

Adverse Events of Special Interest (AESI)

General AESI

Platform-specific AESI

- mRNA
- Viral vector
- Adjuvanted
- Etc.

Population-specific AESI

- Children
- Pregnant women
- Elderly
- Multiple co-morbidities

*SPEAC classification of AESI

VaST Transition Plans

-As of Sept 2020

Pre-authorization or Pre-licensure

- **Discuss prioritized AESI**, including standardized definitions (e.g. Brighton), risk intervals, severity grading
- **Discuss common protocols** for enhanced passive surveillance and active surveillance
- **Discuss approaches to signal refinement and signal evaluation**
- **Review and refine membership** of data review group

Post-authorization or Post-licensure

- Prospectively **review, evaluate and interpret** post-authorization or post-approval vaccine safety data from
  - Ongoing clinical trials
  - Passive, enhanced passive and active surveillance systems
- **Advise on signal refinement and signal evaluation**
- **Advise on data presentation** to ACIP and public

6 conditions for success

1) Ability to capture vaccine exposure in vaccine safety surveillance systems
2) Ability to define background rates in general population and among those with COVID-19 disease
3) Minimize conflicts of interest of data review group
4) Shared review and shared learning across all vaccine safety surveillance systems
5) Ability for data review group to discuss findings independently
6) Well-developed communication plan on safety issues

We have designed our systems to detect safety signals; it's how we handle those signals that will define our country's ability to respond to COVID.