<table>
<thead>
<tr>
<th>#</th>
<th>Time (BST)</th>
<th>Subject</th>
<th>Responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2:00</td>
<td>Welcome [5 min]</td>
<td>Melanie Saville, CEPI</td>
</tr>
<tr>
<td>2</td>
<td>2:05</td>
<td>Background [5 min]</td>
<td>Peter Dull, BMGF</td>
</tr>
<tr>
<td>3</td>
<td>2:10</td>
<td>Fractional dosing – A perspective on vaccine supply [10 min]</td>
<td>Michael Kremer, Becker Friedman Institute, University of Chicago</td>
</tr>
<tr>
<td>4</td>
<td>2:20</td>
<td>Learnings from the UK trial on full / fractional booster doses: CoV-BOOST [10 min]</td>
<td>Saul Faust, Southampton NIHR Wellcome Trust Clinical Research Facility</td>
</tr>
<tr>
<td>5</td>
<td>2:30</td>
<td>Outline of the CEPI/COVAX platform trial concept [10 min]</td>
<td>Robbert van der Most, CEPI</td>
</tr>
<tr>
<td>6</td>
<td>2:40</td>
<td>Additional fractional versus full dose in primed populations: Core trial elements [10 min]</td>
<td>Amol Chaudhari, CEPI</td>
</tr>
<tr>
<td>7</td>
<td>2:50</td>
<td>Governance / Coordination / Support strategy [10 min]</td>
<td>Kerim Chitour, PATH</td>
</tr>
<tr>
<td>8</td>
<td>3:00</td>
<td>CEPI’s Central Lab initiative [5 min]</td>
<td>Valentina Bernasconi, CEPI</td>
</tr>
<tr>
<td>9</td>
<td>3:05</td>
<td>Support options via CEPI/SPEAC incl. DSMB [5 min]</td>
<td>Robert Chen, BC/SPEAC</td>
</tr>
<tr>
<td>10</td>
<td>3:10</td>
<td>Discussion [40 min]</td>
<td>ALL</td>
</tr>
<tr>
<td>11</td>
<td>3:50</td>
<td>Timelines / next steps / EOIs [5 min]</td>
<td>Jakob Cramer, CEPI</td>
</tr>
<tr>
<td>12</td>
<td>3:55</td>
<td>Wrap-up / Closure [5 min]</td>
<td>Amol Chaudhari, Robbert van der Most, Jakob Cramer / CEPI</td>
</tr>
</tbody>
</table>
COVID-19 Vaccines: Options for Dose-Sparing

A Platform Trial / Programme Approach

10th September 2021
A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations

Reasons to believe

Examples of fractional dose vaccination indicate feasibility with different vaccine platforms:

- Inactivated: 1/5 dose id IPV (SCRs)
- Live-attenuated: 1/5 dose YFV-17D (SCRs)
- Non-adjuvanted protein: 1/4 dose HBs Ag (antibody titers)
- Adjuvanted protein: 1/5 dose RTS,S malaria vaccine (protection against challenge)
- mRNA: dose ranging studies

Reduced reactogenicity expected
Positive benefit/risk anticipated
RCT data needed
A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations

→ Platform approach: to define core elements and design features

→ Individual trials addressing targeted needs / gaps with the following scope:
  ➢ **Improve immune response** (and vaccine effectiveness) against SARS-CoV-2 infection / transmission and COVID-19 illness in the context of increasing numbers of VOCs in selected / special populations
  ➢ **Positive effect on vaccine supply**: accelerate vaccination coverage (without compromising VE / public health impact)
  ➢ **Improve reactogenicity (and safety?) profile**
A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations

**Aim:** Data are primarily expected to support pragmatic recommendation by e.g. NITAGs / WHO SAGE (but may also serve to support regulatory approval of additional label claims)

- Focus on needs in LMICs
- It is not the intention to duplicate other programmes / trials generating similar evidence (e.g. on the general need for a booster dose in fully vaccinated healthy populations)
Terminology

• **Priming:**
  ➢ 1 or 2 doses [given 3 weeks – 3 months apart (= dose 1 and 2)]

• **Additional dose:**
  ➢ 1 dose given months (>6 months) or years after priming (= depending on scenarios above: dose 2, 3 or 4 ff.)
  ➢ 2+1 scheme requiring a 3rd dose to complete primary immunization
    ➢ for vaccines with a rapid initial decline in Ab-levels / with insufficient vaccine effectiveness post 2 doses
    ➢ in special populations (e.g. elderly, immunocompromised)

• **Booster dose:**
  ➢ To maintain / broaden immune response over time in the general healthy population
Recent data indicate good immune memory and boostability of **WVI vaccines** (Sinopharm, Sinovac) after a third dose 6 months after primary immunisation.

On Aug 5th, **Moderna** presented data on reactogenicity and (cross-reactive) immunogenicity of a reduced dose (50µg) formulation:

- Monovalent original (D614G) strain [mRNA-1273]
- Monovalent Beta (B.1.351) VOC [mRNA-1273-351]
- Bivalent original / Beta variant (25µg each) [mRNA-1273-211]

**Pfizer / BNT**: early stage clinical data indicate room for antigen-saving considerations.

**Pfizer / BNT** recently released data on 6 months booster showing boostability of immune responses => nAbs.

- Included cross-reactive responses against new VOCs (including Delta).
BNT162b2 3rd dose immune responses

COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain¹,²

- Post dose 3 titers vs. the Delta variant are >5-fold post dose 2 titers in 18-55 y/o & >11-fold post dose 2 titers in 65-85 y/o
- Estimated potential for up to 100-fold increase in Delta neutralization post-dose three compared to pre-dose three
Platform Trial Concept: Prospective randomised trial(s) to assess the immunogenicity of fractional *versus* full dose given as a single *additional* vaccination in previously primed subjects

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Study Population</th>
<th>Visit #1</th>
<th>Visit #2</th>
<th>... F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Primed’ populations, as defined by individual project with hx of ...</td>
<td>Day 1</td>
<td>Day 29 (week 4)</td>
<td>1, 2 years...</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>• One dose (single dose regimen / incomplete 2-dose regimen) or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2 doses (any vaccine, different intervals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Evidence of nat. infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>• Should a different vaccine be tested for full versus fractional dose for ‘booster’ it is recommended to include one comparator arm assessing a full dose of the vaccine used for primary vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>‘Rescue strategy’ → Offer full vaccination with locally registered / available vaccine to those with insufficient immune response</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional blood draw for long term immuno?

a) Should a different vaccine be tested for full versus fractional dose for ‘booster’ it is recommended to include one comparator arm assessing a full dose of the vaccine used for primary vaccination.
b) Fractional dose (not necessarily half dose).
Platform Trial Approach: Core and Flexible Elements

**Defined trial populations, e.g.**
- Immunocompromised / SOT
- Immunocompromised / HIV
- Elderly / immunosenescence
- Primed via natural infection
- Other chronic conditions / risk groups
- 2→3 dose regimen (2+1)
- Post single dose

**Selected vaccines***

**Imune response read-out**

**Day 1:**
- Fractional single booster dose

**Day 29:**
- Immune response (core assay + additional assays defined by project (incl. e.g. CMI, cross-reactivity etc.).):
  - **Primary comparison:** → Individual trial population
  - **Secondary comparisons** → in subgroups, e.g.
    - Within each individual trial
    - Across all trials → overall, across all trials

**Follow-up**

- At least 3 months for safety F/U
- May include an additional blood draw e.g. at 6 months to assess long-term immune response post booster

*) E.g., as available in the country. Vaccine developers may want to contribute to specific trials / projects.
Fractional ‘Booster’ Platform Trial: Core Elements

1. **Full versus fractional single dose** of a selected vaccine. If the ‘booster’ vaccine differs from vaccine given for priming, a control group including the same vaccine (full dose) given for primary vaccination should be considered.

2. **4 week interval** between ‘booster’ dose and primary immunogenicity endpoint.

3. Immune response for primary endpoint assessed based on **binding antibodies** (IgG ELISA).

4. **Reactogenicity / safety** assessment (as co-primary objective).

5. Follow-up (safety) for at least **3 months**.

→ allow comparability / analyses on **core objective** across programmes (meta-analysis type rather than pooled data).
Fractional ‘Booster’ Platform Trial: **Flexible Elements**

**Examples:**

- **Population:** to be justified. Examples:
  - Selected age groups (e.g. elderly) or special populations (e.g. HIV-positives / immunocompromised) possibly requiring e.g. a three-dose-regimen (2+1)
  - Healthy general population post full primary immunization with weakly immunogenic vaccines
  - Incomplete primary immunization
  - Post natural infection

- **Vaccine used**

- **Secondary objectives re immune response** (nAbs, B-cell memory, CMI)

- **Additional time points for immunogenicity assessment** (e.g. long(er) term immune response post 6 months)

- **Additional secondary and exploratory objectives**
  - Including e.g. vaccine effectiveness (trials are unlikely to be sufficiently powered)

- **Follow-up beyond 3 months**
Safety

- Post dose FU – Reactogenicity (7 days); unsolicited AEs (28 days) & SAEs (3 months)
- To ensure consistent assessment of reactogenicity and safety of fractional COVID-19 vaccines, procedures to harmonized across individual projects.
- Vaccine-specific AESIs to be defined for individual projects (We recommend SPEAC / the Brighton Collaboration definitions).
- SPEAC guidance for collection of safety data on COVID vaccines on the SPEAC Sharepoint: https://speacproject.sharepoint.com/:b:/r/sites/Start/SPEAC%20PRIVATE/00.%20Deliverables/SO2/WP2/SO2-D2.4/SO2-D2.4._FINAL%20VERSION_20200731.pdf?csf=1&web=1&e=2b2Npc
- An independent trial specific DSMB is encouraged; Alternatively consider participating in the meta DSMB scheme offered by SPEAC
Other considerations

• Primary immunogenicity endpoint: \textit{Seroresponse rate (SRR)} in the fractional and full dose arms.

• SR to be defined as
  • XX-fold (TBD) rise in GMTs at 28 days post ‘booster’ dose from baseline among subjects with detectable Ab titers pre-booster
  • Post dose detectable Ab titers among subjects with no pre-booster detectable titers

• NI design not entirely fit for purpose related to absolute titres (e.g. GMTs) whereas objective may be \textit{threshold-driven} in this setting (SRR) – TBD

• Samples size for individual trials will be justified on the basis of primary endpoint

• Subgroups for additional analyses should be defined and justified

• Cross-reactive immune response against selected VOCs (Delta variant and preferably other VOCs / VOIs as appropriate)
# Timelines

## Summary of project plan / GANTT

<table>
<thead>
<tr>
<th>Event Description</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVAX/CEPI review and approval</td>
<td>08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core protocol</td>
<td>09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Develop programme structure (coordinator, PSC), contracts signed</td>
<td>10</td>
<td>01</td>
<td></td>
</tr>
<tr>
<td>Onboard individual project</td>
<td>11</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>First trial: FSI → 1st results</td>
<td>12</td>
<td>03</td>
<td></td>
</tr>
<tr>
<td>Last trial: FSI → 1st results</td>
<td></td>
<td>04</td>
<td>05</td>
</tr>
<tr>
<td>Total F/U period (1 year) after last trial started</td>
<td></td>
<td>06</td>
<td>...</td>
</tr>
<tr>
<td>Final results, programme close</td>
<td></td>
<td>12</td>
<td>01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>02</td>
<td>03</td>
</tr>
</tbody>
</table>
Next Steps

Discussion / Proposals:

- Define core / flexible elements
- **Working group meeting with relevant stakeholders and interested groups: 10th September 2021**
  - Obtain EOIs ...
- September / October onwards: Start individual projects
Current state of play

- There are still many operational unknowns
- Time is of the essence
- The initial study will need to be an Investigator sponsored study
  - The site is the regulatory sponsor
  - The vaccine to be used in the study is already available in the country
  - External support needs are minimal
- The onboarding of additional countries/sites can then occur in a stepwise fashion
- This will allow more time to adapt the operational support to the site’s needs
Programme Governance & Execution

Programme Steering Committee (PSC)
- CEPI representatives (CD, RA, ES, ...)
- COVAX Clin Dev SWAT representatives
  - CEPI SAC Members
  - Selected experts in the field

CEPI Project Team
- Financial and Scientific Oversight

Coordination and Implementation Partner (PATH)
- Global Oversight & Quality Control
- Central Data Management & Analysis
- Site Operational Support
- Sample Management and Lab Support

Sponsor A (Country/Consortium A)
PI, Co-PI(s), coordinators, technical staff

Sponsor B (Country/Consortium B)
PI, Co-PI(s), coordinators, technical staff

Sponsor C (Country/Consortium C)
PI, Co-PI(s), coordinators, technical staff

Sponsor D (Country/Consortium D)
PI, Co-PI(s), coordinators, technical staff
COVID-19 Phase 3 Trial Preparation Project at PATH

**Goal:** To enhance capacity at low- and middle-income country clinical trial sites to prepare them for testing COVID-19 vaccine candidates alongside peer sites in high-income countries, including effectively sustaining and managing high-volume (participants & specimens) for rapid enrolling trials implemented in a pandemic setting while adhering to GCP guidelines and quality standards.

All 11 sites had prior relevant experience and demonstrated success in implementing clinical vaccine trials

- Burkina Faso - Institut de Recherche en Science de la Santé
- Costa Rica - Fundación Inciensa (FUNIN), Biomédicas (ACIB)...
- Honduras: Inversiones en Investigación Médica S.A.
- Malawi - Malawi-Liverpool-Wellcome Trust
- Mozambique - Centro de Investigação em Saúde de...
- Pakistan - Aga Khan University Clinical Trials Unit
- Colombia - Centro de Atención y Diagnóstico de Enfermedades...
- Haiti - Les Centres GHESKIO
- Kenya - KAVI University of Nairobi
- Mali - Le Centre pour le Développement des Vaccins du...
- Niger - Epicentre

- **Standard capacity improvements**
  - Hiring and training a core set of qualified trial management staff in GCP and HSR and site-specific procedures
  - Establishing a core set of SOPs, including COVID-19 specific SOPs promoting social distancing and infection prevention measures
  - Identifying a reliable source of COVID-19 surveillance data for country and local area, consistent monthly reporting
  - Consulting with National Regulatory Authorities and Ethics Committees to optimize timelines for review/approval
  - Conducting community/stakeholder consultation meetings to verify community readiness for a trial
  - Completing financial reviews to verify financial competency to manage trial finances

- **Capacity improvements tailored by site**
  - Improving infrastructure to allow for high-volume enrollment, social distancing, and preventing contact between suspected/confirmed patients and healthy study participants
  - Renovating/expanding storage and workspace in labs and pharmacies
  - Establishing satellite sites
  - Purchasing and/or maintaining refrigerators, freezers, and/or basic COVID-19 clinical care and assessment tools (e.g., oximeter, touchless thermometers, oxygen concentrators, etc.)
CEPI Centralized Laboratory Network: key features

Valentina Bernasconi  Scientist at CEPI, Project Leader of CEPI Centralized Laboratory Network
Objectives of the Network

The CEPI Centralized Laboratory Network is open to **all** COVAX funded and non-funded vaccine developers:

- To test samples from pre-clinical to Phase III clinical studies for key immunogenicity and efficacy endpoint evaluation
- To support SARS-CoV-2 vaccine developers in the pathway towards licensure
- To help the identification of Immune Correlates of Protection
- To facilitate rapid evaluation, approval, and dissemination of the most effective vaccine candidates
CEPI Centralized Laboratory Network

- nexelis
  - Canada
- CEPI Centralized Laboratory Network
- Q² Solutions
  - USA
- Universidad Nacional Autónoma de México
  - Mexico
- Public Health England
  - UK
- NIBSC
  - UK
- Viroclinics
  - The Netherlands
- biosciences
- VISMEDERI
  - Italy
- thsti
  - India
- icddr,b
  - Bangladesh
## Assays available within the Network

### Binding antibodies

<table>
<thead>
<tr>
<th>ELISA</th>
<th>Neutralizing antibodies</th>
<th>T cells</th>
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</thead>
<tbody>
<tr>
<td>Pseudo typed virus neutralization</td>
<td>Wild type virus neutralization</td>
<td>ELISPOT</td>
</tr>
<tr>
<td>- Stabilized pre-fusion full length S, RBD, N</td>
<td>- Colorimetric microneutralization assay</td>
<td>- Peptide pool of the whole S protein</td>
</tr>
<tr>
<td>- Total IgG in serum</td>
<td>- Victoria virus isolate</td>
<td>- Cytokines: IFNγ (Th1), IL-5 (Th2)</td>
</tr>
</tbody>
</table>

### Qualification (Nexelis/PHE)

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<tr>
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<th>Completed</th>
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</table>

### Tech transfer (receiving labs)

<table>
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<tr>
<th></th>
<th>In progress (completed for some labs)</th>
<th>In progress (completed for some labs)</th>
<th>In progress (completed for some labs)</th>
<th>In progress</th>
</tr>
</thead>
</table>

### Validation (Nexelis/PHE)

<table>
<thead>
<tr>
<th></th>
<th>Completed</th>
<th>Completed</th>
<th>Completed</th>
<th>NA</th>
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</table>

### Average current capacity (samples per week)

<table>
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<tr>
<th></th>
<th>2500</th>
<th>1500</th>
<th>500</th>
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</table>

### Common key reagents are provided to all the Labs in the Network
- Scalable throughput
Assay harmonization and tech transfer

Common SOPs, Critical reagents, Controls and panels *

S,RBD, N ELISA
Pseudovirus neutralization assay
IFN-γ, IL-5 ELISPOT

Wild-type virus neutralization assay

*Including bridging with WHO International Antibody Standard
Tackling variants

• All viruses, including SARS-CoV-2, change over time

• CEPI Centralized Laboratory Network opens for testing of vaccines performance against SARS-CoV-2 variants:
  • Alpha, B.1.1.7, first identified in the UK
  • Beta, B.1.351, first identified in South Africa
  • Gamma, P.1, first identified in Brazil
  • Delta, B.1.617, first identified in India

• New circulating SARS-CoV-2 strains that might be tackled:
  • Lambda, C.37, first identified in Peru
  • Other variants that will potentially emerge in the future
Apply for sample testing

- **All** COVID-19 vaccine developers are invited to apply to use the Centralized Laboratory Network.

- **To apply for sample testing, please complete and submit the [Sample Analysis Request Form](https://epi.tghn.org/covax-overview/enabling-sciences/#ref1).

More info: [https://epi.tghn.org/covax-overview/enabling-sciences/#ref1](https://epi.tghn.org/covax-overview/enabling-sciences/#ref1)

Any further question? Reach out to [centralizedlab@cepi.net](mailto:centralizedlab@cepi.net)
Practical info

**Step 1:** Complete the Sample analysis request form.

*Please note incomplete applications will not be considered.*

**Step 2:** Your requests will be reviewed by a CEPI internal committee.

*We commit to get back to each Vaccine Developer applicant within two weeks.*

**Step 3:** If your request is approved, CEPI will connect you with one of our partner labs.

**Note 1:** CEPI will fund the approved sample testing. Sample shipment costs and documentation related to the shipment of the samples is the Vaccine Developer’s responsibility.

**Note 2:** Each Vaccine Developer owns the data generated by the analysis of its samples and should commit to share results with the broader research community.
Safety Platform for Emergency vACcines

Introduction to the Implementing partnership with the Brighton Collaboration program of the Task Force for Global Health

Robert (Bob) Chen MD MA
Scientific Director, Brighton Collaboration
Project Lead, SPEAC

CEPI Fx Dose Trial Platform
10 Sept 2021
CEPI-funded portfolio: multiple platforms for multiple pathogens

Risk:
- Each sponsor has own approach
- Safety signal may be missed in a single trial

Opportunity = SPEAC Goals:
- Enhance vaccine safety assessment across CEPI development programs.
- Harmonize vaccine safety monitoring during CEPI preclinical and clinical trials.
- Provide a continuous improvement framework
Work Package 1: DSMB Pool and Meta-DSMB

- **SPEAC Pool of potential DSMB members**
- SPEAC will offer a list of persons by country with CV, and prior experience. There is currently a list of potential members.
- **SPEAC Meta-DSMB**
- Support CEPI by providing context regarding CEPI vaccines with similar constructs/platforms or target disease via liaison members to study DSMBs
- Support developers by providing expertise regarding CEPI vaccine and assessment of their safety
How is the Meta-DSMB different than a DSMB for an individual study?

- The study sponsor constitutes the individual DSMBs and the study DSMB has direct responsibility for oversight of that trial and reports to the sponsor.

- The goal of the Meta-DSMB is to provide overall oversight for all CEPI vaccine clinical trials to identify potential safety concerns:
  - Across trials using the same platform
  - Across platforms for the same disease target.
  - To encourage harmonization, when possible, regarding how safety data is collected and reported to facilitate data comparisons.

- Meta-DSMB members are non-voting liaison members to the individual study DSMBs. They are funded by SPEAC.

- The Meta-DSMB reports to SPEAC and through SPEAC to CEPI. Its role is advisory and supportive.
**SPEAC Meta–DSMB**

- SPEAC is providing liaison observer members for each CEPI funded vaccine trial
- Can serve as a consulting resource for study DMSBs and sponsors.
- Aim: to support sponsors and their studies and to provide safety oversight of CEPI funded studies.

**CURRENT STATUS**

- Meta–DSMB members have been identified: Kathy Edwards (chair), Neal Halsey, Alex Dodoo, Ulrich Heininger, Cyndy Whitney, Walt Orenstein, Shabir Madhi, Juhani Eskola, Mathu Santosham, Najwa Kuhri, Seif Al–Abri, Jim Buttery and consulting statistician Stephen Evans.
- A charter has been developed to be shared with all developers.
Work Package 2: Standards and Tools – Objectives & Outputs

2. To facilitate a harmonized approach to safety data collection and assessment

➢ **Key output:** online vaccine safety "toolbox" containing:
  • Landscape analysis results and publications used
  • Brighton Collaboration guidelines, safety templates
  • Existing and new Brighton AESI case definitions
  • **Companion Guides to AESI case definitions**
    • Risk factors
    • Background rates (systematic literature review)
    • ICD 9/10 CM / MedDRA Codes
    • Guidance for real time investigation and summary of Brighton guidance on data collection
    • Data abstraction and interpretation forms for Medical Chart review to assess AESI
    • Tabular and pictorial checklist and algorithms for assessing AESI level of certainty

**Guides completed for:** anaphylaxis, thrombocytopenia, generalized convulsion, GBS, facial palsy, ADEM, myelitis, encephalitis and aseptic meningitis

https://brightoncollaboration.us/category/pubs-tools/case-definitions/companion-guides/
Preliminary guidance on safety data collection for COVID-19 vaccine safety

This deliverable provides guidance on the collection of safety data for COVID-19 vaccine candidates. This includes a brief discussion of the types of safety data to collect in trials, a sample memory aid template for collection of solicited local and systemic reactions with guidance re: data analysis and presentation, a literature search on enhanced disease and a report of the consensus conference on enhanced disease following immunization.

Click here to download SO2-D2.4_Preliminary guidance on safety data collection for COVID-19 vaccine safety_V1.0
Summary & Value Proposition

THE SPEAC PARTNERSHIP OFFERS NUMEROUS ADVANTAGES

- Expertise: Brighton Collaboration leverages global network of vaccine safety assessment and evaluation experts
  - For DSMBs and assessment of possible safety signals by Meta-DSMB
- Mitigates vaccine program risk by anticipating vaccine safety crises
- Develops tailored practical solutions for vaccine developers/sponsors
  - Safety landscape analysis for disease areas of interest
  - Case definitions for adverse events of special interest
- Improves data quality and comparability by harmonizing safety assessment
Questions?

Project Manager: angel.honrado@cepi.net
Project Lead: robert.chen@cepi.net
## SPEAC Executive Board

<table>
<thead>
<tr>
<th>WP</th>
<th>Key persons</th>
<th>Key relevant expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Meta–DSMB</td>
<td>1· Dr. Steven Black* (USA)</td>
<td>DSMB experts, vaccinologists, pediatric infectious disease (ID) specialists</td>
</tr>
<tr>
<td></td>
<td>2· Dr. Cornelia Dekker (USA)</td>
<td></td>
</tr>
<tr>
<td>2. Toolbox</td>
<td>3· Dr. Barbara Law* (CA)</td>
<td>Former Chief Vaccine Safety Public Health Agency Canada, Chair BC SB, pediatric ID specialist</td>
</tr>
<tr>
<td></td>
<td>4· Dr. Marc Gurwith (USA)</td>
<td>New vaccine technology lead, adult ID specialist</td>
</tr>
<tr>
<td>3. Evaluation</td>
<td>5· Dr. Wan-Ting Huang* (TW)</td>
<td>Medical Epidemiologist; Former Chief Medical Officer, Taiwan CDC</td>
</tr>
<tr>
<td>4. Coordination &amp; project management</td>
<td>6· Dr. Robert Chen* (USA)</td>
<td>Project lead, former CDC</td>
</tr>
<tr>
<td></td>
<td>7· Prof. dr. Miriam Sturkenboom* (NL)</td>
<td>Pharmaco–epidemiologist, scientific coordination</td>
</tr>
<tr>
<td></td>
<td>8· Chantal Veira</td>
<td>Program management TFGH</td>
</tr>
<tr>
<td></td>
<td>9· Ángel Honrado (ES)</td>
<td>Project management, WeDo</td>
</tr>
<tr>
<td></td>
<td>. Maria Pia Aristimuño (ES)</td>
<td></td>
</tr>
</tbody>
</table>

* All with long–standing expertise in vaccine safety research & Brighton Collaboration Science Board. EB is supported by consultants and experts.
• **Goal:** to build trust in the safety of vaccines via rigorous science

• **Problem:**
  - Unlike efficacy, safety generally **cannot** be measured directly.
  - (Relative) safety **inferred** from relative absence of multiple adverse events following immunization (AEFI) studied given size of vaccinated population.
  - (Rare) AEFI easily missed unless **standard** case definition available.

• **Mission:** develop internationally accepted standards for monitoring vaccine safety throughout the vaccine life cycle
  - >750 volunteers from all stakeholders (academia, industry, government)
  - 20 years of enhancing vaccine safety research (by focusing on harmonization)

Founded in 2000
Work Package 2: Standards and Tools – Objectives & Outputs

1. To conduct landscape analyses for potential vaccine safety issues relevant to CEPI candidate vaccines.

➢ **Key output:** list of possible adverse events of special interest (AESI) for each target disease based on:

1. Proven association with immunizations *(e.g. anaphylaxis)*
2. Proven association with a vaccine platform and/or adjuvant *(e.g. MVA platform and myocarditis)*
3. Theoretical concern based on immune-pathogenesis of wild type disease.
4. Theoretical concern related to viral replication (for live-attenuated vaccines).
5. Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccines *(e.g. enhanced disease in a MERS CoV vaccination/challenge mouse model)*
Landscape Analyses to identify AESI related to wild type disease

- **Usual Process:** CEPI target diseases – Lassa Fever, MERS, Nipah, Rift Valley Fever, Chikungunya
  - Identify 8–10 recent review articles (primary references)
  - Articles reviewed, summarized and AESI list created independently by two experts
    - Secondary references of interest identified from those cited in primary references
    - Seek consensus on AESI list

- **COVID-19 – emerging disease with evolving understanding of clinical features**
  - Initial AESI list developed in early February based on first reports out of China
    - Hospitalized patients reported by Huang(n=41), Chen(n=99), Guan(n=1099), Wang(n=138)
    - 44,672 confirmed cases reported by China CDC
  - Daily screening of published reports in PubMed and input from SPEAC EB members to update list (May 25th)
  - May 27th: updated AESI list presented to and adopted by WHO Global Advisory Committee on Vaccine Safety
  - Dec 2020: systematic literature review completed for May 16–Nov 9, 2020; identified 3 new AESI

<table>
<thead>
<tr>
<th>AESI (red font indicates existing case definition)</th>
<th>Rationale to include as an AESI[^1]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Vaccine Associated Enhanced Disease (in press)</td>
<td>1 FI measles &amp; RSV, HIV; 2 Chimeric YF Dengue; 5 SARS / MERS–CoVs</td>
</tr>
<tr>
<td><strong>2</strong> Multisystem inflammatory syndrome in children and adults (in press)</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>3</strong> Acute respiratory distress syndrome (in press)</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>4</strong> Acute cardiovascular injury (Microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis) <strong>CD for Myocarditis / pericarditis nearly ready</strong></td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>5</strong> Coagulation disorder (Thromboembolism, Hemorrhage). <strong>CD for thrombosis/thromboembolism nearly ready</strong></td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>6</strong> Acute kidney injury</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>7</strong> Generalized convulsion</td>
<td>1, 2</td>
</tr>
<tr>
<td><strong>8</strong> Guillain Barré Syndrome</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>9</strong> Acute liver injury</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>10</strong> Anosmia, ageusia</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>11</strong> Chilblain – like lesions</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>12</strong> Single Organ Cutaneous Vasculitis</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>13</strong> Erythema multiforme</td>
<td>3, 4</td>
</tr>
<tr>
<td><strong>14</strong> Anaphylaxis</td>
<td>1, 2</td>
</tr>
<tr>
<td><strong>15</strong> Acute aseptic arthritis</td>
<td>2 (r-VSV)</td>
</tr>
<tr>
<td><strong>16</strong> Meningoencephalitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>17</strong> Acute disseminated encephalomyelitis</td>
<td>4</td>
</tr>
<tr>
<td><strong>18</strong> Thrombocytopenia</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td><strong>19</strong> Acute pancreatitis, rhabdomyolysis, Subacute pancreatitis</td>
<td>3, 4</td>
</tr>
</tbody>
</table>

[^1]: 1. Proven association with immunization  
2. Proven association with specific vaccine platform  
3. Theoretical concern based on immunopathogenesis  
4. Theoretical concern related to viral replication during wild type disease  
5. Theoretical concern based on demonstration in an animal model
3. To develop *standardized templates* with key benefit/risk assessment considerations.
   - Tool to facilitate discourse by increasing transparency/comparability of info on platform technology
   - Originally
     - Viral vector vaccines: (wild type virus of vector; vector itself; vaccine(s) constructed w/ vector)
   - More recently
     - Protein subunit (e.g., molecular clamp, VLP)
     - Nucleic acid (e.g., RNA, DNA)
     - Inactivated viral vaccines
     - Live attenuated viral vaccines
rVSVΔG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment

Thomas P. Monath\textsuperscript{a,1}, Patricia E. Fast\textsuperscript{b}, Kayvon Modjarrad\textsuperscript{c}, David K. Clarke\textsuperscript{d}, Brian K. Martin\textsuperscript{a,2}, Joan Fusco\textsuperscript{a,1}, Richard Nichols\textsuperscript{a,1}, D. Gray Heppner\textsuperscript{a,1}, Jakub K. Simon\textsuperscript{c}, Sheri Dubey\textsuperscript{c}, Sean P. Troth\textsuperscript{c}, Jayanthi Wolf\textsuperscript{e}, Vidisha Singh\textsuperscript{f}, Beth-Ann Coller\textsuperscript{e}, James S. Robertson\textsuperscript{e,}\textsuperscript{g,}\textsuperscript{a}, For the Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG)\textsuperscript{3}

\textsuperscript{a} NewLink Genetics Corp, Ames, IA, United States
\textsuperscript{b} International AIDS Vaccine Initiative, New York, NY 10004, United States
\textsuperscript{c} Walter Reed Army Institute of Research, Silver Spring, MD 20910, United States
\textsuperscript{d} Projectcure Inc, Pearl River, NY 10965, United States
\textsuperscript{e} Merck & Co., Inc., Kenilworth, NJ 07033, United States
\textsuperscript{f} Immunology and Molecular Pathogenesis, Emory University, Atlanta, GA 30322, United States
\textsuperscript{g} Independent Expert, United Kingdom
### 3. Characteristics of wild type agent

<table>
<thead>
<tr>
<th>Category</th>
<th>Information</th>
<th>Comments/Concerns</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In healthy people</td>
<td>Infection of humans with wild type VSV (wtVSV) New Jersey and Indiana serotypes can cause an influenza-like disease (usually without vesicle formation), incubation period 48 hrs, resolving in 3–5 days without complications. Mucosal ulceration and lymphadenopathy are reported. Rare cases are severe enough to warrant hospitalization. Two published human cases of encephalitis caused by VSV have been reported, but are a rare complication of infection.</td>
<td>Occupational exposure to wt or lab-adapted VSV strains (in veterinarians, farmers in livestock operations, laboratory workers). The reporting rate of naturally acquired overt disease with wtVSV in humans is very low, but in areas of Central and South America, infection appears to be common, with up to 94% of some populations being sero-positive. Surveys of individuals in close contact with VSV-infected livestock have shown high rates of seroconversion. Most infections may be asymptomatic or escape medical attention. VSV sensu stricto is not present in Africa or in Europe. Closely-related vesiculoviruses cause sporadic or epidemic encephalitis (Piry, Chandipura viruses in South America and India, respectively).</td>
<td>[50–59,65]</td>
</tr>
<tr>
<td>• In immunocompromised</td>
<td>Not known in humans</td>
<td>Immunosuppression with steroids did not potentiate wtVSV disease in experimentally infected swine. Defects in innate immunity may underlie disease expression. VSV is exquisitely sensitive to IFN-α/β. Studies in mice lacking IFN receptors indicated that IFN response controls wtVSV and an intact innate immune response likely controls VSV replication. 7–18% of children 0–5 years of age reported to be seropositive in areas surveyed in South and Central America.</td>
<td>[60–62]</td>
</tr>
<tr>
<td>• In neonates, infants, children</td>
<td>Disease potential in children seems to be the same as that for adults. There is no evidence that wtVSV can cause abortions in livestock following natural infection. However, in ferrets experimentally infected with wtVSV-I during the second half of pregnancy transplacental infection, fetal resorption, abortion or neonatal death were observed.</td>
<td></td>
<td>[57,63]</td>
</tr>
<tr>
<td>• During pregnancy and in the unborn</td>
<td>Unknown</td>
<td></td>
<td></td>
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<tr>
<td>• Are there any other susceptible human populations</td>
<td>Wild-type VSV-NI and Indiana cause disease in livestock. The virus is historically transmitted by biting insects such as Aedes albopictus.</td>
<td></td>
<td>[51,60,64,65]</td>
</tr>
<tr>
<td>• Animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#</td>
<td>Time (BST)</td>
<td>Subject</td>
<td>Responsible</td>
</tr>
<tr>
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<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>2:00-2:05</td>
<td>Welcome [5 min]</td>
<td>Melanie Saville, CEPI</td>
</tr>
<tr>
<td>2</td>
<td>2:05-2:10</td>
<td>Background [5 min]</td>
<td>Peter Dull, BMGF</td>
</tr>
<tr>
<td>3</td>
<td>2:10-2:20</td>
<td>Fractional dosing – A perspective on vaccine supply [10 min]</td>
<td>Michael Kremer, Becker Friedman Institute, University of Chicago</td>
</tr>
<tr>
<td>4</td>
<td>2:20-2:30</td>
<td>Learnings from the UK trial on full / fractional booster doses: CoV-BOOST [10 min]</td>
<td>Saul Faust, Southampton NIHR Wellcome Trust Clinical Research Facility</td>
</tr>
<tr>
<td>5</td>
<td>2:30-2:40</td>
<td>Outline of the CEPI/COVAX platform trial concept [10 min]</td>
<td>Robbert van der Most, CEPI</td>
</tr>
<tr>
<td>6</td>
<td>2:40-2:50</td>
<td>Additional fractional versus full dose in primed populations: Core trial elements [10 min]</td>
<td>Amol Chaudhari, CEPI</td>
</tr>
<tr>
<td>7</td>
<td>2:50-3:00</td>
<td>Governance / Coordination / Support strategy [10 min]</td>
<td>Kerim Chitour, PATH</td>
</tr>
<tr>
<td>8</td>
<td>3:00-3:05</td>
<td>CEPI’s Central Lab initiative [5 min]</td>
<td>Valentina Bernasconi, CEPI</td>
</tr>
<tr>
<td>9</td>
<td>3:05-3:10</td>
<td>Support options via CEPI/SPEAC incl. DSMB [5 min]</td>
<td>Robert Chen, BC/SPEAC</td>
</tr>
<tr>
<td>10</td>
<td>3:10-3:50</td>
<td>Discussion [40 min]</td>
<td>ALL</td>
</tr>
<tr>
<td>11</td>
<td>3:50-3:55</td>
<td>Timelines / next steps / EOIs [5 min]</td>
<td>Jakob Cramer, CEPI</td>
</tr>
<tr>
<td>12</td>
<td>3:55-4:00</td>
<td>Wrap-up / Closure [5 min]</td>
<td>Amol Chaudhari, Robbert van der Most, Jakob Cramer / CEPI</td>
</tr>
</tbody>
</table>
For Discussion

• Do additional doses work?
  ➢ Evidence from clinical trials (immunogenicity and safety/reactogenicity)

• Are primary immunization schedules incomplete?
  ➢ Considerations for specific vaccines and special populations

• Do we need additional doses?
  ➢ Largely data from observational studies
Submit an *Expression of Interest* to eoi@cepi.net

- **What?** → objectives
- **Which?** → vaccine(s) [info on procurement]?
- **Who?** → trial population
- **Where?** → country / region
- **When?** → timeline
Conclusion

• Slide deck to be published on: https://epi.tghn.org/

• Further questions on the approach: Dr. Amol Chaudhari [amol.chaudhari@cepi.net]

• Questions around fractional / booster / additional doses will also be addressed on an ongoing base by the COVAX Clin Dev SWAT team (next workshop planned for 30th September 2021 – TBC)