Clinical Trials during Covid19 Pandemic

CRA Academy Conference
14 Dec 2020
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FAcadTM MRQA
• As of 7 December there have been over 65.8 million cases and over 1.5 million deaths reported since the start of the pandemic. (Source: WHO)

It was first identified in December 2019 in Wuhan, China.

The World Health Organization declared the outbreak a Public Health Emergency of International Concern.
Infodemics

Infodemic is a portmanteau of "information" and "epidemic" that typically refers to a rapid and far-reaching spread of both accurate and inaccurate information about something, such as a disease.
Viruses cannot travel on radio waves/mobile networks. COVID-19 is spreading in many countries that do not have 5G mobile networks. COVID-19 is spread through respiratory droplets when an infected person coughs, sneezes or speaks. People can also be infected by touching a contaminated surface and then their eyes, mouth or nose.

FACT: 5G mobile networks DO NOT spread COVID-19

World Health Organization
#Coronavirus #COVID19

8 April 2020
To date there has been no information nor evidence to suggest that the new coronavirus could be transmitted by mosquitoes. The new coronavirus is a respiratory virus which spreads primarily through droplets generated when an infected person coughs or sneezes, or through droplets of saliva or discharge from the nose. To protect yourself, clean your hands frequently with an alcohol-based hand rub or wash them with soap and water. Also, avoid close contact with anyone who is coughing and sneezing.

FACT:
The new coronavirus CANNOT be transmitted through mosquito bites.
The prolonged use of medical masks can be uncomfortable. However, it does not lead to CO2 intoxication nor oxygen deficiency.

While wearing a medical mask, make sure it fits properly and that it is tight enough to allow you to breathe normally.

Do not re-use a disposable mask and always change it as soon as it gets damp.

* Medical masks (also known as surgical masks) are flat or pleated; they are affixed to the head with straps or have ear loops.
COVID-19 and readjusting clinical trials

- The COVID-19 pandemic has disrupted clinical trials worldwide.

- Virus has severely affected the ability to conduct trials in safe and effective ways.

- Especially true when considering that trials often deal with vulnerable populations.

- The effect of COVID-19 has been enormous, with thousands of trials—around 80% of non-COVID-19 trials—being stopped or interrupted.
Disruptive effects on all biomedical research

- Laboratories are closed
- Communications have been shut down
- Conferences have been cancelled
- Supply chains have been lost
- Financial losses
- Many researchers were pulled away from working on CTs to work in emergency medical care
- Disproportionate effect even on those who can work from home—statisticians and epidemiologists
- New trials to address COVID-19 were fast tracked
- Since the emergence of COVID-19 in Dec, 2019, 4174 clinical trials related to COVID-19 have been registered with ClinicalTrials.gov.
COVID-19 and readjusting clinical trials

• Unprecedented reorientation in clinical trials research towards COVID-19

• Trials that were stopped, in many cases, were stopped from enrolling new patients.

• Already enrolled mostly continued to receive treatment as institutions and researchers worked to make changes to how care was provisioned to deal with the reality of COVID-19

• One of the key parts of their guidance has been physical distancing
REGULATORY GUIDANCE
Resources

- EMA COVID-19 Guidance
- FDA COVID-19 Guidance
- MHRA COVID-19 Guidance
- PMDA COVID-19 Guidance
- WCG IRB COVID-19 Guidance
- CDC Public Resources
- WHO Public Advice
• In March, 2020 (revised in Dec), FDA issued guidance: called on researchers and trial sponsors to “determine that the protection of a participant’s safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol”

• **FDA** Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

• **EMA**: GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC, version 3.0 28 Apr 20
Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected by COVID-19

- March 16, 2020
- Limiting study visits to those needed for participant safety or coincident with clinical care.
- Conducting virtual study visits
- Arranging flexibilities for required laboratory tests or imaging needed for safety monitoring to occur at local laboratories or clinics
- Canceling large gatherings of 50 or more people
- Limiting or suspending unnecessary travel
OVERSIGHT
## Impact per country

<table>
<thead>
<tr>
<th>Country</th>
<th>IMP management</th>
<th>Home Visits</th>
<th>Local Imaging/Labs</th>
<th>Informed Consent</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>in compliance with safety instructions, patient information and traceability. USM then substantial modification for approval with specification of the conditions for delivery will be needed</td>
<td>The collection of information remotely is recommended on an exceptional basis, with a focus on safety data and primary objective endpoints.</td>
<td>Local imaging facilities or local labs could be used as per USM</td>
<td>consent can be obtained via phone, email confirmation or validated electronic systems, but written consent must still be obtained at the first opportunity.</td>
<td>Existing containment guidelines must be followed. Postponement of site visits should be considered according to national recommendations and local constraints. Centralized monitoring remains possible with sponsor/site contact subject to the availability of the research teams in intense situations. Sending copies of medical records, even pseudonymized, is not authorized</td>
</tr>
<tr>
<td>Italy</td>
<td>Increased IMP supplied can be provided to</td>
<td>Home visits: Possibility for the Sponsor to sign</td>
<td>Clinical Exams: Private institutes/labs can also</td>
<td>Exceptions to the method for obtaining</td>
<td>exceptional measures such as telephone</td>
</tr>
</tbody>
</table>
## RISK ASSESSMENT

<table>
<thead>
<tr>
<th>Country (population)</th>
<th>Positivity rate</th>
<th>No. new cases in the last 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>US <em>(329 mil)</em></td>
<td>4.60%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Bulgaria <em>(7mil)</em></td>
<td>3.80%</td>
<td>5.72%</td>
</tr>
<tr>
<td>Colombia <em>(60mil)</em></td>
<td>NA</td>
<td>24.20%</td>
</tr>
<tr>
<td>Czech R <em>(11 mil)</em></td>
<td>10.50%</td>
<td>14.32%</td>
</tr>
<tr>
<td>Georgia <em>(4 mil)</em></td>
<td>NA</td>
<td>6.60%</td>
</tr>
<tr>
<td>Mexico <em>(125mil)</em></td>
<td>40.20%</td>
<td>44.30%</td>
</tr>
<tr>
<td>Poland <em>(40 mil)</em></td>
<td>4.50%</td>
<td>6.78%</td>
</tr>
<tr>
<td>Romania <em>(20mil)</em></td>
<td>6.60%</td>
<td>8.91%</td>
</tr>
<tr>
<td>Russia <em>(145 mil)</em></td>
<td>1.90%</td>
<td>2.50%</td>
</tr>
<tr>
<td>Ukraine <em>(40mil)</em></td>
<td>12.80%</td>
<td>17.36%</td>
</tr>
<tr>
<td>Serbia <em>(7mil)</em></td>
<td>1.10%</td>
<td>1.36%</td>
</tr>
<tr>
<td>South Africa <em>(60mil)</em></td>
<td>10.10%</td>
<td>15.90%</td>
</tr>
</tbody>
</table>
POSITIVITY RATE

•*Johns Hopkins positivity calculation: Number of cases divided by the number of negative tests + number of cases (the number of people tested positive divided by the number of people tested).

•**The WHO has issued guidance stating that governments should see positivity rates below 5% for at least 14 days before relaxing social distancing measures.

THE CDC’S TEST POSITIVITY FORMULA

Number of positive tests in a given period

\[
\frac{\text{positive tests}}{\text{total tests in a given period}} = \frac{\text{positive tests}}{\text{positive tests} + \text{negative tests}}
\]
<table>
<thead>
<tr>
<th></th>
<th>1-Dec-20</th>
<th>7-Dec-20</th>
<th>28-Sep</th>
<th>5-12 Oct</th>
<th>20-Oct-20</th>
<th>27-Oct-20</th>
<th>3-Nov-20</th>
<th>10-Nov-20</th>
<th>17-Nov-20</th>
<th>24-Nov-20</th>
<th>1-Dec-20</th>
<th>7-Dec-20</th>
<th>New cases in 7 days</th>
<th>New cases in 7 days</th>
<th>New cases in 7 days</th>
<th>New cases in 7 days</th>
<th>New cases in 7 days</th>
<th>New cases in 7 days</th>
<th>New cases in 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2% downturn</td>
<td>7.3% downturn</td>
<td>501-1000</td>
<td>501-1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;3000</td>
<td>&gt;3000</td>
<td>&gt;3000</td>
<td>296149</td>
<td>295802</td>
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<td>326281</td>
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<td>548595</td>
<td>684493</td>
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<td></td>
</tr>
<tr>
<td>15.3% downturn</td>
<td>15.9% up</td>
<td>101-500</td>
<td>101-500</td>
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<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;3000</td>
<td>&gt;3000</td>
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<td>1521</td>
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<td>8454</td>
<td>15282</td>
<td>21641</td>
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</tr>
<tr>
<td>20.4%~ up</td>
<td>20.3%~ up</td>
<td>501-1000</td>
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<td>&gt;1000</td>
<td>&gt;3000</td>
<td>&gt;3000</td>
<td>&gt;1000</td>
<td>501-1000</td>
<td>1000-1-3000</td>
<td>1000-1-3000</td>
<td>1000-1-3000</td>
<td>47346</td>
<td>43214</td>
<td>62769</td>
<td>51054</td>
<td>53580</td>
<td>64209</td>
</tr>
<tr>
<td>17% downturn</td>
<td>17.1%~ up</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;3000</td>
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<td>14988</td>
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<td>84305</td>
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</tr>
<tr>
<td>11% up</td>
<td>10% up</td>
<td>101-500</td>
<td>501-1000</td>
<td>501-1000</td>
<td>501-1000</td>
<td>&gt;1000</td>
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<td>12296</td>
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<td>45.1% downturn</td>
<td>44.8% downturn</td>
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<td>500-1-1000</td>
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<td>93617</td>
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</tr>
<tr>
<td>16.5% downturn</td>
<td>17% up</td>
<td>101-500</td>
<td>501-1000</td>
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<tr>
<td>11.6% downturn</td>
<td>12.1% up</td>
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<td>501-1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
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</tr>
<tr>
<td>3% downturn</td>
<td>3.1%~ up</td>
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<td>501-1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;3000</td>
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<td>16.8% downturn</td>
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<td>501-1000</td>
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</tr>
<tr>
<td>10.2% up</td>
<td>11.6% up</td>
<td>101-500</td>
<td>101-500</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;3000</td>
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<td>8082</td>
<td>13681</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>14.5% up</td>
<td>14.6%~ up</td>
<td>101-500</td>
<td>101-500</td>
<td>101-500</td>
<td>101-500</td>
<td>101-500</td>
<td>101-500</td>
<td>100-1-500</td>
<td>100-1-500</td>
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<td>10218</td>
<td>11180</td>
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<td>12115</td>
<td>11206</td>
<td>10454</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The specific risks to COVID-19 risks and issues may include:

1. Delay in site activations due site availability, country restrictions, delays in execution of CTAs or regulatory/EC/IRB approvals.

2. Treatment Impact: subject not able to come to the site
- Safety: labs, vitals, ECG physical exam
- Efficacy: Clinical assessments, PK, Scales
**The specific risks to COVID-19 risks and issues may include:**

3. Recruitment Impact – (i.e. subject’s withdrawing consent, site’s closing or limiting hours for patients to be seen), patients may not be able or willing to visit the site; sites may be asked to stop any study related activity.

4. Travel Restrictions per site and impact on Monitoring activities.

5. Remote Source Data Verification monitoring is not accepted in all countries.

6. IMP shipment to subject’s home- Local courier to be used, but check for any regulatory restrictions and sites willing to use this service; additionally, site pharmacy may not be available to dispense study drug.

7. Patient unable to travel to the site

8. Patient “Door to Door” transport- Local restrictions

9. Source Data Verification backlog
RISK MITIGATION

SUBJECT VISITS: HOME VISITS, PHONE VISITS, VIDEO CALLS

IMP DELIVERY: shipment of IMP by courier to subject’s home, pick up by 3rd party, delivery by site staff

SHIPMENT OF SAMPLES TO THE CENTRAL LAB RISK: Local Lab to be used

SCALE MANAGEMENT: MMSE could not be done over the phone- video call, to be checked with a license holder

ON SITE IMVs: Remote SDV/SDR (video review, phone call, redacted source documents to be sent to a secure mailbox)
Coronavirus Disease 2019 (COVID-19): Risk Assessment and Mitigation Strategies for the Collection of Patient-Reported Outcome Data through Clinical Sites

Version 3.0
June 5, 2020
“If people can’t come in to a clinic or their hospital at the usual, regular intervals...”

- Provide with a medication for a longer period of time
- Shift from the distribution of drugs at the trial site to direct-to-patient courier services,
- Telemedicine: but barriers to incorporate more widely are in large part administrative and bureaucratic, such as cost and reimbursement
SITE CONTINGENCY CHECKLIST OFF-SITE VISITS (HOME VISITS)

Herewith we confirm that the following procedure will be followed in case of home/off-site visits performed during the COVID19 pandemic:

- A decision to perform an off-site visit will be made after a careful consideration of Risk/Benefit for a study subject.
- Investigational staff will ONLY perform a home/off site visit provided that all staff members are healthy and free from any flu-like symptoms.
- Verbal Consent for Home/off site visit will be obtained prior to the home/off site visit and documented in Medical Records as per Instruction on suggested verbiage provided by Sponsor.
- ONLY Authorized Investigational staff will be performing study visits as per Delegation Log.
- Investigational staff will be using the following personal safety equipment: mask, gloves, boots, overall or other as applicable.
- Investigational staff will ensure that the home/off site visit will not impose any unnecessary risk on a trial subject.
- Procedures performed during home/off site visits will be performed according to the directives provided by Sponsor related to COVID-19.
- IP delivered to the subject/caregiver during the home/off site visits will be acknowledged by signature and date and will be a part of subject study medical records. Returned IMP should be immediately acknowledged in IRT Suvoda system.
- All of the above will be documented in subject’s trial medical record/source documents.
Unanticipated Costs

- Costs incurred to arrange for participants to receive care at their local sites or virtually, rather than the study site, for required visits
- Supply chain disruptions
- Personnel disruptions due to illness or closure of facilities
- Additional lab testing (e.g. for COVID-19)
- Increased transportation costs
Conclusion

- Clinical trials are disrupted, especially in the 1\textsuperscript{st} & 2\textsuperscript{nd} quarter of 2020
- Many studies resumed in 3\textsuperscript{rd} quarter, but...
- Guidelines by health authorities do exist (FDA, EMA, National- ALIMS)
COVID19 VACCINE DEVELOPMENT

CRA Academy Conference
14 Dec 2020
Aleksandra Pesic MSc PharmMed
LLM
MRQA
FAcadTM
Guidance documents

• FDA/June 2020- Development and Licensure of Vaccines to Prevent COVID-19
• FDA/Oct 2020- Emergency Use Authorization for Vaccines to Prevent COVID-19
• EMA- Guidance for medicine developers and other stakeholders on COVID-19
• EMA Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines
DRAFT landscape of COVID-19 candidate vaccines –
26 November 2020

49 candidate vaccines in clinical evaluation

<table>
<thead>
<tr>
<th>COVID-19 Vaccine developer/manufacturer</th>
<th>Vaccine platform</th>
<th>Type of candidate vaccine</th>
<th>Number of doses</th>
<th>Timing of doses</th>
<th>Route of Administration</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinovac</td>
<td>Inactivated</td>
<td>Inactivated</td>
<td>2</td>
<td>D.14 days</td>
<td>M</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Wuhan Institute of Biological Products/Sinopharm</td>
<td>Inactivated</td>
<td>Inactivated</td>
<td>2</td>
<td>D.21 days</td>
<td>M</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Beijing Institute of Biological Products/Sinopharm</td>
<td>Inactivated</td>
<td>Inactivated</td>
<td>2</td>
<td>D.21 days</td>
<td>M</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Bharat Biotech</td>
<td>Inactivated</td>
<td>Whole-Yellow Inactivated</td>
<td>2</td>
<td>D.18 days</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>University of Oxford/AstraZeneca</td>
<td>Non-Repeating</td>
<td>ChAdOx1-S</td>
<td>2</td>
<td>D.28 days</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>CanSino Biological Inc/Beijing Institute of Biotechnology</td>
<td>Non-Repeating</td>
<td>adenovirus type 5 vector</td>
<td>2</td>
<td></td>
<td>M</td>
<td></td>
</tr>
</tbody>
</table>

Source: WHO, 2020 Dec
Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee  Updated Dec. 13, 2020

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>LIMITED</th>
<th>APPROVED</th>
<th>ABANDONED</th>
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</thead>
<tbody>
<tr>
<td>40</td>
<td>17</td>
<td>15</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Vaccines testing safety and dosage  Vaccines in expanded safety trials  Vaccines in large-scale efficacy tests  Vaccines in early or limited use  Vaccines approved for full use  Vaccines abandoned after trials
Researchers are currently testing **58** vaccines in clinical trials on humans, and **15** have reached the final stages of testing. At least 85 preclinical vaccines are under active investigation in animals.
Dec. 10  A vaccine from Australia’s **University of Queensland** is abandoned.

**Leading vaccines**

<table>
<thead>
<tr>
<th>Developer</th>
<th>Type</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech</td>
<td>mRNA</td>
<td>2, 3</td>
<td>Approved in Canada and other countries. Emergency use in U.S. and other countries.</td>
</tr>
<tr>
<td>Moderna</td>
<td>mRNA</td>
<td>3</td>
<td>Under F.D.A. review.</td>
</tr>
<tr>
<td>CanSino</td>
<td>Adenovirus</td>
<td>3</td>
<td>Limited use in China.</td>
</tr>
<tr>
<td>Gamaleya</td>
<td>Adenovirus</td>
<td>3</td>
<td>Early use in Russia.</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>Adenovirus</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Oxford-AstraZeneca</td>
<td>Adenovirus</td>
<td>2, 3</td>
<td></td>
</tr>
<tr>
<td>Novavax</td>
<td>Protein</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vector Institute</td>
<td>Protein</td>
<td>1, 2</td>
<td>Early use in Russia.</td>
</tr>
<tr>
<td>Sinopharm-Beijing</td>
<td>Inactivated</td>
<td>3</td>
<td>Approved in U.A.E.</td>
</tr>
<tr>
<td>Sinopharm-Wuhan</td>
<td>Inactivated</td>
<td>3</td>
<td>Limited use in U.A.E.</td>
</tr>
<tr>
<td>Sinovac</td>
<td>Inactivated</td>
<td>3</td>
<td>Limited use in China.</td>
</tr>
</tbody>
</table>

**Below is a list of all vaccines that have reached trials in humans.**

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Pfizer/ BioNTech

On Dec. 8 the FDA released their independent analysis of the clinical trials. They determined that the vaccine has an efficacy rate of 95 percent.
In an unprecedented move in the coronavirus vaccine field, AstraZeneca announced on Dec. 11 that it would collaborate with the Russian creators of the Sputnik V vaccine, which is also made from adenoviruses. The two teams will combine their vaccines to see if they deliver stronger protection together than either does on its own. The trial is expected to start by the end of 2020.
Important consideration

• RICH COUNTRIES PRE_ORDERING HUGE QUANTITIES OF VACCINE DOSES
• UNFAIR DISTRIBUTION