Issues with COVID-19 Vaccines in Advanced Stage Clinical Trials in India

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ISSUES WITH COVID-19 VACCINES IN ADVANCED STAGE CLINICAL TRIALS IN INDIA

11 November 2020

Webinar 3: Regulating COVID-19 Vaccine Clinical Trials

Malini Aisola and Siddhartha Das

Transparency & Need for Public Scrutiny

- Real-time availability of information regarding vaccine development
- Publicly available information is little and scattered across sources
  - news reports, replies to the Parliament, press releases, information shared during media briefings, SEC minutes
- Opacity and even misinformation
- Focus on 4 vaccines candidates which are in most advanced stages & being actively tested and developed in India

Regulatory Process & Government Involvement in Vaccine Development

- Minimal details in SEC minutes
- Members of SEC Experts not being shared
- Regulatory Guidelines for Vaccine Development, CDSCO (21 September 2020)
- Restricted Emergency Use
- CTRI not up to date with protocol amendments
- Terms of engagement of Government institutions involved in facilitating trials (ICMR, ICMR institutions, BIRAC)

BBV152 (COVAXIN, Bharat Biotech in collaboration with ICMR)

- Inactivated whole virion candidate vaccine (BBV152) developed by Bharat Biotech using the virus isolate (NIV-2020-770) provided by ICMR-NIV Pune. Characterisation, safety & tolerability studies in small animals were undertaken by NIV. **Agreement between ICMR & Bharat Biotech must be made public given extensive and continuing role of govt in development**

- Preclinical & animal challenge studies published. But detailed clinical trial protocols for Phase I/II clinical trials & now Phase III not available to public

Adaptive, seamless Phase I/II trial

- Phase I: 4 arms of 3 vaccine candidates with differences in antigen concentrations (3µg and 6µg), with two different adjuvants with placebo (375 participants in 4:1 ratio)
  - Safety (primary) and immunogenicity (secondary)
  - On**e serious adverse event** was reported where the subject was hospitalized with viral pneumonitis and was said to have recovered. Not come to light in public domain and ruling of DSMB
- Protocol changed for Phase II:
  - Dosing regimen modified from 14 days to 28 days
  - Number of participants reduced from 750 to 380 due to dropping of placebo arm
  - Comparison of BBV152-A and BBV152-B candidates
  - Reason for amending protocol to expedite the phase 2 trial

“Protocols for adaptive trials should include pre-specified criteria for adding or removing vaccine candidates or dosing regimens and protocols for seamless trials should include pre-specified criteria (e.g., safety and immunogenicity data) for advancing from one phase of the study to the next.”

Phase III

- Phase III protocol:
  - “BBV-152B formulation is chosen based on the Phase 1 interim report which shows that the immunogenicity of BBV-152B is higher compared to BBV-152A although the difference was not statistically different.”
- Raises questions about Phase II
- How are the data being analyzed

SII-ChAdOx1 nCoV-19 (Oxford vaccine manufactured by Serum Institute of India)

- ChAdOx1-S, version of non-replicating viral vector vaccine developed by University of Oxford/AstraZeneca manufactured by SII.
- Oxford/AstaZeneca vaccine undergoing phase III clinical trials abroad.
- Permission to conduct Phase II/III 'bridging' studies in India taking place on COVISHIELD (SII)
- Chief differences between Oxford/AstraZeneca vaccine and COVISHIELD? Approval for Phase II/III was on basis of published data of Oxford/AstraZeneca vaccine

- Bridging study – understood as broadly supplementary study performed to allow extrapolation of foreign clinical data to local context (address ethnic diversity, appropriateness of dosing etc.) Rationale should be made available for granting permission for COVISHIELD (which does not appear to have pre-clinical and Phase I data)

- COVISHIELD compared with Oxford/AstraZeneca in Phase II – non-inferiority study? Results not known

- Total sample size for Phase II/III is 1600 (rationale for sample size & data analysis)
  - Phase II: 400 (300 will get COVISHIELD and 100 to get Oxford)
  - Phase III: 1200 (800 to get COVISHIELD and 400 to get placebo)

- Tech transfer agreement needs to be shared (eg of Fiocruz, Brazil)
- Global supply arrangements?

ZyCoV-D (Zydus Cadila/Cadila Healthcare)

- DNA vaccine (ZyCov-D) developed by Cadila Healthcare Ltd.
- Pre- clinical toxicity studies were conducted in small animals: mice, rats, rabbits and guinea pigs. ICMR partnered for conduct of parallel pre-clinical studies in rhesus macaques. No data or results available
- No detailed clinical trial protocol for Phase I/II or information about interim results
- Gaps in recording permissions by SEC in minutes
- Serious concerns about conflicts of interest:
  - 3/9 sites are operated by Zydus Cadila (GCS Medical College, Zydus Hospitals and Healthcare Research Pvt Ltd., and Zydus Research Centre)

Sputnik V (Russian Direct Investment Fund, Dr. Reddy's)

- Dr Reddy's Labs has received approval for adaptive Phase II/III trials
- Non-randomized, open label Phase I/II trials in Russia received heavy criticism from international experts. Did SEC review the concerns prior togiving permission?
- Detailed protocols for Indian trials not available
- Rationale for sample size:
  - 100 subjects in Phase II (to begin soon)

Summary of general issues with vaccine trials

- Data & results of pre-clinical, completed animal challenge studies, interim analysis of clinical trial phases not being published (including for some in advanced state of trial process)
- Detailed protocols for each phase of clinical trials should be available in public domain while candidate is undergoing clinical trials
- Conflicts of interest – lack of independence of clinical trial sites, lab conducting data assessment & adjudication
- Membership of Data Monitoring Safety Boards (should be independent of influence of sponsor)
- Lack of justification for small sample sizes & duration of follow up
- No clarity on mechanisms in place to address potential liability and compensation to individuals in the event of unexpected adverse events