WHO perspective on Human Challenge Trials in Vaccine Development and Licensing

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WHO standards and other services to facilitate regulatory oversight of vaccines in developing countries

- Facilitating registration (regulatory standards – Guidelines, Recommendations and measurement standards)
- Prequalification and emergency assessment procedures
- Collaborative procedures and joint assessments
- Vaccine safety initiatives
WHO norms and standards for biologicals

Global written standards

Total 93 docs (Recommendations/ Guidelines)

- General docs that apply to vaccines & BTP: 10
- General documents that apply to all vaccines: 12
- Vaccine specific: 63
- BTP specific: 8

Scientific evidence

1) Standardization of assays
2) Further development and refinement of QC tests
3) Scientific basis for setting specifications

Measurement standards: essential elements for development, licensing and lot release

www.who.int/biologicals
1) Provide key principles for evaluation of biologicals as a basis for setting national requirements;

2) Leave space to NRAs to formulate additional/ more specific requirements;

3) Living documents that will be developed further in line with the progress in scientific knowledge and experience

4) Assist with the implementation of the guidelines into regulatory and manufacturers practices through:
   - Global, regional and national workshops involving regulators, manufacturers and other relevant experts
   - Trainings, advisory groups

5) Consider guidance issued by other bodies – intention to complement them, not to create a conflict.
Revised Guidelines on clinical evaluation of vaccines (TRS 1004, annex 9)

- Introduction
- Scope
- Glossary
- Vaccine Clinical Development Programs
- Immunogenicity
- Efficacy and effectiveness
- Safety
- Authors and Acknowledgements
- References
Not all diseases are suitable for "challenge-protection studies"

Regulatory framework

Quality and safety of pathogenic challenge strain

GCP

Various purposes for HCT in vaccine development:

- Often a type of efficacy indicating study
- Better understanding of pathogenesis of, and immunity to, the organism to guide decisions on immune responses that a vaccine might need to elicit in order to protect against disease
Various purposes for HCT in vaccine development (cont.):

- Proof of concept
- to identify potential ICP and other elements which will be then validated in an efficacy study
- Down or up selection of vaccine candidates
- Provision of a basis for licensure (rare case)
- Post-licensure studies to explore waning immunity, need for booster or duration of protection
- other
Study design of human challenge trials:

- the purpose of the study is influencing study design
- Different models according to the purposes and study design
- Challenge organism
- Usefulness for positive or negative prediction

Operational aspects

- Relevant committees
- Qualified investigators
- Protocol
- Special facilities to prevent spread of challenge organism
- High level of control
Some key ethical considerations:

- Minimize risk to subjects and maximize benefits
- Review by an independent ethics committee
- Informed consent
- Other issues and references to more detailed sources of information
Quality and safety of challenge strains

- Strain characterization:
  - Details like patient isolate, passage history etc
  - Phenotype
  - Genotype
- Purity
- Potency
- Stability
- Safety

16/11/2018 WHO Guidelines
Challenges identified by DCVRN

- Outcomes of survey of DCVRN representatives
  - HCT have not been conducted in their countries
  - WHO guidelines for regulators recognized as a standard
  - Need for further assistance from WHO

- The following concerns were noted: safety of participants, risks of spreading challenge organism to the environment, availability of suitable care for (infected) participants, coercive (excessive) payments for participation, public perceptions of unsafe or unethical conduct

- The need for Phase-3 studies to confirm HCT results
Challenges in the international context

- Lack of expertise and experience for reviewing HCT

- Responsibilities for oversight of HCT are not defined at the national level:
  - Unclear role of various expert groups/committees
  - Lack of understanding role of regulators in HCT

- Infrastructure, CT sites, inspections

- Lack of trust in "experimental studies"

- Risk benefit analysis, RMP

- Lack of publicly available data due to lack of CT registration but also selected data for publication
Way forward

- Implementation workshops:
  - At the global and regional level are very much needed
  - Case studies and review of examples
  - Topics of particular interest:
    - Immune response to vaccines
    - Quality of challenge strains
    - Design of HCT
    - Data from HCT in the context of licensing
    - HCT as part of development of vaccines for PHE
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Thank you

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