Clinical Evaluation
Phases 1,2,3,4

Matt Laurens, MD MPH
Associate Professor of Pediatrics
Center for Vaccine Development
Institute for Global Health
University of Maryland School of Medicine
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Objectives

- List five major parties involved in performing clinical trials
- List three requirements that all vaccines must have documented prior to licensure
- State the number of volunteers and objective of each phase (1-4) of vaccine trials
- Appreciate the complexity and cost of performing a clinical trial
Definitions

Clinical Trial - not just any trial involving humans, but trial to evaluate the safety and efficacy of medications or medical devices

Drug - a substance used to treat an illness, relieve a symptom, or modify a chemical process in the body for a specific purpose

Biological - pertaining to biology or to life and living things

Vaccine - antigenic material administered to stimulate an immune response to achieve a desired effect

Efficacy - capacity to produce a desired effect in a clinical trial

Effectiveness - capacity to produce a desired effect in the real world
Clinical Trial Phases

• Phase 1: “N” in tens; safety
• Phase 2: “N” in hundreds; safety & immunogenicity
• Phase 3: “N” in thousands; safety & efficacy
• Phase 4: “N” in hundreds of thousands and millions post-licensure; safety & other
Who are the major parties?

• All are engaged in the research
• Sponsor
• Investigator
• Regulatory Agency
  • Food and Drug Administration (FDA)
  • European Medicines Agency (EMEA)
• Investigational Review Board
• Volunteer
Considerations of Sponsor

- Problem
- Vaccine part of solution
- Vaccine design plausible
- Expect vaccine safe
- Expect vaccine immunogenic
- Expect vaccine works
- Formulation practical
- Manufacture possible
- Market receptive

Estimated distribution of rotavirus deaths
Responsibilities of Sponsor

- FDA compliance
- Protocol generation
- Investigational New Drug (IND) application and maintenance
- Investigator selection
- Investigator brochure
- Monitoring
  - Safety
  - Data
- FDA communication
Protocol

- Purpose and objectives
- Background
- Information on protective immunity
- Number of participants
- Eligibility criteria
- Trial design
- Dose and method of administration
- Outcomes
- Statistical tests
- Follow-up and risk reduction
Consent

- Informed
- It’s a process
- Non-coercive
- Clear and simple (7th grade)
- Written
- Purpose, procedure, experimental nature
- Discomforts and risks
- Alternatives
- Contact information
- Freedom to withdraw
Records

- Uniform across sites
- Case Report Forms (CRFs)
- Source documents
- Privacy
- Quality Management Plan
- Data Management Plan
- Vaccine accountability
- Vaccine storage
- Specimen shipping
- SOPs and MOPs
Safety Monitoring

- Independent Safety Monitor (ISM)
- Safety Monitoring Committee (SMC)
- Data Safety Monitoring Board (DSMB)

- Adverse Events (AEs)
- Serious Adverse Events (SAEs)
Data Monitoring

• Audit trial documents or facilities
• Meet investigators before trial
• Provide feedback during trial
• Review at trial termination
Considerations of Investigators

• Assess if ethical to proceed
  – Safe?
    • more info in phase 3 than 1
    • Relative safety
  – Likely to be efficacious?
  – Would give to self or family?

• Know the study
  – Protocol
  – ICF
  – IB
Responsibilities of Investigators

- IRB approval
- IRB communication
- Record keeping
- Report AEs and SAEs
- Perform trial: vaccinate and follow
- Proof of Good Clinical Practice (GCP)
Considerations of Regulatory Agency

GXP: manufacturing, clinical, laboratory, statistical?

A vaccine must have documented evidence that it is:

- Safe
- Immunogenic
- Efficacious

Also weigh in on:

- Product Development Plan
- Clinical Development Plan
- Post-licensure
Sample Clinical Development Plan

- PG545 development plan, IND strategy: H2 2008
- Small molecule heparanase inhibitor discovery program: H2 2008
- PI-88 Melanoma trial: H1 2009
- PG11047 Phase I results: H2 2009
- Epigenetic platform first candidate clinical trial start: H2 2009
- Anti-proliferation platform clinical development expansion: H2 2009 and on-going
- Epigenetics platform lead candidates selection and progression: H2 2009 and on-going
- PG11047 Phase II commencement: H1 2010
- Epigenetics Phase II commencement: H1 2011
- PI-88 Phase III trial results: 2011
- PI-88 Market launch: 2011 / 2012
- New Technology in-licensing: As occur
- M&A growth opportunities: As occur
Fig. 1. The timeline for development of RTS,S through 2015 spans 30 years. The effort by GlaxoSmithKline (GSK) can be traced back to a collaboration with Walter Reed Army Institute of Research (WRAIR) initiated in 1984.

David C. Kaslow, Sophie Biernaux

**RTS,S: Toward a first landmark on the Malaria Vaccine Technology Roadmap**

Vaccine, Volume 33, Issue 52, 2015, 7425–7432

http://dx.doi.org/10.1016/j.vaccine.2015.09.061
Responsibility of regulatory agency

- Protect Public Health
  - Assure safety and efficacy
  - Drugs, biologicals, medical devices, and food
Responsibility of regulatory agency

- Code of Federal Regulations (CFR)
  - 45 CFR part 46 - DHHS protection of human subjects
  - 21 CFR parts
    - Part 11 - Electronic Records; Electronic Signatures
    - Part 50 - Protection of Human Subjects
    - Part 54 - Financial Disclosure by Clinical Investigators
    - Part 56 - Institutional Review Boards
    - Part 312 - Investigational New Drug Application (IND)
    - Part 314 - Applications for New Drug (NDA)
    - Part 600 - Biological Products
    - Part 812 - Investigational Device Exemptions
IND

– 1572: investigator agreement to comply
– Investigator CVs
– Chemistry, manufacturing, control
– Pharmacology and toxicology
– Previous human experience
– Updates while “under IND”
– Reports to all “under IND”
Considerations of the IRB

- Is the research feasible?
- Does the investigator have adequate expertise?
- Is the study scientifically sound?
- Inclusion/exclusion justifiable?
- Is consent obtained?
- Is the risk appropriate and minimized?
Responsibilities of the IRB

• Review and approve research
• At least 5 people
• At least 1 non-scientist
• At least 1 not affiliated with the institution
Considerations of volunteer

• Is the vaccine safe?
  – To me
  – To others

• Will there be any benefit to me?
  – Medical
  – Financial - should not be coercive
Responsibilities of volunteer

- Protocol specific
- Honesty
- Follow-up visits
Resources Required

• Clinic and office space (sometimes inpatient)
• Vaccine and specimen storage area
• Emergency equipment
• Experts
  – Clinical team
  – Vaccines
  – Data management
  – Regulatory affairs and clinical monitoring
  – Microbiology lab
  – Immunology lab
Phase I

- First use in humans
- Few volunteers (10’s)
- Healthy adults
- Purpose = safety
- Risk to benefit is high
- Screening very strict
- Monitoring is frequent, intense
Phase I Vaccine Trials at CVD

- Anthrax
- Avian influenza
- Malaria
- Shigella

- Intranasal Measles
- Ebola
- Zika
Phase I *Shigella*

- First use in humans CVD 1208S
- 13 volunteers (10 vaccine 3 placebo double-blind)
- Very healthy adults: strict eligibility
- Purpose = safety and dose range $10^7, 10^8, 10^9, 10^{10}$
- Risk to benefit is high
- Inpatient with 6 months of follow-up
Objectives

• Primary
  – Safety - clinical
  – Immunogenicity

• Secondary
  – Dose Response
  – Extent and duration of shedding - micro
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<th>Vaccine</th>
<th>Admit&lt;sup&gt;k&lt;/sup&gt;</th>
<th>Antibiotic</th>
<th>Fluid Culture</th>
<th>Culture</th>
<th>IgA&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Lactoferrin</th>
<th>Serology&lt;sup&gt;d,j&lt;/sup&gt; (15 mL)</th>
<th>ASC&lt;sup&gt;e&lt;/sup&gt; (35 mL)</th>
<th>ASC homing&lt;sup&gt;f&lt;/sup&gt; (50 mL)</th>
<th>WBC w/diff&lt;sup&gt;g&lt;/sup&gt; (5 mL)</th>
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<td>Telephone to assess occurrence of fever, Reiters symptoms, persistent/recurrent diarrhea, hospitalization, medications, medical visits, serious medical concerns</td>
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Phase I

What do you know after your phase I trial?

• Are there any common serious adverse events that preclude further development?
• Are the limited immune response data enough to encourage further trials?
Safety Monitoring *Shigella*

- SMC
  - Local Infectious Disease expert
  - NIH representative
  - Expert at another university
- Met before each dose escalation
- Reviewed data and deliberated
- Approved escalations
Phase II

- May be multiple studies
- Each has specific endpoints
- Larger numbers of volunteers (50-100’s)
- Examples of questions: dose, formulation, regimen, target groups
- Accumulation of safety data
Phase II *Shigella*

- 60 volunteers (50 vaccine and 10 placebo)
- Main question of timing of dosing: 1, 2, and 3mo
- Eligibility minus HLAB27
- Purpose immunogenicity after 3 doses $10^9$
- Risk to benefit is slightly lower
- Outpatient and follow 6 months
Phase IIb

• Special type of phase II study
• Human challenge study
• Efficacy tested using small numbers of volunteers
Phase IIb *Shigella*

- Inpatient
- Challenge with wildtype *Shigella*
- 15 vaccine recipients, 15 placebo
- Observe 2 weeks inpatient
- 42 days outpatient
- Phone call 90 days
Phase II

What do you know after your phase II trial?

• Continued safety and acceptability
• Immune response of formulation and dose regimen
• Shedding
• Efficacy in controlled challenge setting
Phase III Trials

• Typically the pivotal trial for licensure
  – Data supports recommended uses
• Large sample sizes
• Most common objective
  – Efficacy
• Other objectives
  – Immune correlate of protection
  – Safety: less common events
Phase III Trials

• Design
  – Typically randomized controlled trial
  – Comparator: placebo or other vaccine

• Primary outcomes
  – Incidence of disease in both groups
  – Incidence of adverse events

• Vaccine Efficacy
  – \([\frac{\text{Inc}_{\text{control}} - \text{Inc}_{\text{vaccine}}}{\text{Inc}_{\text{control}}}] \times 100\%\)
Phase III Trials

• Efficacy issues
  – Subgroup efficacy importance
    • Gender, age, etc.
  – Efficacy of different disease outcomes
    • Culture-proven, probable, hospitalized, etc.
Phase III Trials

• Sample size
  – Must know control incidence and desired efficacy to determine sample size with given power
  – Build in
    • Drop out rate
    • Deviations from protocol

• Vaccine
  – Final formulation
Phase III Trials

• Eligibility criteria require balance
  – If too strict, limited indication
  – If too loose, jeopardize licensure

• Outcome measure
  – Strict definition for disease of interest
  – Capacity to capture all cases with equal probability
Trial of Rotavirus Vaccine in Africa

A double-blind, randomized, controlled Phase III study to assess the efficacy of 3 doses of Rotateq to prevent severe rotavirus gastroenteritis in African infants.
Phase III study

• We conducted a large double-blind, placebo-controlled, randomized clinical trial to evaluate the efficacy of three doses of pentavalent rotavirus vaccine (PRV), RotaTeq® (Merck & Co., Inc., Whitehouse Station, NJ)
  – Primary objective: Efficacy against severe RVGE, regardless of rotavirus serotype
  – Secondary objectives: Efficacy against (1) RVGE of any severity, (2) severe RVGE by individual rotavirus serotypes, (3) severe gastroenteritis (GE) of any etiology, and (4) severe RVGE using different severity score cut-points as measured with the Vesikari (VSS) and Clark (CSS) scoring systems
Study Design

Pivotal Phase III efficacy study
• Multi-center, double blind, controlled, randomized
• Enrollment: 4568 infants
• Study duration for each subject: 20 months
• Two study groups:
  • Rotateq
  • Placebo
• Catchment design for all cases of gastroenteritis
• Collect clinical severity information to classify cases
• Compare incidence in vaccine vs placebo
## Efficacy

<table>
<thead>
<tr>
<th>RVGE</th>
<th>Year 1 Efficacy (95% CI)</th>
<th>Year 2 Efficacy (95% CI)</th>
<th>Total Follow-up Period Efficacy (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Severe*</td>
<td>64.2% (40.2, 79.4)</td>
<td>19.6% (&lt;0.0, 44.4)</td>
<td>39.3% (19.1, 54.7)</td>
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<tr>
<td>Any severity</td>
<td>49.2% (29.9, 63.6)</td>
<td>19.0% (&lt;0.0, 35.4)</td>
<td>30.5% (16.7, 42.2)</td>
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*Vesikari score of $\geq 11$
Phase III

What do you know after your phase III trial?

• Continued safety and acceptability
• Does the vaccine work in natural setting
• What immune response is protective
Phase IV Trials

• Post-licensure
• Some reasons for Phase IV trials
  – Real world issues - effectiveness
  – Expanded spectrum of recipients
  – Vaccine coverage
  – Optimize schedule or dose
  – Rare adverse event detection
  – Administration with other vaccines
  – Indirect protection
  – Ecology, e.g., serotype replacement
Introduction of Hib vaccine in Mali

75% - 81% vaccine effectiveness
Vaccine coverage

B

% with PRP antibody concentration

Unk doses (n=5)
1 dose (n=7)
2 doses (n=22)
3 doses (n=146)
Helpful links:

- http://www.hhs.gov/ohrp/
- http://www.fda.gov/
- http://www.umaryland.edu/hrp/
- http://www.ich.org
- http://www.ecfr.gov
- www.clinicaltrials.gov
- https://www.cdc.gov/vaccines/basics/test-approve.html
Thank You!