Vaccines Clinical Trials: Planning and Executing Clinical Trials

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Topics to cover before lunch

- Determining end points for clinical trials
- Hiring your own clinical research team or to outsource to CROs?
- How to select the right CROs
- Defining the roles of sponsor vs CROs in managing the trial
- How to select and engage site investigators (site feasibility assessment)
- How to prepare a budget for clinical trials (cost involved in a trial and its breakdown)?
- Clinical trial agreement
- Issues with trial sponsorship
- (who should be the trial sponsor)
- Regulatory and IRB approval
About the Trainer

- Physician Investigator for Rotavirus vaccine phase 2 and 3 trials
- Director Clinical Research GSK Vaccine conducted rotavirus, influenza, pandemic influenza, childhood pneumococcal, MMRV, HPV vaccines clinical trials
- Vice-President Emergent Biosolutions involved in influenza, TB, anthrax vaccine development
- CEO of Singapore Clinical Research Institute, sponsor for MUC-1 therapeutic cancer vaccine
Overview of Clinical Trials Operations
4 phases in the development of a Vaccine

**Preclinical**
- Research

**Phase I - II**
- Early Development
  - First administration to man

**Phase III**
- Late development
  - Decision of feasibility investment
  - Start of pivotal efficacy studies
  - Results of pivotal studies available

**Phase IV**
- Registration & launch
  - Agreement on detailed profile of the product and position on the market
  - Registration and price request
  - Launch

**Post marketing surveillance**
Terms used for Vaccine Trial

- **Safety**: Is the vaccine safe?
- **Reactogenicity**: Reaction caused by the vaccine (e.g., fever, rash, swelling)
- **Immunogenicity**: Is the antibodies produced high?
- **Efficacy**: Does the vaccine able to protect you against the infection

Note: immunogenicity is not equals to efficacy
What are the end points for Vaccine clinical Trials? Using HPV vaccines as an example

- **Eg HPV causing cervical cancer:**
  - Exposure to HPV infection
  - HPV infection causing carcinoma-in-situ
  - Carcinoma-in-situ developed into cervical cancer

- **Generally Regulatory Authority requires Efficacy end points:**
  - Eg HPV vaccine trials end point should be prevention of cervical cancer (ie. xx cases in vaccinated group with cervical cancer vs yy cases in the placebo group)
  - Sorrogate end points could be development of carcinoma in situ
  - Other end points could be prevention of HPV infection

- **Immuno surrogate end points : Antibodies against HPV infection**
What are the end points for Vaccine clinical Trials?
Using Rotavirus vaccine as an example

- Eg Rotavirus infection causing Rotavirus acute gastroenteritis
  - Exposure to Rotavirus infection
  - Infection causes viral gastroenteritis
  - There are other bacteria causes gastroenteritis not related to Rotavirus

- Generally Regulatory Authority requires Efficacy end points:
  - Efficacy end point is prevention of RV gastroenteritis
  - All subjects which are admitted to the hospital for gastroenteritis needs to be tested for RV and other types of infection, only analyse cases due to RV gastroenteritis

- Immuno surrogate end points : Antibodies against RV infection
Safety end points for Vaccine clinical Trials?

- If the safety event is serious and rare, it would required a large sample size
  - Eg Intussusception in rotavirus vaccine

- If the safety event is not serious or due to urgent need in licensing a new vaccine (eg pandemic vaccine)
  - Smaller sample size is acceptable
  - Needs to conduct post-marketing surveillance to pick up these safety events
Stakeholders in clinical trials

- **Sponsors** (Pharmaceutical company, NGOs)
- **Investigators** (Hospital doctor)
- **Subjects** (Patients)
Sponsor’s Responsibilities (GCP)

- QA & QC
- CRO
- Medical Expertise
- Trial Design
- Trial Mgt, Data Handling, & Record Keeping
- Investigator Selection
- Allocation of Responsibilities
- Compensation to Subjects and Investigators
- Financing
- Notification/Submission to RA
- Confirmation of Review by IRB
- Safety Reporting
- Information on IP
- Manufacturing, Packaging, Labelling, and Coding IP
- Supplying & Handling IP
- Record Access
- Safety Information
- ADR Reporting
- Monitoring
- Audit
- Noncompliance
- Premature Termination or Suspension of a Trial
- Clinical Trial/Study Reports
- Multicentre Trials
Relationship between the parties

- Sponsors
- Subjects
- Investigators
- Ethics Board
TRADITIONAL PHARMA SPONSORED STUDIES FUNDING MODEL

Pharmaceutical company

Hospital and Investigators

Pharmaceutical company

Commercial CRO

Hospital and Investigators
EXAMPLE OF A PARTNERSHIP CO-FUNDING FOR INVESTIGATOR-INITIATED STUDY IN SINGAPORE INVOLVING PARTNERSHIP WITH ARO
# Overview of a Clinical Trials Activities

<table>
<thead>
<tr>
<th>Pre-grant activities</th>
<th>Supportive Study activities</th>
<th>Post-study activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protocol design</td>
<td>• QA &amp; compliance</td>
<td>• Manuscripts writing</td>
</tr>
<tr>
<td>• Budgeting</td>
<td>• Project management</td>
<td>• Secondary analysis</td>
</tr>
<tr>
<td>• Site feasibility</td>
<td>• Software licenses (Oracle, SAS)</td>
<td>• Re-check data</td>
</tr>
<tr>
<td>• Consultations on trial operations</td>
<td></td>
<td>• Regulatory submission and approval</td>
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<tr>
<td>• Project management (e.g. with external funder)</td>
<td></td>
<td>• Product launch</td>
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**Main study activities**
- Project management
- Monitoring
- Data management
- Biostatistics
- Use of database (Oracle or REDCap)

**Sponsor has Clinical development plan**
- Grant approved
- Study starts
- Study ends
- Data cleaned
- Launch of product
Partnership between CRO and Hospital in conducting a clinical trial

**CRO responsibilities**
- Sponsor
- Protocol design
- Sample size calculation
- Overall project management
- Preparation of research database
- Monitoring of data entry
- Management of data investigations
- Monitoring of safety event
- Analysis of data
- Publication

*Staff involved:*
- Epidemiologists,
- Biostatisticians
- Project Manager
- Clinical Research Associates
- Research Informatics
- Data Management

**Site responsibilities**
- Site feasibility
- Protocol submission to IRB/HSA
- Screening of suitable patient
- Recruitment of patient
- Consent taking
- Examination of patients
- Conduct Lab/imaging tests
- Investigational drug administration
- Follow-up of patient
- Data entry
- Safety reporting to IRB and HSA
- Site study closure

*Staff involved:*
- Investigators (doctors)
- Clinical Research Coordinators
- Research assistants
Clinical Research Associate (CRA) Vs Clinical Research Coordinators (CRC)

- CRC works at the hospital/site. They are like “research nurses” and reports to the Investigator. Many of their roles are similar to nurses which are recruiting patients, explaining the consent (but the consent has to be taken ultimately by Investigator), takes blood, give investigational vaccine and arrange next appointment.

- CRA works for the pharma companies or CROs. The are like “study auditor”. They goes to the hospital to check if the study is conducted correctly, data entered accurately, the patients recruited follow the protocol etc.
Clinical Trials in a Nut Shell

- Approved Protocol
- Investigator selection
- Approval Process
- Patient recruitment and participation
- Data entered and reviewed
- Data filed and registration obtained
- Presentation and publication of report
- Statistical Analysis

Scientific Collaboration for Research Innovation
How to successfully conducted a Clinical Trial

- Clinical Project Manager is the overall “Project Manager” of the study
- Need to be aware of the gaps in responsibilities because of multiple stakeholders providing support
- To work with all partners to include their budgets for grant submission
- To keep all the stakeholders updated regularly on the trial status
- To see the site investigator as a partner and not a service provider
- Running the trials efficiency without compromising basic quality
Selecting a Contract Research Organisation (CRO)
CRO Industry

- CRO industry is booming, taking a larger piece of worldwide R&D expenditures -- $14 billion by CROs in 2012
- The industry is fragmented with over 1000 CROs, including:
  - A small group of large, full service multinational entities representing 50% of worldwide CRO revenue
  - The remaining CROs being small to mid-sized entities providing a more limited menu of services, including:
    - Niche CROs providing services in a limited geographic region or on a specific disease state or therapeutic model
Advantages of using CROs

- **Reduce:**
  - Time needed to develop and commercialize a new drug
  - Sponsor’s fixed costs associated with personnel, equipment and facilities needed for its R&D function

- **Provide:**
  - Ready access to needed expertise and/or technology
  - Greater access to potential investigators
  - Knowledge of regulatory climate in foreign markets
Potential Risks of using CROs

- Risks generally associated with reduced control of the clinical trial process by the Sponsor
- Risks include:
  - Delays in completion of studies
  - Lost or poor data
  - Regulatory infractions produce indirect consequences
    - FDA regulations/GCPs
    - HIPAA
    - Fraud and Abuse
  - Private litigation exposure
Preliminary Studies/Feasibility studies
Types of preliminary studies

Preliminary studies you have conducted

- Proof-of-concept
- Proof-of-value
- Pre-clinical
- Pilot / Feasibility study
- Review of historical data
Preliminary studies - usefulness

For team to **assess**

- working concept / principle
- safety / acceptability
- organizational / logistics
- effect size / random error due to measurement, study population

Demonstrate to funders **credibility** of

- proposal, protocol, team, setting

A hospital-based surveillance of rotavirus gastroenteritis in children <5 years of age in Singapore.

Phua KB1, Tee N, Tan N, Ramakrishnan G, Teoh YL, Bock H, Liu Y.

Author information

Abstract

BACKGROUND:
In Singapore, 2 rotavirus vaccines were licensed in October 2005 and July 2007, respectively, for vaccinating infants aged ≥ 6 weeks against rotavirus gastroenteritis. These vaccines are optional and are not included in the National Childhood Immunization Program. This study aimed to determine the incidence of rotavirus gastroenteritis-associated hospitalizations among children <5 years of age.

METHODS:
Children <5 years, who were hospitalized for acute gastroenteritis, were enrolled between September 2005 and April 2008. Stool samples were tested for the presence and serotyping of rotavirus. Incidence and proportion of gastroenteritis and rotavirus gastroenteritis cases were calculated with 95% confidence intervals.

RESULTS:
Among 1976 children included in the according-to-protocol cohort, 781 were rotavirus positive with a median age of 24 months (range: 0-59 months). The overall incidence of rotavirus gastroenteritis hospitalizations during the entire study period in children <5 years of age was 4.6 (95% confidence interval: 4.3-4.9) per 1000 person-years with the highest number of cases observed in children 13-24 months of age (26.5%). G1P[8] (18.3%) and G9P[8] (9.9%) were the most common rotavirus types. Rotavirus gastroenteritis hospitalizations peaked between January and March.

CONCLUSION:
Rotavirus infection was the primary cause of acute gastroenteritis hospitalizations among children <5 years of age, constituting nearly one-third of gastroenteritis hospitalizations in Singapore. The predominant strain observed in Singapore was G1P[8]. Results of this study suggest the need for implementation of rotavirus vaccination into National Childhood Immunization Program in Singapore.
Reviewers

Over worked
Under paid
Pressed for time

Experts in your area
Experts not in your area
Statisticians
Group Discussion 1

- Group the participants into 2 groups

- Qs: Do you engage external CROs to conduct clinical trials or hire in house staff? (please discuss pros and cons)
Group Discussion 1 (answers)

- **Advantage of outsourcing:**
  - External expertise
  - Able to handle many countries trials at the same time
  - Understand the local law and regulations
  - Don’t need to “hire and fire”:

- **Advantage of in house team:**
  - Able to control the trial
  - Able to plan for marketing engagement
  - Lower cost
Clinical Trial Management
Agenda

• GCP
• Monitoring
• Clinical Trial Registry
• Safety Reporting
• Project Management
GCP
Good Clinical Practice
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
Scientific Collaboration for Research Innovation
GCP

What does it covers?

What is GCP?
Ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve participation of human subjects.

Why is it needed?
To ensure that the RIGHTS, SAFETY and WELL BEING of the trial subjects are protected.
Ensure the CREDIBILITY of clinical trial data.

Ethics + Quality Data = GCP
Relationship between the parties

- Sponsors
- Investigators
- Subjects
- Ethics Board
Regulatory Approval Required before an Investigational New Drug (IND) trial can start

- IRB (Institutional Research Board or Ethics Board)

- FDA equivalent (Country drug regulatory)
Sponsors

- Normally the Pharmaceutical companies
- Pre-clinical research done (eg animal testing)
- Ready to test on human
- Provide funding for the clinical trials
- Provide protocol for the clinical trials
- Headed by a Director, Clinical Research with a team of Clinical Research Associates
Investigators

- Normally are the senior medical doctors in the hospital or university
- They are independent from the sponsors
- Role is to recruit patients for the clinical trials
- Employ research nurses to assist them in recruitment and running of the clinical trials
- Maybe assisted by their institution’s clinical trial unit
Subjects

- Normally are patients who are seeking treatment in the hospital
- They are recruited by the Investigators
- Must signed informed consent before participation in the clinical trials
- Maybe in the placebo or treatment group
- Closely monitored for side-effect
Why do we need Investigators

- Clinical trials must be conducted by independent experts (i.e. investigators) to protect the safety of the subjects
- Sponsors cannot be involved in the recruitment and treatment of the subjects to prevent conflict of interest
- Sponsor would monitor and audit the conduct of the clinical trial to ensure quality and safety
Incentive for Sponsors

- Able to obtain results from clinical trials to submit to the regulatory authority for the license
- As the study is done by independent investigators, it would provide credibility to market the product
- Successful clinical trial will result in successful marketing of the drugs later
Incentive for Investigators

- Able to obtain funding for their research
- Able to provide new investigational drugs to their patients who are sick
- Able to learn more about this new drug
- Able to participate in the scientific discussion and eventually be recognized as an expert in the treatment of the disease
- Improve reputation of the institution
Incentive for Subjects

- Able to obtain new drugs for their illness, which means new hope for fatal disease
- Maybe paid a nominal sum for their participation in the clinical trial
- Treatment of the disease maybe free as the cost is paid by the sponsors
Monitoring
What is it?

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

SG-GCP / ICH-GCP 1.38
Monitoring

What is the purpose?

- The **rights** and **well-being** of human subjects are protected.
- The reported trial data are **accurate**, **complete**, and **verifiable** from source documents.
- The conduct of the trial is in **compliance** with the currently approved protocol / amendment(s), with GCP, and with the applicable regulatory requirement(s).

SG-GCP / ICH-GCP 5.18.1
Monitoring
Evolution of monitoring

- Standard Monitoring
- Reduced monitoring
- Risk Based Monitoring
- Data Driven Trial
- Predictive Analysis
Monitoring
Risk Based Monitoring

Benefits of Risk Based Monitoring (RBM)

- Improve Quality.
- Enhance patient safety.
- Increase site effectiveness.
- Increase trial operations.
- Reduce costs.
CLINICAL TRIAL REGISTRY

www.clinicaltrials.gov
Clinical Trial Registry SG
Who?

- FDA MA (Mandates registry in 1997).
- ClinicalTrials.gov.
- ICMJE (Publications).
- WHO (Creates global network).
- FDA AA (Expands registry & adds results reporting).
- EMA (EU Clinical Trials Register).
- HSA CT Registry.
  - Launched in 2012 and is changing to adds results reporting.
Clinical Trial Registry SG What is the benefit?

- Identify ongoing CT in Singapore.
- Track new advancement in therapies.
- Generate new ideas.
- Promotes evidence based medicine.
- Helps patient finds trial.
- Systematic reviews on clinical trial data.
SAFETY & ADVERSE EVENTS
Safety & AE
Typical Safety Data

- Adverse Events
- Serious Adverse Events
- Adverse Reactions
- Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Pregnancy
- Lab data
- Vital Signs

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

- SGGCP 2.3
Safety & AE
What is AE?

- Any untoward medical occurrence
- Not necessarily causal relationship with treatment
- Unfavourable /unintended sign
Safety & AE
What is SAE

• Results in death.

• Is life threatening.

• Requires hospitalisation or prolongation of stay.

• Results in persistent or significant disability/incapacity.

• Consists of congenital anomaly or birth defect.
Safety & AE
What is SUSAR

• A serious adverse reaction.

• Unexpected—not consistent with information already available in the protocol and the Investigators Brochure.

• AE that is both UNEXPECTED and is an SAE.
### Safety & AE Reporting workflow

- Not all SAE are reportable to authorities

<table>
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<tr>
<th>Nature of Report</th>
<th>Report? (Y/N)</th>
<th>Timeframe of Report</th>
<th>Form Preferred</th>
<th>Content of Submission</th>
<th>Responsibility for Reporting to CTB</th>
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<td>Serious, and Unrelated</td>
<td>NO</td>
<td>Not Applicable</td>
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<tr>
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<td>Not Applicable</td>
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<td>Serious, Related, and Unexpected Death * / Life Threatening Events</td>
<td>YES</td>
<td>Expedited Reporting:</td>
<td>CIOMS-I</td>
<td>Where applicable:</td>
<td>Sponsor</td>
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<tr>
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<td>• Initial report by 7 calendar days</td>
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<td>▪ Dear Healthcare Professional Letter</td>
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<tr>
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<td>• Follow-up report as complete as possible within 8 additional calendar days</td>
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<td>▪ Company’s comments</td>
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<td></td>
<td>• Subsequent follow-up reports: As it becomes available</td>
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<td></td>
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<tr>
<td>Serious, Related, and Unexpected Non Fatal/ Non Life Threatening Events</td>
<td>YES</td>
<td>Expedited Reporting:</td>
<td>CIOMS-I</td>
<td>Where applicable:</td>
<td>Sponsor</td>
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<td>• Initial report: 15 calendar days</td>
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<td>▪ Dear Healthcare Professional Letter</td>
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<tr>
<td></td>
<td></td>
<td>• Follow-up report: As it becomes available</td>
<td></td>
<td>▪ Company’s comments</td>
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</tr>
</tbody>
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Safety & AE Reporting workflow

1. Serious Adverse Event Occurs
2. Unexpected and Drug-related
3. Is product in a clinical trial in Singapore?
   - Yes: Is product registered in Singapore?
     - Yes: Check source of the report
       - Clinical Trial: Local and Overseas (e.g. CIOMS Format) → Expedited Reporting to CTB
       - Spontaneous: Overseas (e.g. CIOMS Format) → Expedited Reporting to CTB
     - No: Not for Reporting to CTB
   - No: Not for Reporting to CTB
Safety & AE
IRB Reporting

• < 24 Working Hours
  • AE is of high risk
  • Death or Potential Life Threatening unexpected SAE.

• < 1 week
  • AE / UE is of low risk
• Follow Up Reports
PROJECT MANAGEMENT
Project Management
Why Project management?

- Project Manager
- Data manager
- Quality
- Biostatistician
- Timeline
- Risk
- Study documents
- Study Budget
- Research Monitors

Scientific Collaboration for Research Innovation
Project Management Study Constrain

Project Triangle

Time

Quality

Cost
Project Management
Project Gantt Chart
Clinical Research Maze

Enter at your own Risk

Data Analyses
Sae Reports
Feasibility
Scientific Review
Reg
Docs
Study Coordinator Support
Drug Accountability
Bionformatics
Budget
Ctc
Fda
Baa
Gcp
Crfs
Irbc
Rac
Audits
Paci
Patient Bills
Funding
Mtac
Baa
Hippa
Biostats
Contract
Coind
Clinical Trials Budgeting
Budget components

- Clinical Trial Budget
  - Internal costs (Budget considered at institution level)
  - External costs (Budget of cost incurred apart from institution)
Internal costs (non-exhaustive)

- **Research unit**
  - Research unit start up fee, administrative costs
  - Study coordinator(s)
  - Telecommunication (phone, internet, fax)
  - Stationary (files, study specific rubber stamp etc.)

- **Institution / hospital**
  - Clinical trial insurance
  - Drugs/device costs
  - Clinic charges
  - Laboratory tests
  - Radiology and other scans (ultrasounds, scopes etc)
  - Archival costs
Internal costs (non-exhaustive)

- Project related:
  - Screen failure (screening costs)
  - Investigator fees (if sponsored trial)
  - IRBs and HSA submissions (check on respective websites for details)
  - Patient reimbursements (transport, provision of relevant concomitant drugs)
  - Lab kits, study related consumables (e.g. Butterfly needles, vacutainers)
  - Special equipment necessary for the project (e.g. -20°C centrifuge, -80°C freezer)
  - Translation of study related documents
  - Archival of study related documents in accordance to the institution's guidelines.
External costs (non-exhaustive)

- **CRO**
  - **Biostatistics**
    - Protocol development (includes sample size calculation, review and amendments)
    - Data Safety Monitoring Board (DSMB) / Interim analysis
    - Final analysis
    - Manuscript support
  
  - **Data Management**
    - Case report form (CRF) creation / eCRF
    - Query management
    - Data cleaning
    - Data status report
  
  - **Research Informatics**
    - Systems
    - Database (creation, maintenance, troubleshoot, storage)
    - Support
External costs (non-exhaustive)

- CRO (cont’)
  - **Project Management**
    - Overall management of the project
    - Manage external CRO and relevant vendors (e.g., Courier)
    - Provide timely updates to the client on recruitment status, project status, milestones tracking
  
  - **Clinical monitoring on site**
    - Ensure that trial procedures are conducted in accordance to protocol and ICH GCP.
    - Providing reports of the site’s status to the client (essential document review, ICF documents etc.)
  
  - **Pharmacovigilance**
    - Safety database
    - Safety reporting to relevant authorities (In Singapore - IRB & HSA).
External costs (non-exhaustive)

- CRO (cont’)
  - Quality Assurance
    - Audits
    - Compliance visits
  - Sample management
    - Courier
    - Sample processing (Central laboratory – common analysis of samples)
    - Sample storage
  - Study drugs (Investigational Product)
    - IP labelling
    - Storage warehouse / pharmacy
    - Transportation of IP to various sites.
Clinical Trials Agreement
Clinical Trial Roles and Responsibilities

**Sponsor**
- Develops Protocol
- Provides Contractual and Budgetary guidelines to Contract Research Organization (CRO)

**CRO**
- Negotiates Investigator Budget with Hospital
- Negotiates Clinical Trial Terms and Conditions with Hospital
- Pays Hospital through funding supplied by Sponsor
- Monitors study sites for source document comparison and Case Report Form Retrieval

**Hospital**
- Sends invoices to CRO
- Sends final data to Sponsor or CRO Designee
- Indemnified by Sponsor (usually through a Letter of Indemnification)
Common “sticking points” between Sponsors/CROs and Universities in Contract Negotiation

Confidentiality
- Protection of Sponsor Confidential Information
- Maintenance of Patient Records

Intellectual Property
- Sponsor Protocol
- Hospital Idea
- Who should own it?

Publication
- When can results be published?
- Why can publication be delayed?
- What about multi-center publications?

Indemnification
- Some Hospital cannot reciprocate Sponsor indemnification, even for employee’s misconduct.
Group Discussion 2

- Group the participants into 2 groups

- To discuss the criteria in selecting a suitable CROs to run your clinical trial
Group discussion 2 answers:

- To discuss the criteria in selecting a suitable CROs to run your clinical trial
  - Experience in vaccine trials
  - Experience in local regulations and operations
  - Global CROs vs local CROs
  - Whether you have site office in the country (eg sales team)
  - Cost of CROs (fixed vs variable cost)
  - Local sponsor role required of the CRO
Group Discussion 3

- Group the participants into 2 groups

- What are some of the key considerations/criteria you need to consider when you select a site/hospital to do clinical trial?
Case Discussion 3 Answers:

- **Selection criteria for sites**
  - Experience in vaccine trials
  - Number of subjects available for trials
  - Regulatory approval pathway (e.g., IRB set up)
  - Good quality sites
  - Investigator who knows how to conduct trials
  - Investigator who is potential Key Opinion Leader
  - Cost of trials
  - Able to commit to the timelines
Key Issues in Vaccine Clinical Trials

Dr Teoh Yee Leong
MBBS, MMed (PH), FAMS
Consultant Public Health Physician
Topics to cover in the afternoon

- Timelines in starting a trial
- Cold chain management of investigational product
- Dealing with delays (mitigation plans)
- Issues of deaths or serious adverse events in clinical trials
- Interim analysis and data safety monitoring board
- Study report
- Regulatory submission after study completion
- Post marketing surveillance
- Publication issues (who should be in the authorship)
- Engagement of Investigators to be speaker
Discovery of Vaccine – Dr Edward Jenner

Source: users.wfu.edu/hildjm5/images/Smallpox.jpg
Smallpox vaccination, 1959
Vaccination

Basic principle of vaccination:
- Mimicking initial invasion of a specific infectious agent.
- Encounter will trigger the hosts defence mechanisms like a real infection.
- The host will mount a specific primary immune response in most cases → establishment of immunological memory.
What is the value of vaccines in the world today?

What are the challenges in vaccine trials?
The value of vaccines: a global success story
The Demand

Industrialized Countries

Developing Countries

1 billion

5 billion

Earlier and more widespread access to existing and new vaccines for all should be the standard
Is Vaccine development less popular than Pharmaceutical drugs?

- Relatively higher R&D cost
- Vaccine is normally given once, drugs are normally taken regularly (less profit)
- Vaccines are more difficult to administered due to “cold chain” logistics
- Vaccines is more important in poorer countries as a prevention tools (less profit from these countries)
- But vaccine contributes more to public health!
- Vaccine is more complicated and difficult to understand
The vaccine field is growing and developing dramatically. 2005 will see the global vaccine market pass the US $10 billion mark, a ten fold increase on the market 10 years ago.

Source: World vaccine congress, 2006
Availability

NEEDS

EARLY DEMAND

MATURE DEMAND

15 - 20 years

GENERAL USE

Private market

Public market

Private market

Public market
Changing Vaccines Paradigm

**Current**
- Communicable disease prevention
- Infant vaccination
- Low cost/dose
- Lifelong protection
- High benefit/cost ratio
- Govt subsidised
  - Direct protection
  - Herd immunity
  - Reduced costs curative care

**+ New**
- Therapeutic
- All life stages
- Short-term protection
- Smaller target populations
  - Limited herd immunity
  - Higher cost per dose
  - High cost technology in development & production

Public

Private
Desired goal: improved vaccine availability

- Vaccines are very valuable
- Private and public markets co-exist in all countries
  - Private, semi-private, public
  - externally funded for the “very poorest”
- Rapid introduction and uptake of new vaccines
- Sustainable financing with reasonable pricing

‘Deliver vaccines to all people who need them, wherever they are.’
Immunization Has a Great impact on Public Health

‘One of the best bargains in medicine . . .’

International Federation of Pharmaceutical Manufacturing Associations. May 2003
Value of vaccines for the individual

Every year...

- 3 million deaths are prevented
- 750,000 children are saved from disability

... due to vaccines

\[\text{Ehreth J. } \textit{Vaccine} \ 2003;21:4105-4117\]
Vaccines: a Miracle of Medicine

- Vaccines have literally transformed the landscape of medicine over the course of the 20th century

- Before vaccines, parents in the United States could expect that every year:
  - Polio would paralyze 10,000 children
  - Rubella (German measles) would cause birth defects and mental retardation in as many as 20,000 newborns
What have vaccines achieved?

- Smallpox – eradicated
- Poliomyelitis (most countries) – eliminated
- Measles (Americas, parts of Europe) – eliminated
- Other diseases – dramatic reductions
  - tetanus
  - diphtheria
  - pertussis (whooping cough)
  - rubella
  - meningitis (due to *Haemophilus influenzae* type b)
  - liver cancer (due to hepatitis B)
Benefit-cost analysis of commonly used vaccines (savings per $ spent)

- DTPa: $24 saved per $ invested
- IPV: $10 saved per $ invested
- MMR: $12 saved per $ invested
- Varicella: $5 saved per $ invested
- Hepatitis B**: $20 saved per $ invested
- Haemophilus influenzae b: $3 saved per $ invested

*Includes work loss, deaths and disability

**Perinatal/infant

Centres for Disease Control and Prevention 2002
New Advances in the Vaccine Field

- New vaccines for existing diseases (eg HPV/Cervical cancer, Rotavirus)
- New vaccines for new disease (eg Bird flu)
- Combination vaccines (eg 6-in-1 Infanrix Hexa)
- New Adjuvant technology for better vaccine (eg HPV vaccine, Pandemic flu vaccine)
Future Research Trends in Vaccines?

- Combination vaccines: eg Infanrix Hexa, MMR-V
- Vaccines for other infectious diseases: eg dengue, malaria, HIV/AIDS
- Vaccines for cancer prevention: eg cervical cancer
- Vaccines for pandemic: eg SARs and avian flu
- Therapeutic vaccines: eg lung cancer vaccine
- Painless vaccines
- Vaccines for prevention of chronic diseases
- Vaccines against smoking addiction
4 phases in the development of a Drug

Preclinical
Research

Phase I - II
Early Development

Phase III
Late development

Phase IV
Registration & launch

-2 -1 0 1 2 3 4 5 6 7 8 9 10

Identification of target antigen
Established concept in animal model
First administration to man
Agreement on feasibility investment
Decision of pivotal efficacy studies
Results of pivotal studies available
Agreement on detailed profile of the product
Registration and price request
Launch

Post marketing surveillance
Some Differences in Clinical Trial

- Pharmaceutical drugs
  - Less number of subjects
  - Subjects with existing disease
  - Mainly adults and elderly
  - Mainly oral (no pain)
  - No cold chain requirement

- Vaccines
  - Larger number of subjects
  - Healthy subjects
  - Mainly children and young adults
  - Mainly injection (pain!)
  - Require cold chain
Challenges in Vaccine Trials

- Some doctors are not familiar with vaccines, side-effect, contraindications etc.
- More difficult to convince healthy subjects, especially children to participate in vaccine trials
- Need to take consent from parents if child is below 21 years old
- Problem with cold-chain occurs (e.g., power failure)
- Need to vaccinate large number of subjects in order to detect efficacy in rare diseases
- Efficacy study may take many years as the subjects need to be exposed to the infection later in life to check for efficacy
- Need to co-admin with other vaccines in childhood, as it’s unethical to deprive a subject of his routine vaccination to study the new vaccine
How should vaccines be stored?

When using vaccines it is vital to transport and store them properly. If a vaccine is exposed to extremes of temperature and loses its potency, it may not provide the protection it is expected to.

Some live-attenuated viral vaccines are particularly sensitive to heat and light, especially in a liquid form. For this reason some vaccines are distributed as freeze-dried powders to be reconstituted with water for injection before they are administered. Once the vaccines have been reconstituted, they should be administered as soon as possible.

Most of GSK’s killed inactivated vaccines and sub-unit vaccines, including Engerix-B, Havrix, Tritanrix, Infanrix and their combinations, are adjuvanted vaccines and are presented as liquid suspensions of fine particles of antigen adsorbed onto aluminium salts. Adjuvanted vaccines should be stored in a refrigerator at +2°C to +8°C, they must never be frozen.
**What is the cold chain?**

The cold chain: The term used to describe the chain of continuous care taken by those transporting goods, e.g., vaccines, to ensure a constant temperature.

- Vaccines must be stored properly by the manufacturer, the end user, and during distribution.

- The temperature at which a vaccine must be stored depends on the vaccine.

**Vaccines that can be frozen**

- Shipped in foam containers packaged in dry ice.
- Cold chain monitors record any exposure to higher than recommended temperatures.

**Vaccines that cannot be frozen**

- Maintaining an optimum temperature during transportation is vital if the vaccines are to remain effective and safe.
Vaccination

SUCCESSFUL VACCINE

- The right immune profile to give optimal protection
- A vaccine must retain antigenicity but not pathogenicity
Some Ethical Issues in Vaccine Trials

- Informed consent from parents – what if parents consented by the child refused?

- Need to use indirect markers like immune response instead of efficacy (e.g., cannot purposely expose subjects to HIV infection to test for efficacy of HIV vaccine)
ETHICAL CHALLENGES IN VACCINES CLINICAL TRIALS

A/Prof Teoh Yee Leong
MBBS, Master of Medicine (Public Health), FAMS
CEO Singapore Clinical Research Institute
"Nonsense. As long as it's done ethically, animal testing is an invaluable scientific tool."
US CDC Vaccination Schedule - majority of vaccines are for infants and children

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>19-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
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<td>Hepatitis B (HepB)</td>
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<td>Rotavirus 1 (2-dose series); Rotavirus 5 (3-dose series)</td>
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<td>Diphtheria, tetanus, &amp; acellular pertussis (DTaP)</td>
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<td>Tetanus, diphtheria, &amp; acellular pertussis (Td)</td>
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<td>Haemophilus influenzae type b (Hib)</td>
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<td>Pneumococcal conjugate (PCV13)</td>
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<td>Pneumococcal polysaccharide (PPSV23)</td>
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<td>Inactivated poliovirus (IPV) (&lt;18yrs)</td>
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<td>Polio (IPV) / LAIV 2 doses for some: see footnote 8</td>
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<td>Measles, rubella, and mumps (MMR)</td>
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<td>Varicella (VAR)</td>
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<td>Hepatitis A (HepA)</td>
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<td>Human papillomavirus (HPV2, females only; HPV4: males and females)</td>
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<td>Meningococcal C (Hib-MenCY ≥ 6 wks; MCV4-Dz; ≥ 9 mos; MCV4-CRM ≥ 2 yrs)</td>
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Legend:
- **Range of recommended ages for all children**
- **Range of recommended ages for catch-up immunization**
- **Range of recommended ages for certain high-risk groups**
- **Range of recommended ages during which catch-up is encouraged and for certain high-risk groups**
- **Not routinely recommended**

See footnotes for more information.
I am not a Small Adult!
Why is Paediatric Clinical Trials Important?

- Some of the pharmaceutical products (eg vaccines) are only for children, not adults
- Regulatory Authority requires safety and efficacy data in children before it allows indication for children
- With the increase affluence in the society, parents can afford better drugs for children (larger market)
Good Clinical Practices (GCP) for Clinical Trials in Children

2.4.6.2. **Children:**

Before undertaking trial in children the investigator must ensure that:

a. children will not be involved in research that could be carried out equally well with adults;

b. the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;

c. a parent or legal guardian of each child has given proxy consent;

d. the assent of the child should be obtained to the extent of the child’s capabilities such as in the case of mature minors, adolescents etc;

e. research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;

f. interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;

g. the child’s refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardian;

h. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child subject as any available alternative interventions;

i. the risk presented by interventions not intended to benefit the individual child subject is low when compared to the importance of the knowledge that is to be gained.
Some Ethical Issue in Paediatric Trials

- Consent needed from parents/guardians. Is grandparents considered “guardian”?
- What if one parent consented but the other objected?
- What happens if parents consented by child is not keen?
- Issues on blood taking
- What would the Ethics Board view about trials in children?
Some General Differences in Adult vs Children Clinical Trial

- **Adult trials**
  - Adult can give consent
  - Adult can understand the procedure required (e.g., blood taking)
  - Ethics Board is well versed
  - Higher tolerance for adverse event
  - Better compliant

- **Children trials**
  - Children cannot give consent
  - Children cannot understand the procedure
  - Ethics Board may not be familiar with children study
  - Lower tolerance for adverse event
  - Lower compliant if parents are unhappy with the pain and side effect
Some General Differences in Vaccines Clinical Trial

- Pharmaceutical drugs
  - Less number of subjects
  - Subjects with existing disease
  - Mainly adults and elderly
  - Mainly oral (no pain)
  - No cold chain requirement

- Vaccines
  - Larger number of subjects
  - Healthy subjects
  - Mainly children and young adults
  - Mainly injection (pain!)
  - Require cold chain
Ethical Issues in Healthy subjects trial

- As subjects are healthy, there is less incentive for them to participate in the study:
  - Need to ensure the incentive (eg payment) is not too high and acceptable by Ethics Board
  - Need to ensure the trial medication/vaccine is very safe
Terms used for Vaccine Trial

- Safety: Is the vaccine safe?
- Reactogenicity: Reaction caused by the vaccine (e.g., fever, rash, swelling)
- Immunogenicity: Is the antibodies produced high?
- Efficacy: Does the vaccine able to protect you against the infection

Note: immunogenicity is not equals to efficacy
Other Challenges in Vaccine Trials

- Need to vaccinate large number of subjects in order to detect efficacy in rare diseases

- Efficacy study may take many years as the subjects need to be exposed to the infection later in life to check for efficacy

- Need to co-admin with other vaccines in childhood, as it's unethical to deprive a subject of his routine vaccination to study the new vaccine
Need to co-administered with other vaccines

<table>
<thead>
<tr>
<th>Vaccination against</th>
<th>Birth</th>
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<th>18</th>
<th>6-7 ^</th>
<th>10-11 ^^</th>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>BCG</td>
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<tr>
<td>Hepatitis B</td>
<td>HepB (D1)</td>
<td>HepB (D2)</td>
<td>HepB (D3) #</td>
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<tr>
<td>Diphtheria, Tetanus, Pertussis</td>
<td>DTaP (D1)</td>
<td>DTaP (D2)</td>
<td>DTaP (D3)</td>
<td>DTaP (B1)</td>
<td>TdaP (B2)</td>
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<td>Poliovirus</td>
<td>IPV (D1)</td>
<td>IPV (D2)</td>
<td>IPV (D3)</td>
<td>IPV (B1)</td>
<td>OPV (B2)</td>
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<td>Haemophilus influenzae type b</td>
<td>Hib (D1)</td>
<td>Hib (D2)</td>
<td>Hib (D3)</td>
<td>Hib (B1)</td>
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<tr>
<td>Measles, Mumps, Rubella</td>
<td>PCV (D1)</td>
<td>PCV (D2)</td>
<td>PCV (B1)</td>
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<td>Pneumococcal Disease</td>
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<td>Human Papillomavirus</td>
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Note:
- BCG: Bacillus Calmette-Guérin
- HepB: Hepatitis B vaccine
- DTaP: Paediatric diphtheria and tetanus toxoids and acellular pertussis vaccine
- Tdap: Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine
- IPV: Inactivated polio vaccine
- OPV: Oral polio vaccine
- Hib: Haemophilus influenzae type b vaccine
- MMR: Measles, mumps, and rubella vaccine
- PCV: Pneumococcal conjugate vaccine
- D1/D2/D3: First dose, second dose, third dose
- B1/B2/B3: First booster, second booster, third booster
- ^: Primary 1
- ^^: Primary 5
- #: Third dose of HepB vaccination can be given with the third dose of DTaP & OPV for parents' convenience
- ##: Second dose of MMR can be given between 15 - 18 months

For persons aged 0 to < 18 years
Deaths in Vaccine Trials

GSK fined over vaccine trials; 14 babies reported dead

By Javier Cardenal Taján

BuenosAiresHerald.com staff

GlaxoSmithKline Argentina Laboratories Company was fined 400,000 pesos by Judge Marcelo Aquinsky following a report issued by the National Administration of Medicine, Food and Technology (ANMAT in Spanish) for irregularities during lab vaccine trials conducted between 2007 and 2008 that allegedly killed 14 babies.

Likewise, two doctors -Héctor Abate, and Miguel Tregnaghi- were fined 300,000 pesos each for irregularities during the studies.

The charges included experimenting with human beings as well falsifying parental authorizations so babies could participate in the vaccine-trials conducted by the laboratory from 2007 to 2008.

Since 2007, 15,000 children, under the age of one, from Mendoza, San Juan and Santiago del Estero provinces have been included in the research protocol, a statement of what the study is trying to achieve. Babies were recruited from poor families that attended to public hospitals for medical treatment.

A total of seven babies died in Santiago del Estero, five in Mendoza, and two in San Juan.
Other Challenges in Vaccine Trials

- Some doctors are not familiar with vaccines, side-effect, contraindications etc.
- More difficult to convince healthy subjects, especially children to participate in vaccine trials
- Problem with cold-chain occurs (eg power failure)
- Need to use indirect markers like immune response instead of efficacy (eg cannot purposely exposed subjects to HIV infection to test for efficacy of HIV vaccine)
- Need to offer the vaccine to the placebo group after the vaccine is licensed
Case Study: H5N1 Pre-pandemic vaccine

- Many countries are interested to purchase the vaccine
- But not all countries are keen to have the clinical trials done in their country:
  - Political pressure as perception of using the citizens of the country as “laboratory mice”
  - Worry of introducing H5N1 virus in the community
  - Unknown long-term effect on the trial subjects
- A lot of meeting to present the clinical and safety data to the country’s regulatory authority to enable the trial to start
Some Advice on Healthy Volunteer Study

- Understand that recruitment maybe slower, not to have too tight timeline for recruitment
- Be prepared for more questions from Ethics Board and Regulatory Authority
- Not to overcompensate subjects to attract volunteers for recruitment
- No compromise on safety of the trial medications/vaccines
- Be prepared to answer allegations that “………people in our country are being used as laboratory mice for this unlicensed medicine…”
- A proper Data Safety Monitoring Board to monitor the safety of the trial
Interim Analysis
Interim Analyses

- Also called “data-dependent stopping” or “early stopping”
- Continuing a trial: there needs to be active monitoring so that a trial is not continued simply because it was begun.
- Some issues involved in stopping:
  - ethics
  - precision of results
  - data quality
  - resource availability
- Usually, we use accumulated data to decide what to do
- Sometimes outside information is provided to encourage us to stop a trial (e.g. a trial using same drug had very bad/good effects elsewhere)
- Early stopping can be due to efficacy but also to other reasons (e.g. accrual too slow).
Some Examples of Why a Trial Maybe Stopped half way

- Treatments found to be convincingly different
- Treatments found to be convincingly not different
- Side effects or toxicities are too severe
- Data quality is poor
- Accrual is slow
- Definitive information becomes available from an outside source making trial unnecessary or unethical
- Scientific question is no longer important
- Adherence to treatment is unacceptably low
- Resources to perform study are lost or diminished
- Study integrity has been undermined by fraud or misconduct
Data Safety and Monitoring Committees

- Most comparative/phase III clinical trials have Data Safety and Monitoring Committees.
- Their goal is to ensure that the trial is safe and warrants continuation.
- A qualitative review of adverse events is performed.
Statistical Considerations in Interim Analyses

- Consider a safety/efficacy study (phase II)
- “At this point in time, is there statistical evidence that….”
  - The treatment will not be as efficacious as we would hope/need it to be?
  - The treatment is clearly dangerous/unsafe?
  - The treatment is very efficacious and we should proceed to a comparative trial?
Statistical Considerations in Interim Analyses

- Consider a comparative study (phase III)
- “At this point in time, is there statistical evidence that….”
  - One arm is clearly more effective than the other?
  - One arm is clearly dangerous/unsafe?
  - The two treatments have such similar responses that there is no possibility that we will see a significant difference by the end of the trial?
Statistical Considerations in Interim Analyses

- We use interim statistical analyses to determine the answers to these questions.

- It is a tricky business:
  - interim analyses involve relatively few data points
  - inferences can be imprecise
  - we increase chance of errors.
  - if interim results are conveyed to investigators, a bias may be introduced
  - in general, we look for strong evidence in one or another direction.
Post Marketing Surveillance
MMRV vaccine
FEBRILE SEIZURES IN PQ

- Post-licensure observational study conducted by the CDC (Vaccine Safety Datalink Rapid Cycle Analysis)

- 9 cases of febrile convulsions were reported per 10,000 children receiving the first dose of ProQuad within 7-10 days of the vaccination

- 4 cases of febrile convulsions were reported per 10,000 children receiving the first dose of MMR II plus VARIVAX within 7-10 days of the vaccinations

- The risk of febrile convulsions during 7-10 days after vaccination was about 2.3 times higher in children who received ProQuad, when compared to those who received MMR II plus VARIVAX given separately

- one additional case for every 2000 recipients aged 12–23 months who had received ProQuad™, Merck’s MMRV vaccine[1]
BACKGROUND

- ACIP withdrew its preference for the combined MMRV vaccine over the separately administered MMR and varicella vaccines in 2008[1]

- The benefits of the MMRV vaccine nonetheless outweigh its risks [2]

- The incidence of fever after Priorix-Tetra™ (MMRV) administration is higher than after Priorix™ (MMR) or Priorix™ and Varilrix™ administered at the same visit [2]

- The very limited size of the clinical database and the low frequency of febrile seizures do not allow any conclusion to be made about a putative difference in incidence of febrile seizures in Priorix-Tetra™ vs Priorix™ or Priorix™ + Varilrix™ recipients

1: CDC 2008; 2: FDA 2008
Risks versus Benefits?

Clinical data on *Priorix-Tetra* in children aged 12 to 24 months, receiving their first dose of the vaccine as follows:

- The incidence of fever after the first dose of *Priorix-Tetra* is approximately 1.5–fold higher than after *Priorix + Varilrix* given at the same visit.

- The incidence of febrile convulsions after *Priorix-Tetra* varies from less than 0.1% when considering the cases at least possibly related to vaccination to a range of 0.1 to 0.2% when considering all cases, over a period of 42 days after vaccination.

- The incidence of febrile convulsions after *Priorix-Tetra* is numerically higher than after *Priorix + Varilrix*, however due to the very low incidence of febrile convulsions and the limited size of the clinical safety database, no definite conclusions can be drawn on the significance and the magnitude of this difference.

- The Company believes that, in line with the opinion voiced by the ACIP, *Priorix-Tetra* vaccination benefits outweigh any potential risk associated with the uncommon adverse event of febrile convulsions.
Authorships
Authorships

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Planning for Authorships

- For large scale multi centre trials, need to set up an authorship committee to agree on the authorships.

- Generally the key Principal Investigators should be the first few authors, pharma companies scientific staff can be co-authors, external authors should be more than pharma authors.
Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: Randomised, double-blind, controlled study

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\textsuperscript{c} Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong
\textsuperscript{d} Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong
\textsuperscript{e} Department of Paediatrics, National Taiwan University Hospital, Taipei, Taiwan
\textsuperscript{f} Department of Paediatrics, National University of Singapore, Singapore 119074, Singapore
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\textbf{ABSTRACT}

This study evaluates the safety and efficacy against severe rotavirus gastroenteritis of the oral live attenuated human rotavirus vaccine RIX4414 (Rotarix\textsuperscript{TM}) during the first 2 years of life in Asian infants from high-income countries. Healthy infants were enrolled to receive 2 doses of RIX4414 (N = 5359) or placebo (N = 5349). From 2 weeks post-dose 2 to 2 years of age, vaccine efficacy was 96.1\% (95\%CI:85.1\%; 99.5\%) against severe rotavirus gastroenteritis, 100\% (95\%CI:80.8\%; 100\%) against wild-type G1P[8] and 93.6\% (95\%CI:74.7\%; 99.3\%) against circulating non-G1 rotavirus types. No intussusception cases were reported within 31 days post-vaccination. RIX4414 shows a good safety profile and offers high protection during the first 2 years of life with potentially significant public health impact in this population.

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Group Discussion 4

- Group the participants into 2 groups

- What can you do when the recruitment is behind the timelines?
Case Discussion 4 Answers:

- If the timelines of recruitment is slow
  - For the same site:
    - Involved more investigators
    - Consider referral centres from primary care clinics
    - Meetings with Investigators and clinical research coordinators to brainstorm ideas
    - Media awareness
    - Incentive for recruitment, incentive for subjects
  - For new sites
    - Consider setting up new sites, new countries
    - Need to coordinate data collection
Rotavirus Disease

Case Study on Vaccine trial
And how vaccine can prevent the disease
From Clinical Trials to Post-Marketing surveillance:
A case study from the point of an Investigator and Sponsor
Pathogenesis

Rotaviruses adhere to the GI tract epithelia (jejunal mucosa)

↓

Atrophy of the villi of the gut

↓

Loss of absorptive area

↓

Flux of water and electrolytes

↓

NSP4 viral enterotoxin

↓

Enteric nervous system activation

VOMITING AND DIARRHEA

Clinical Course

- Range of clinical symptoms:
  - watery diarrhea, vomiting, fever, abdominal pain, dehydration

- Self-limiting disease in healthy well-nourished children
  - incubation period 0.5–4 days
  - duration of symptoms 4–8 days

- First rotavirus infection usually most severe:
  - subsequent infections = progressively milder symptoms

- Complications of infection:
  - dehydration, electrolyte imbalance, hospitalization, concomitant bacterial infections, death
**Treatment and Prevention**

- **Main goals of treatment:**
  - Control the diarrhea
  - Prevent vomiting
  - Control other symptoms
  - Maintain effective fluid and electrolyte balance with oral re-hydration therapy (ORT)
  - Replacement of fluid loss

- **Prevention measures:**
  - Breast feeding
  - Regular disinfection of play areas and toys
  - Frequent hand washing
  - Rigorous hygiene practices in hospital wards
  - Development of rotavirus vaccines

Why Singapore?

Population: 3.8 million
Annual births: 40,000
Area: 620 sq. km
Study subject: Target = 2460, Study Sites = 8

- Choice of study sites
  - Major paediatric government hospitals
  - Government subsidised polyclinics for mass childhood immunisations
  - High patient load, eg. Polyclinics in new estates, with young couples and babies.
  - P.I.s interested to carry out clinical trials
Primary Healthcare - Polyclinics

- Provide mass immunisation, developmental assessment, and basic healthcare needs
Television News Telecast
Increase awareness of clinical trial

- Liase with PR agency to arrange for press release
  - Major newspapers, eg. Straits Times, Lianhe Zaobao, New Paper, Project Eyeball, etc.
  - NewsRadio interview (NewsRadio 95.8 FM)
  - Television News telecast, eg. Channel News Asia, TCS News 5, TCS News 8, etc.
Vaccine against rotavirus on extended trial

Eight centres have been approved by the Ministry of Health for a key project that will involve 2,600 children.

By LIANG HWEI TING

MRS JENNY TAN and her husband were frantic with worry last Friday when their only child, a girl, had severe diarrhoea and threw up everything she ate.

The 18-month-old infant was admitted to Mt Alvernia Hospital where she was put on intravenous drip and remained under observation until yesterday morning.

Doctors diagnosed her as having diarrhoea caused by viral infection. The case of little Gina is not unusual in Singapore. Before they reach the age of five, two out of three children here would have suffered from rotavirus infection. It is responsible for about 140 million cases of diarrhoea worldwide each year, with more than 870,000 resulting in death.

No child has been known to have died from rotavirus infection in Singapore in recent years, but the infection accounts for about 10 per cent of admissions to a general paediatric unit and 5 per cent of admissions to government hospitals here.

To prevent children here from being infected with the virus, the Ministry of Health has approved eight centres to administer rotavirus vaccination on a trial basis. When completed, the trial will be one of the largest vaccine projects in Singapore, involving 2,600 children.

The vaccination programme will be spearheaded by KK Women’s and Children’s Hospital, National University Hospital and selected National Healthcare Group and SingHealth polyclinics.

About 360 children have been recruited for the project so far. The child must be at least three months old and healthy. Children from rotavirus infection have been recruited by Dr Phoong Kang, principal investigator, to study the vaccine’s efficacy.

Professor Quak Seng Hoh, principal investigator at NUSL, said: “There is a need to prevent the disease at a very young age as studies have shown that more than 70 per cent of children hospitalised for acute diarrhoea are below two years of age.

Two doses of oral rotavirus vaccine are given, one when the infant is three months old and the second a month later. In addition to the rotavirus vaccine, children will also receive a primary series of children’s vaccines, namely a DTPa vaccine to protect against diphtheria, tetanus and whooping cough, and a Hib vaccine to protect against brain and spinal-cultural infection.

These vaccines, as well as the rotavirus vaccine, will be given free in the study. Parents interested in enrolling their infants can contact the research nurse at the participating centres.
Regular Investigators Meeting

- Update recruitment status
- Create competitiveness amongst investigators
- Brainstorming for new ideas for better recruitment
Brainstorming session with research nurses

Sharing best practices
KK Hospital.. The biggest women and children hospital in Singapore.
SGH Bacteriology lab & NUH lab

SGH lab is ISO 9001 certified lab.

This is Where GE Stool sample being Tested for Rota & Other bacteria.
Dispatch rider for stool samples collection

Be careful, Shariff!
Safety first!
Vaccine storage in clinic

Temperature log sheet

Alarm
At Zuellig warehouse,

It's very cold here!
After first IS was reported….

- Reinforcements made

- Research nurses
- Continuous reminder
- Parents of subjects

- Investigators
- Lunch time talks by PIs
- Doctors in hospitals

- Additional notice of study participation on birth cert.
Conclusions from Phase II (007) Study

Two doses of RIX 4414 HRV Vaccine had been shown to be

Well tolerated and safe with reactogenicity profile similar to placebo

Highly immunogenic

No interference with concomitant vaccines
Clinical Profile per Study
Study 007 – Singapore

A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals’ oral live attenuated human rotavirus (RIX4414) vaccine at different viral concentrations (10^{4.7}, 10^{5.2} and 10^{6.1} ffu) in healthy infants previously uninfected with RIX4414 and approximately 3 months of age, when administered concurrently with DTPa-IPV/Hib and HBV vaccines.

*Phua et al. JID 2005;192:S6-S16*
**Clinical Profile per Study – Study 007 – Singapore**

**Vaccine take**

% Vaccine take per groups

- **RIX4414 10^{4.7}**
- **RIX4414 10^{5.2}**
- **RIX4414 10^{6.1}**
- **Placebo**

_Viral titres expressed in ffu = foci forming units_

---

**Viral titres expressed in ffu = foci forming units**

- **RIX4414 10^{4.7}**
- **RIX4414 10^{5.2}**
- **RIX4414 10^{6.1}**

Phua et al. JID 2005;192:S6-S16
Immunogenicity - Effect on co-administered vaccines

Rates of seropositivity to antigen in routine infant vaccines 1 month post-dose 3

**Clinical Profile per Study – Study 007 – Singapore**

**Immunogenicity**

**Effect on co-administered vaccines**

**Rates of seropositivity to antigen in routine infant vaccines 1 month post-dose 3**

- **RIX4414 10^{4.7}**
- **RIX4414 10^{5.2}**
- **RIX4414 10^{6.1}**
- **Placebo**

**Viral titres expressed in ffu = foci forming units**

- **1** ELISA, cut off at 0.1 UI/mL
- **2** ELISA, cut off at 5 EL.U/mL
- **3** AUSAB, Abbott Laboratories cut off at 10mIU/mL
- **4** ELISA, cut off at 0.15 µg/mL
- **5** Virus microneutralization cut off titer ≥ 8

---

**Phua et al. JID 2005;192:S6-S16**
Reactogenicity

Solicited symptoms reported within 15 days post-vaccination, DTPa-IPV/Hib co-administered

- RIX4414 $10^{4.7}$
- RIX4414 $10^{5.2}$
- RIX4414 $10^{6.1}$
- Placebo

Viral titres expressed in ffu = foci forming units

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever $\geq 38$ C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss appetite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phua et al. JID 2005;192:S6-S16
Initiatives taken to improve enrolment

- 6 weekly RN meeting
  - Discussion on Center specific recruitment issues, DQ resolutions, updates of recruitments
- Monthly PI meeting
  - Updates on recruitments, issues and study related matters
- Communication with Investigational Team and Non-study site staff
- Use of booklets (cover.jpg) & posters (poster.jpg)
- Participation of SingHealth Polyclinics (SHP)
- Promoting awareness of study among referral site staff
- Public talk on disease awareness (Mind Your Body 9 Feb 2005 pg 20 fyi.jpg)
Phase III Rota-028 Study in Singapore
### Rota-028: Recruitment by Centre

<table>
<thead>
<tr>
<th>Centre</th>
<th>Recruitment Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMK</td>
<td>622</td>
</tr>
<tr>
<td>BBK</td>
<td>611</td>
</tr>
<tr>
<td>CCK</td>
<td>867</td>
</tr>
<tr>
<td>HGG</td>
<td>774</td>
</tr>
<tr>
<td>JRG</td>
<td>664</td>
</tr>
<tr>
<td>TPY</td>
<td>524</td>
</tr>
<tr>
<td>WDL</td>
<td>739</td>
</tr>
<tr>
<td>YSH</td>
<td>518</td>
</tr>
<tr>
<td>KKH</td>
<td>774</td>
</tr>
<tr>
<td>Mt. E</td>
<td>111</td>
</tr>
<tr>
<td>NUH</td>
<td>338</td>
</tr>
</tbody>
</table>

End date of Recruitment: 31st Aug 2005

Total: 6,542
Here comes …

Huh...?
What’s the big deal?
Vaccine Approval in Singapore, Oct 2005

- Singapore’s Innovative Therapeutic Group (ITG) able to perform full dossier review, independent of FDA/EMEA
- Approved Rotarix in Oct 2005
What is required for product license?

- Results from clinical trials worldwide
- Results from local clinical trial (if there is, added advantage)
- Data to show the vaccine is safe and effective
What is next?

- Prepare for product launch
- Training of sales team using data from clinical trial
- Topics:
  - Disease burden
  - Clinical presentation of rotavirus infection
  - Clinical trial data
  - How to convince the doctors to buy the vaccine
Rotarix vaccine launch

Rotavirus berbahaya

Dr. Raul & Tech.
Post Marketing Surveillance - Intussusception

Figure 3 Distribution of IS cases by gender (Total number of cases N=167). *Data collected from May to December - 2002. **Data collected from January to June - 2010.
From Clinical Trial to Product Launch

- Jan 2001 : Phase 2 Rota trial in Singapore polyclinics
- Dec 2003 : Phase 3 Rota trial in Singapore polyclinics
- Oct 2005 : Rotarix license granted in Singapore
- Feb 2006 : Rotarix was officially launched in Singapore
- June 2006 : Rotarix is available in government hospitals
- From Phase 2 to commercial product available : 5.5 years
Other Safety and Efficacy Data
Vaccine efficacy against severe RV GE

From 2 weeks post-dose 2 to 1 year of age

<table>
<thead>
<tr>
<th></th>
<th>Vaccinees n=9,009</th>
<th>Placebo n=8,858</th>
<th>Vaccine efficacy (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>12</td>
<td>77</td>
<td><strong>84.7</strong> (71.7 - 92.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Vesikari score ≥11</strong></td>
<td>11</td>
<td>71</td>
<td><strong>84.8</strong> (71.1 - 92.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Human RV strain and IS risk

- No evidence linking wild-type human rotavirus to IS
  - US epidemiology refutes link\textsuperscript{1,2}

- Anecdotal reports of RV detection with cases of IS (Japan)

- No link between RV infection seasonality and IS \textsuperscript{1,2}

\textsuperscript{1}Rennels et al, Pediatr Infect Dis J 1998 17 924–925, \textsuperscript{2}Chang EJ et al PIDJ 2002
Occurrence of Definite IS Cases Compared to RotaShield™-Associated Cases

Dose 1

IS cases

Dose 2

IS cases

V = Vaccine
P = Placebo

Vesikari T et al. ESPID 2005, abstract 31

IS Surveillance 0 to 31 days and post each dose

(Vaccine group)

Total IS Cases

N=31,673

Total 0 → 31 days

6

0 → 31 days post dose 1

1

0 → 31 days post dose 2

5

(Placebo group)

Total IS Cases

N=31,552

Total 0 → 31 days

7

0 → 31 days post dose 1

2

0 → 31 days post dose 2

5

Differential Risk = -0.32/10,000 vaccines (95% CI: -2.91 - 2.18)

Relative Risk = 0.85 (95% CI: 0.30 - 2.42)

1O'Ryan M., abstract, ICAAC, 2004, Washington, USA
## IS Surveillance

### 0 to 31 days and 0 to 100 days

<table>
<thead>
<tr>
<th></th>
<th>Vaccine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31,673</td>
<td>31,552</td>
</tr>
</tbody>
</table>

**0 → 31 days**

- **Differential Risk**: \(-0.32/10,000\) vaccines (95% CI: -2.91 - 2.18)
- **Relative Risk**: \(0.85\) (95% CI: 0.30 - 2.42)

**0 → 100 days**

- **Differential Risk**: \(-2.23/10,000\) vaccines (95% CI: -5.70 - 0.94)
- **Relative Risk**: \(0.56\) (95% CI: 0.25 - 1.24)

---

2. Vesikari T., abstract, ESPID, 2005, Valencia, Spain
Motivations for Investigators

- The trial will benefit the patients
- The investigators can learn more about clinical research
- The investigators may have lesser clinical workloads
- The investigators have a chance to attend overseas conferences
Motivations for Subject parents

- Subjects get free vaccine for participation in the clinical trial
- Express queue number
- Dedicated research nurse for this study
- Able to get this new vaccine before it is commercially available
Group Discussion 5

- Group the participants into 2 groups

- What you should do if there is a death in a study and the regulatory authority suspend the study?
Case Discussion 5 Answers:

- If there is a death:
  - Don’t panic, most likely not related
  - Need to have baseline data on mortality rate in the similar population
  - Look for medical history of the deceased – history of medical illness, congenital disease
  - Inform Data Safety Monitoring Board
  - Only when it is absolutely necessary then unblind the case to see if it is in the vaccinated to placebo group
  - To provide other safety data from other trials
4 phases in the development of a Drug

**Preclinical**
- Research
  - Identification of target antigen
  - Obtention of target antigen
  - Establishment of concept in animal model

**Phase I - II**
- Early Development
  - First administration to man

**Phase III**
- Late development
  - Agreement on feasibility of investment
  - Decision of pivotal efficacy studies
  - Start of pivotal studies available

**Phase IV**
- Registration & launch
  - Agreement on detailed profile of the product and position on the market
  - Registration and price request
  - Launch

**Post marketing surveillance**
Thanks to my daddy, I am protected against Rotavirus now!
Thank You