Vaccines Clinical Trials: Executing the operations of a trial

A/Prof Teoh Yee Leong
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CEO, Singapore Clinical Research Institute
Adjunct Associate Professor, Saw Swee Hock School of Public Health, National University Singapore

Topics to cover before lunch

- 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

April 9, 2009 THE STRAITS TIMES 19

MIND YOUR BODY

The Pro

MYB speaks to health professionals in this weekly column

Medical detective

Public health physician Teoh Yee Leong, 40, director of clinical R&D and medical affairs, GlaxoSmithKline Biologicals, searches for clues for the cause of disease outbreaks. POON CHIAN HUI reports

ST PHOTO: AZIZ HUSSIN

Dr Teoh Yee Leong says his job is to keep the population healthy by devising plans to control disease spread.

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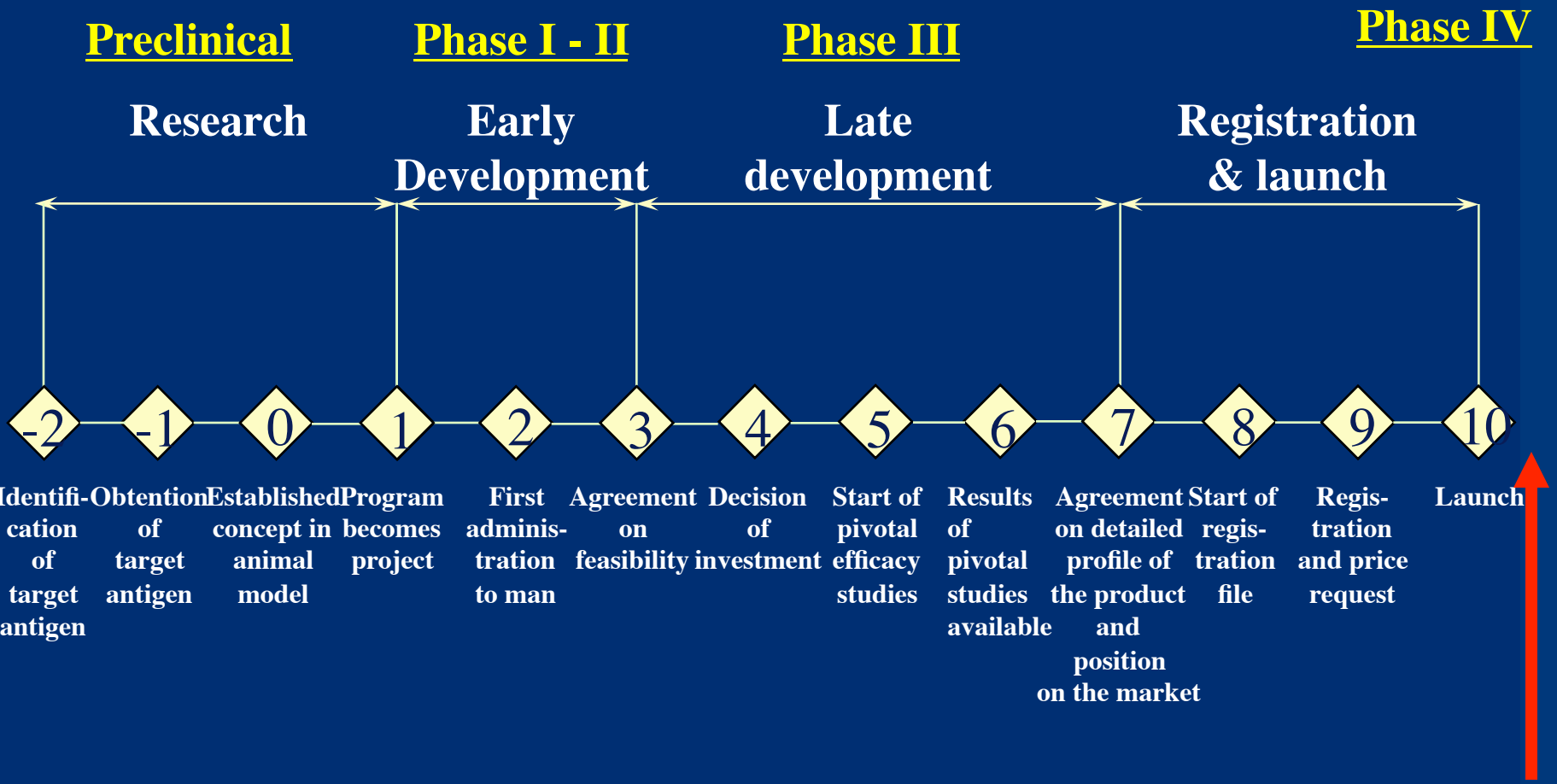
Overview of Clinical Trials Operations

4 phases in the development of a Vaccine



Stakeholders in clinical trials

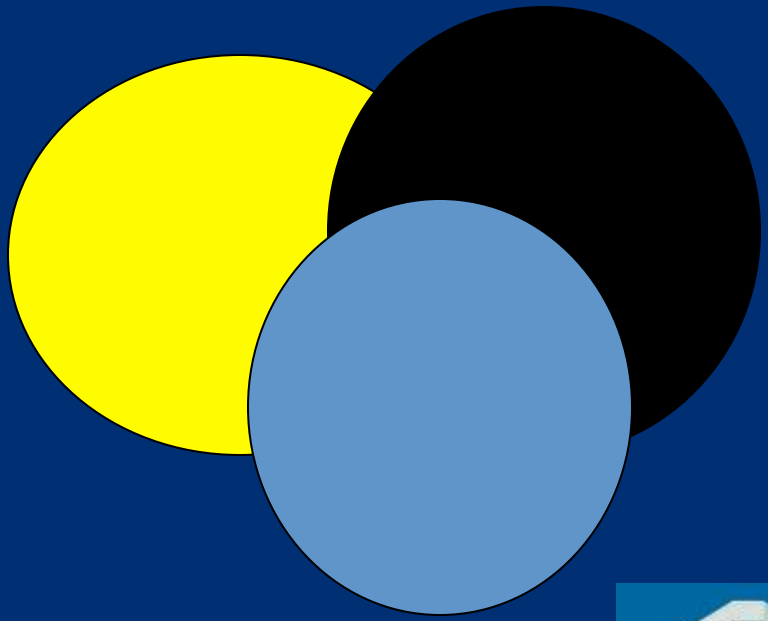
- Sponsors (Pharmaceutical company, NGOs)
- Investigators (Hospital doctor)
- Subjects (Patients)

Sponsor's Responsibilities (GCP)

Relationship between the parties

Ethics Board

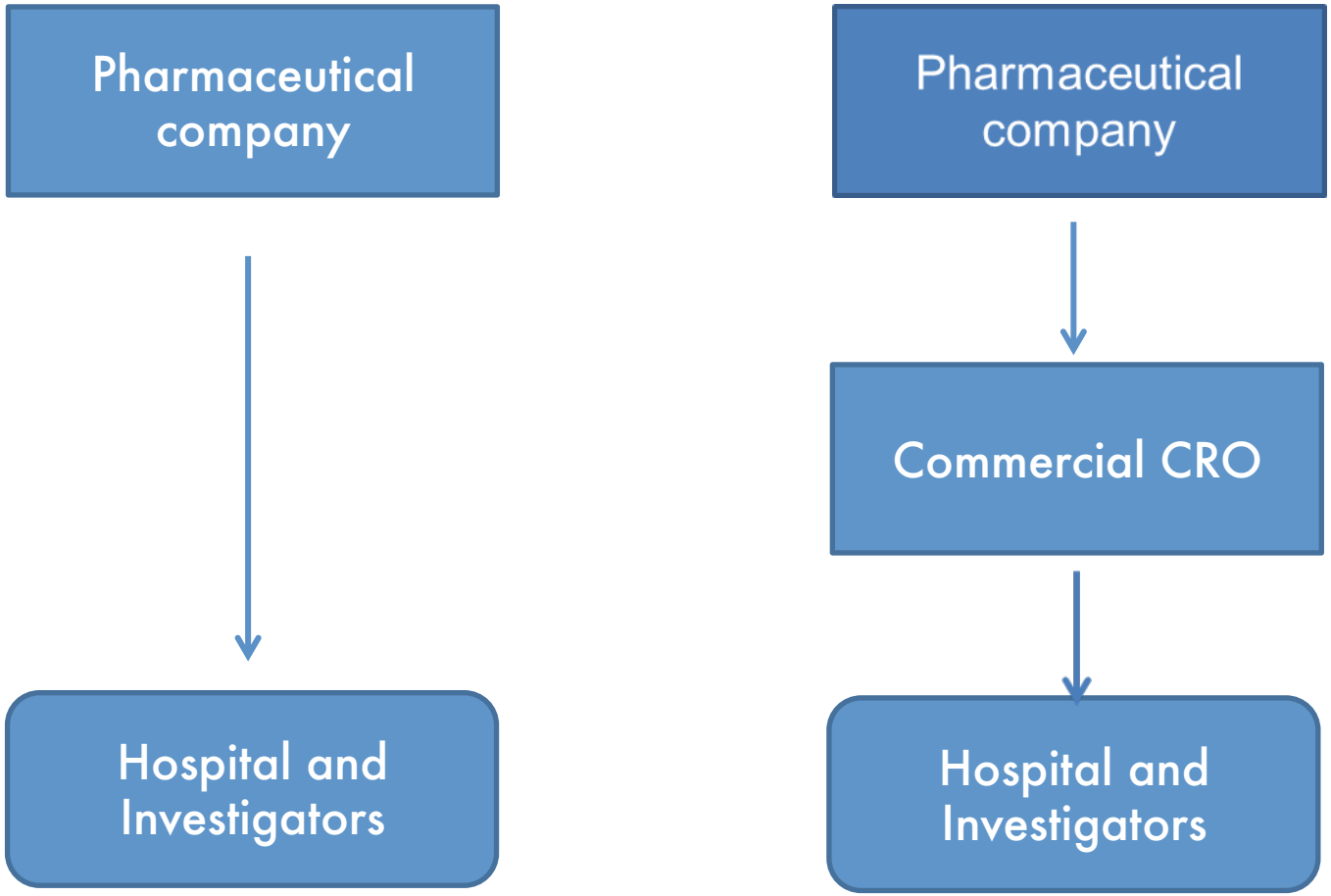
Subjects



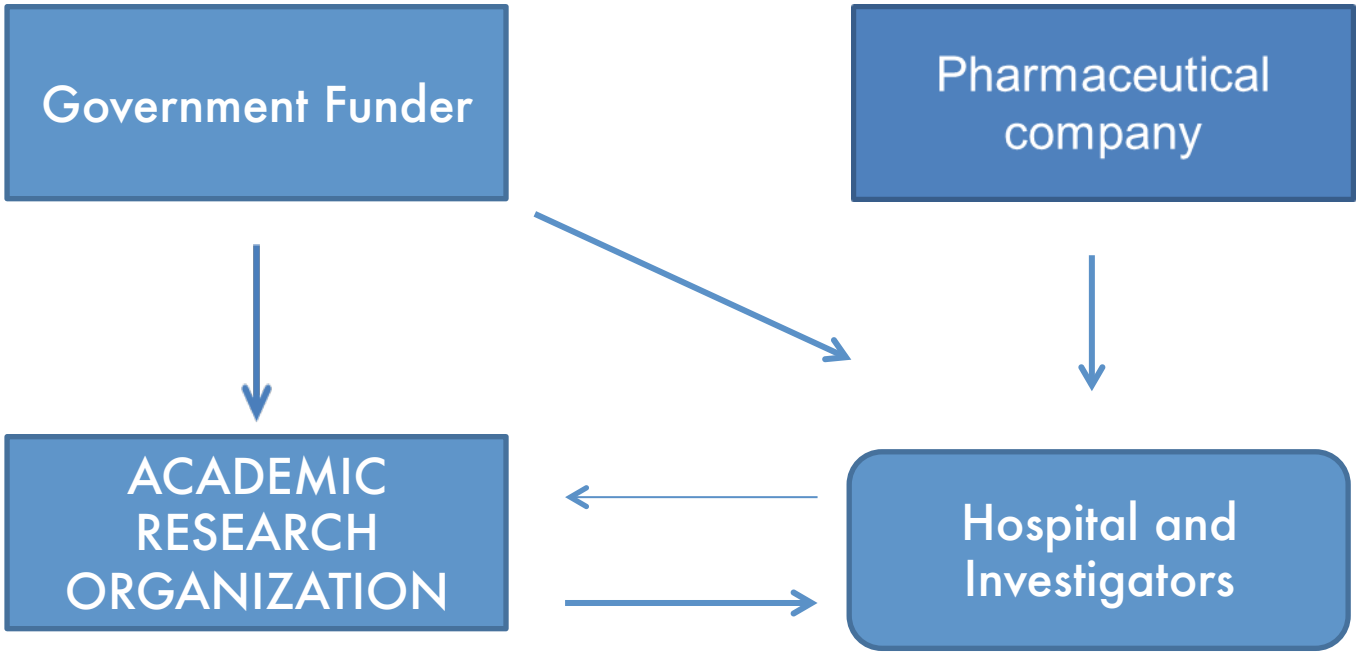
Investigators

Sponsors

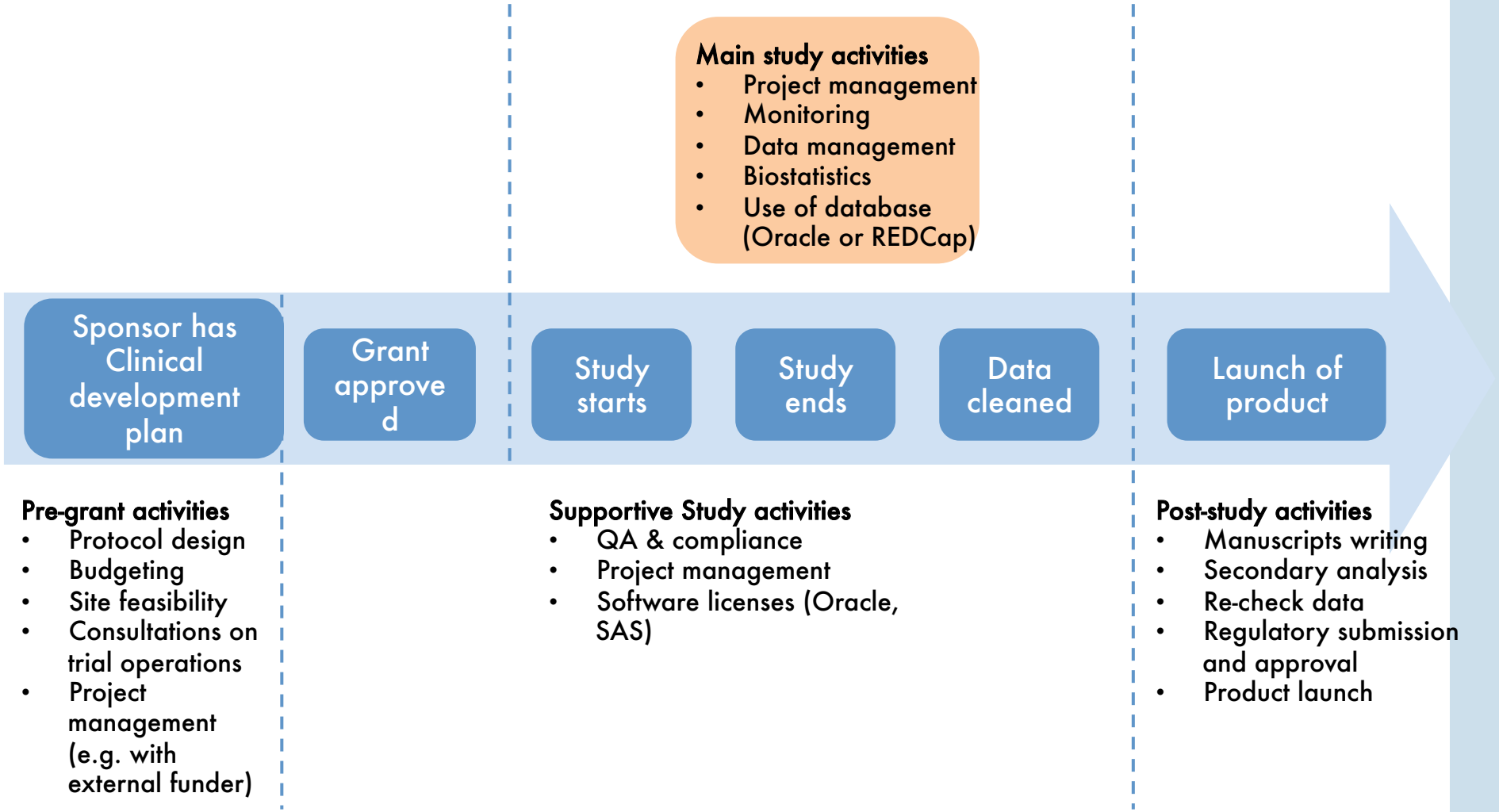
TRADITIONAL PHARMA SPONSORED STUDIES FUNDING MODEL



EXAMPLE OF A PARTNERSHIP CO-FUNDING FOR INVESTIGATOR-INITIATED STUDY IN SINGAPORE INVOLVING PARTNERHIP WITH ARO



Overview of a Clinical Trials Activities



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

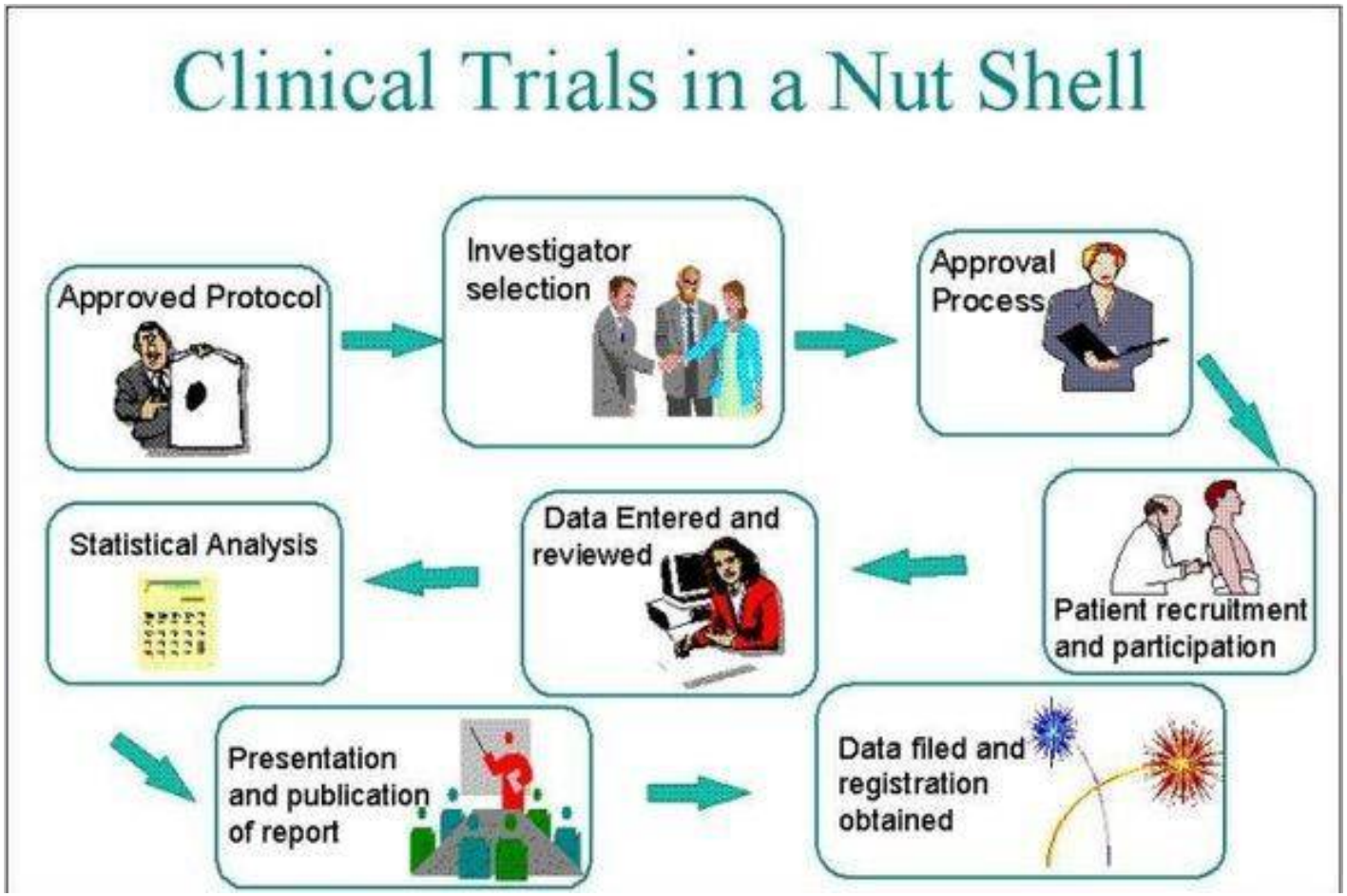
Staff involved:
Investigators (doctors)
Clinical Research Coordinators
Research assistants

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



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

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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

Global CROs

Fig. 1 **Estimated growth returns**

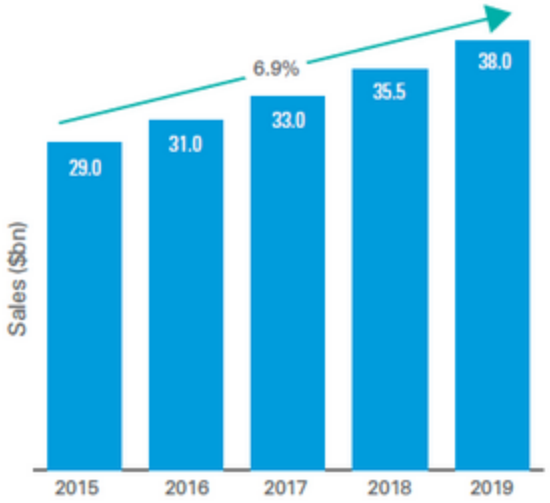
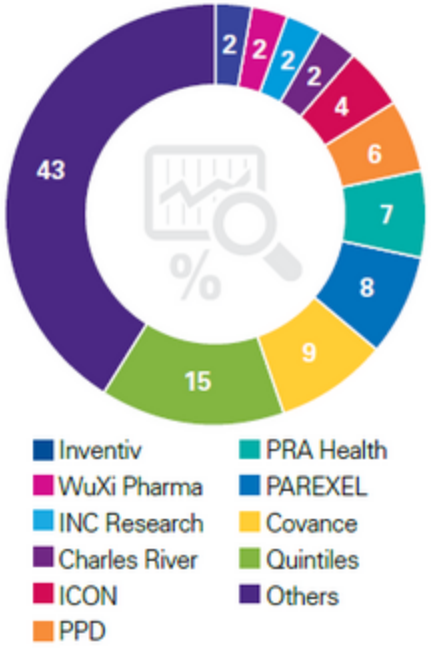


Fig.2 **Highly fragmented markets**



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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

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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

Pediatr Infect Dis J. 2013 Dec;32(12):e426-31. doi: 10.1097/INF.0b013e31829f2cb0.

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

Phua KB[1], 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 gastro enteritis, 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 gastro enteritis 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)

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Clinical Trial Management

Agenda

- GCP
- Monitoring
- Clinical Trial Registry
- Safety Reporting
- Project Management

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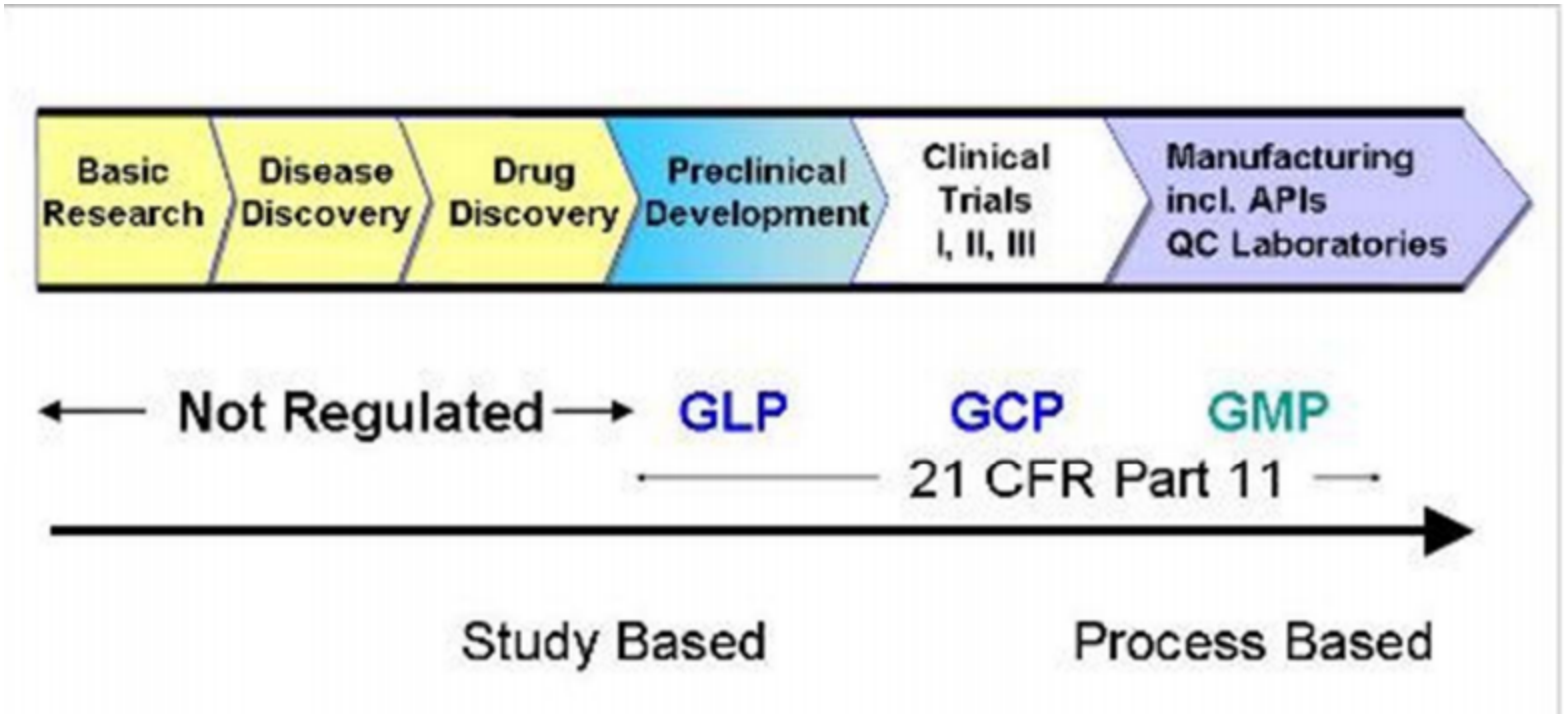
GCP
Good Clinical Practice

GCP Introduction

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.


Basic Research
Disease Discovery
Drug Discovery
Preclinical Development
Clinical Trials I, II, III
Manufacturing incl. APIs QC Laboratories
Not Regulated
GLP
GCP
GMP
21 CFR Part 11
Study Based
Process Based

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.

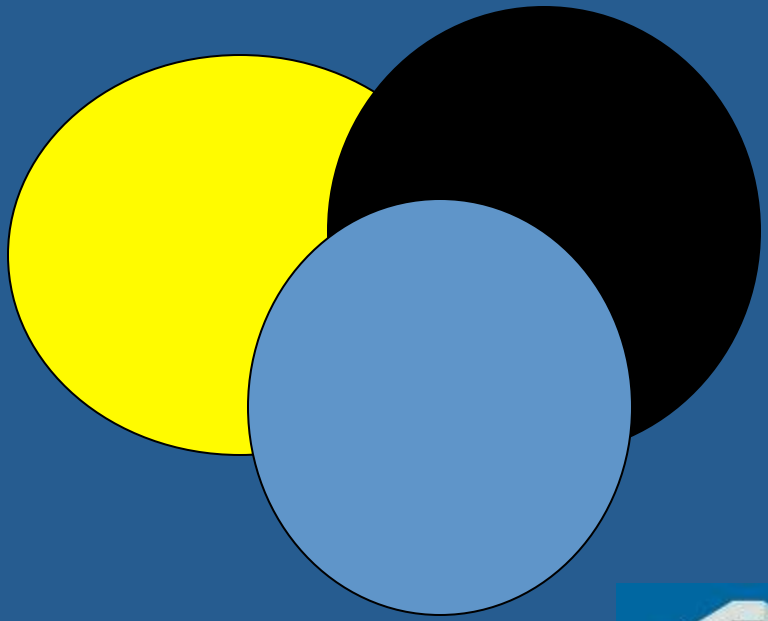
Ensure the CREDIBILITY of clinical trial data.

Ethics + Quality Data = GCP

Relationship between the parties

Ethics Board

Subjects



Investigators

Sponsors

Regulatory Approval Required before an Investigational New Drug (IND) trial can start

- IRB (Institutional Research Board or Ethics Board)
- FDA equivalent (Country drug regulatory)

Stakeholders in clinical trials

- Sponsors (Pharmaceutical company, NGOs)
- Investigators (Hospital doctor)
- Subjects (Patients)

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

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MONITORING

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.

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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.

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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

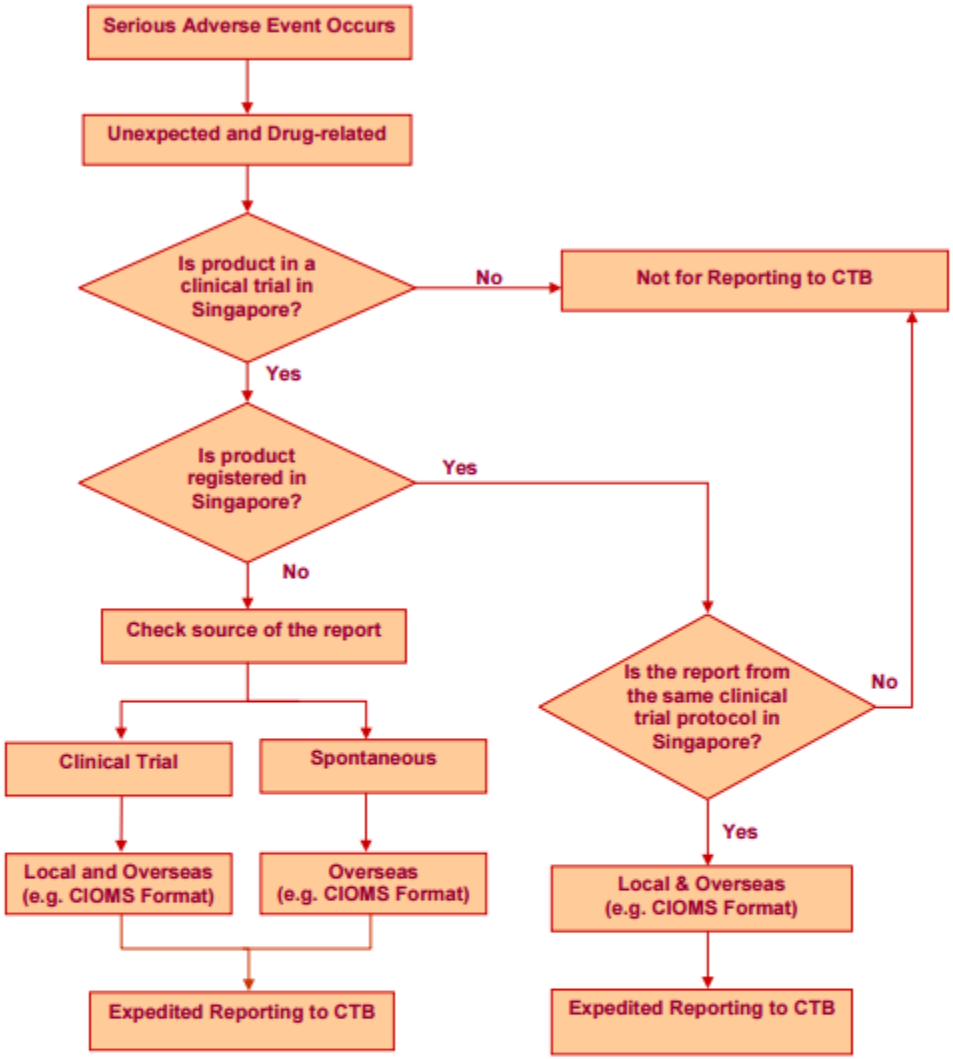
- A serious adverse reaction.
- Unexpected-not consistent with information already available in the protocol and the Investigators Brochure.
- AE that is both UNEXPECTED and is an SAE.

Safety & AE Reporting workflow

- Not all SAE are reportable to authorities

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

Safety & AE Reporting workflow



Safety & AE IRB Reporting

- < 24 Working Hours
  - AE is of high risk
  - Death or Potential Life Threathening unexpected SAE.
- < 1 week
  - AE / UE is of low risk
- Follow Up Reports

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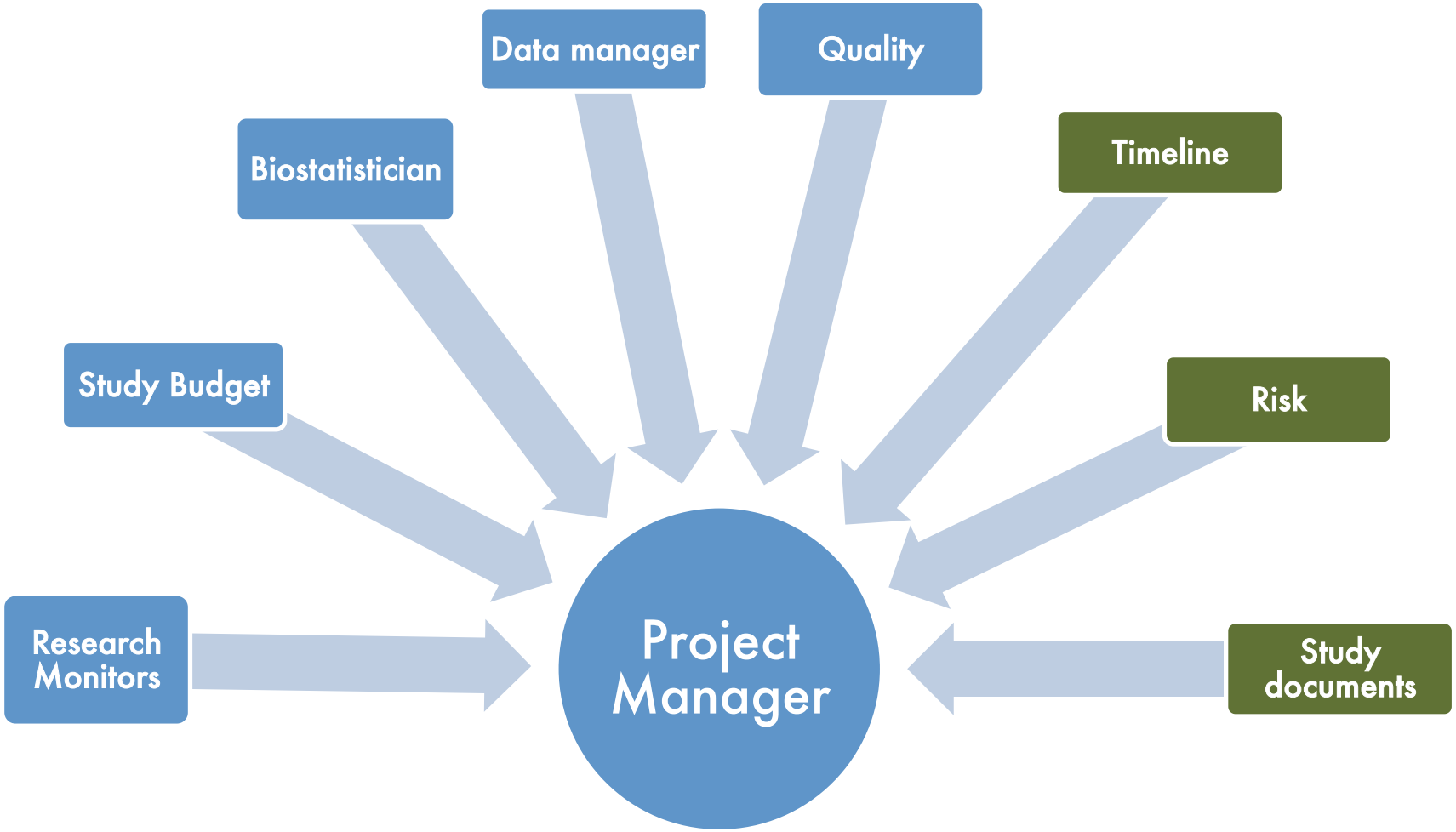
PROJECT MANAGEMENT

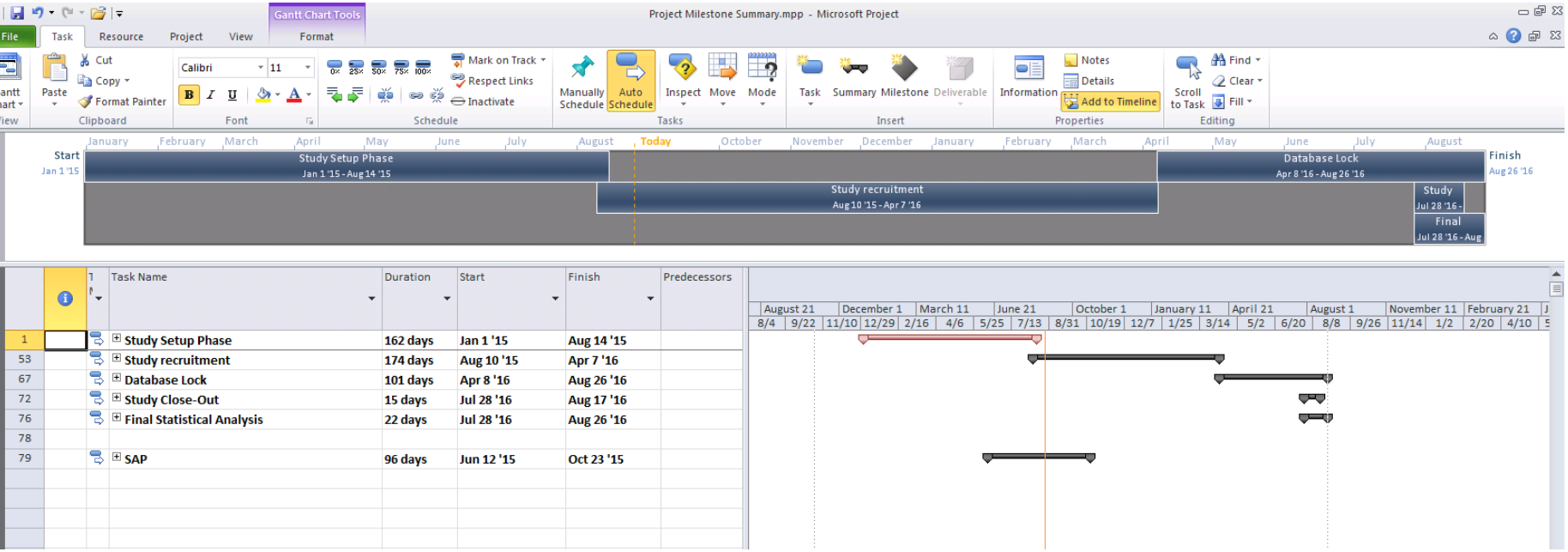
Project Management
Why Project management?



Project Management
Study Constrains

Project Triangle

Project Management
Project Gantt Chart



Project Management
Project Gantt Chart

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Project Milestone Summary.mpp - Microsoft Project

Gantt Chart Tools

Task | Resource | Project | View | Format

Cut | Copy | Format Painter | Paste | Clipboard

Calibri | 11 | Font

Mark on Track | Respect Links | Inactivate | Schedule

Manually Schedule | Auto Schedule | Inspect | Move | Mode | Tasks

Task | Summary | Milestone | Deliverable | Insert

Information | Notes | Details | Add to Timeline | Properties

Scroll to Task | Find | Clear | Fill | Editing

January February March April May June July August **Today** October November December January February March April May June July August

Start Jan 1 '15

Study Setup Phase
Jan 1 '15 - Aug 14 '15

Study recruitment
Aug 10 '15 - Apr 7 '16

Database Lock
Apr 8 '16 - Aug 26 '16

Study
Jul 28 '16 -

Final
Jul 28 '16 - Aug

	Task Name	Duration	Start	Finish	Predecessors
1	Study Setup Phase	162 days	Jan 1 '15	Aug 14 '15	
2	CTA and Budget	91 days	Jan 1 '15	May 7 '15	
10	Protocol	31 days	Jan 1 '15	Feb 12 '15	
13	CRF	25 days	May 8 '15	Jun 11 '15	
17	eCRF	46 days	Jun 12 '15	Aug 14 '15	
20	Randomization	26 days	May 8 '15	Jun 12 '15	
26	Informed Consent Form	15 days	May 8 '15	May 28 '15	
30	IRB	51 days	May 29 '15	Aug 7 '15	
34	Regulatory Authority	51 days	May 29 '15	Aug 7 '15	
38	Study Operations Manual	26 days	Jun 12 '15	Jul 17 '15	
43	Monitoring Plan	26 days	Jun 12 '15	Jul 17 '15	
48	Investigational Product Manual	41 days	Jun 5 '15	Jul 31 '15	
53	Study recruitment	174 days	Aug 10 '15	Apr 7 '16	
67	Database Lock	101 days	Apr 8 '16	Aug 26 '16	
72	Study Close-Out	15 days	Jul 28 '16	Aug 17 '16	
76	Final Statistical Analysis	22 days	Jul 28 '16	Aug 26 '16	

August 21 | December 1 | March 11 | June 21 | October 1 | January 11 | April 21 | August 1 | November 11

8/4 9/22 11/10 12/29 2/16 4/6 5/25 7/13 8/31 10/19 12/7 1/25 3/14 5/2 6/20 8/8 9/26 11/14 1/2

Project Management
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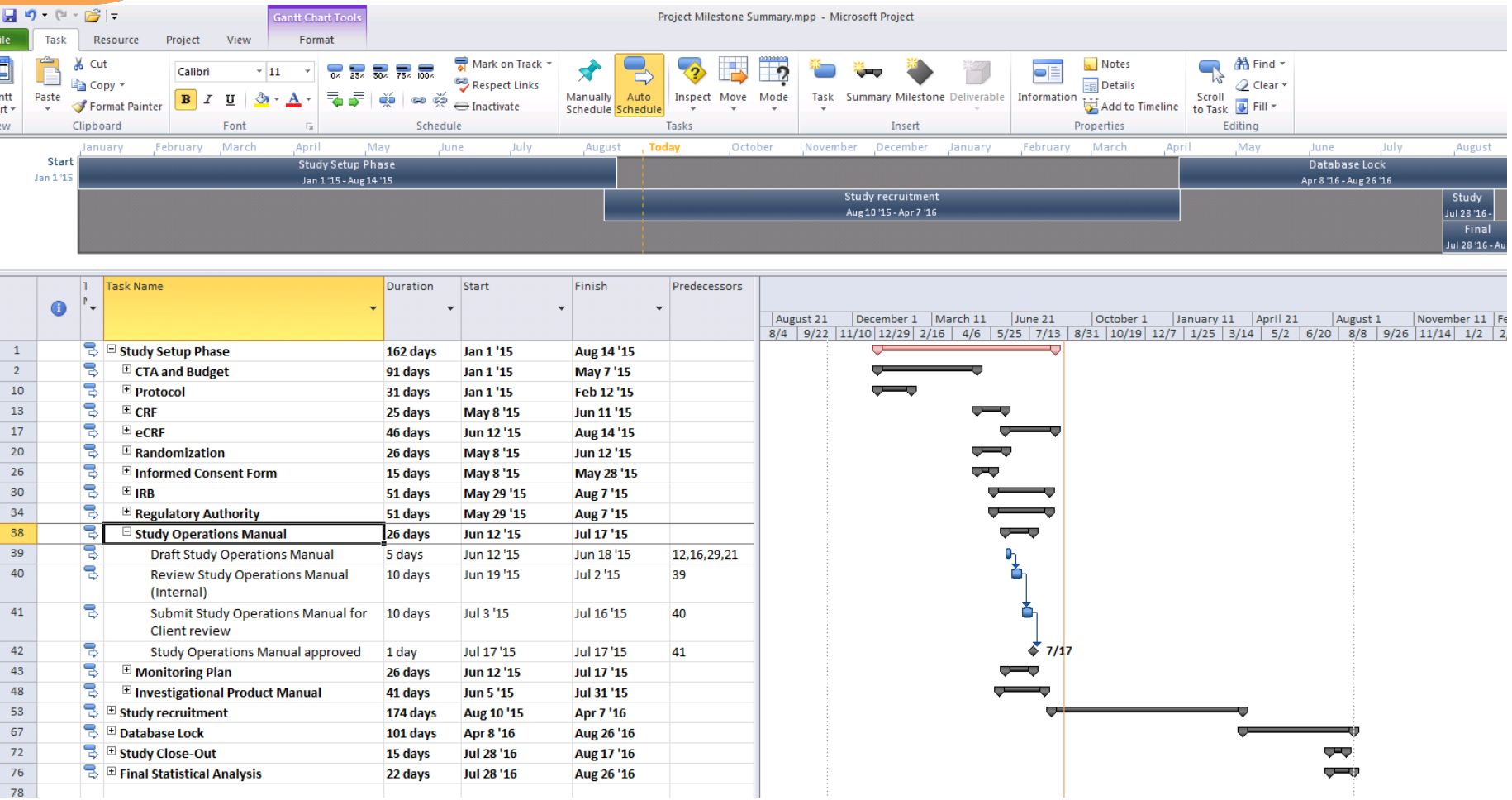

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39	Draft Study Operations Manual	5 days	Jun 12 '15	Jun 18 '15	12,16,29,21
40	Review Study Operations Manual (Internal)	10 days	Jun 19 '15	Jul 2 '15	39
41	Submit Study Operations Manual for Client review	10 days	Jul 3 '15	Jul 16 '15	40
42	Study Operations Manual approved	1 day	Jul 17 '15	Jul 17 '15	41
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78					


Clinical Research Maze
Enter at your own Risk
SUBJECTS
Data Analyses
AUDITS
Training
CITI
BAA
IND
CONTRACT
SAE REPORTS
GCP
CRFs
CTRC
PATIENT BILLS
FEASIBILITY
IRB
FUNDING
SCIENTIFIC REVIEW
BUDGET
CTA
MTA
HIPPA
BIOSTATS
REG
FDA
DOCS
Grants
STUDY COORDINATOR SUPPORT
Drug Accountability
BIOINFORMATICS

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Clinical Trials Budgeting

Budget components

Clinical Trial Budget

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

Project cost tracking

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 (eg. Butterfly needles, vacutainers)
- Special equipment necessary for the project (eg -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 (eg. 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.

SINGAPORE CLINICAL RESEARCH INSTITUTE

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 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?

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

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.

The Demand

Industrialized Countries

1 billion

Developing Countries

5 billion

Earlier and more widespread access to existing and new vaccines <u>for all</u> should be the standard

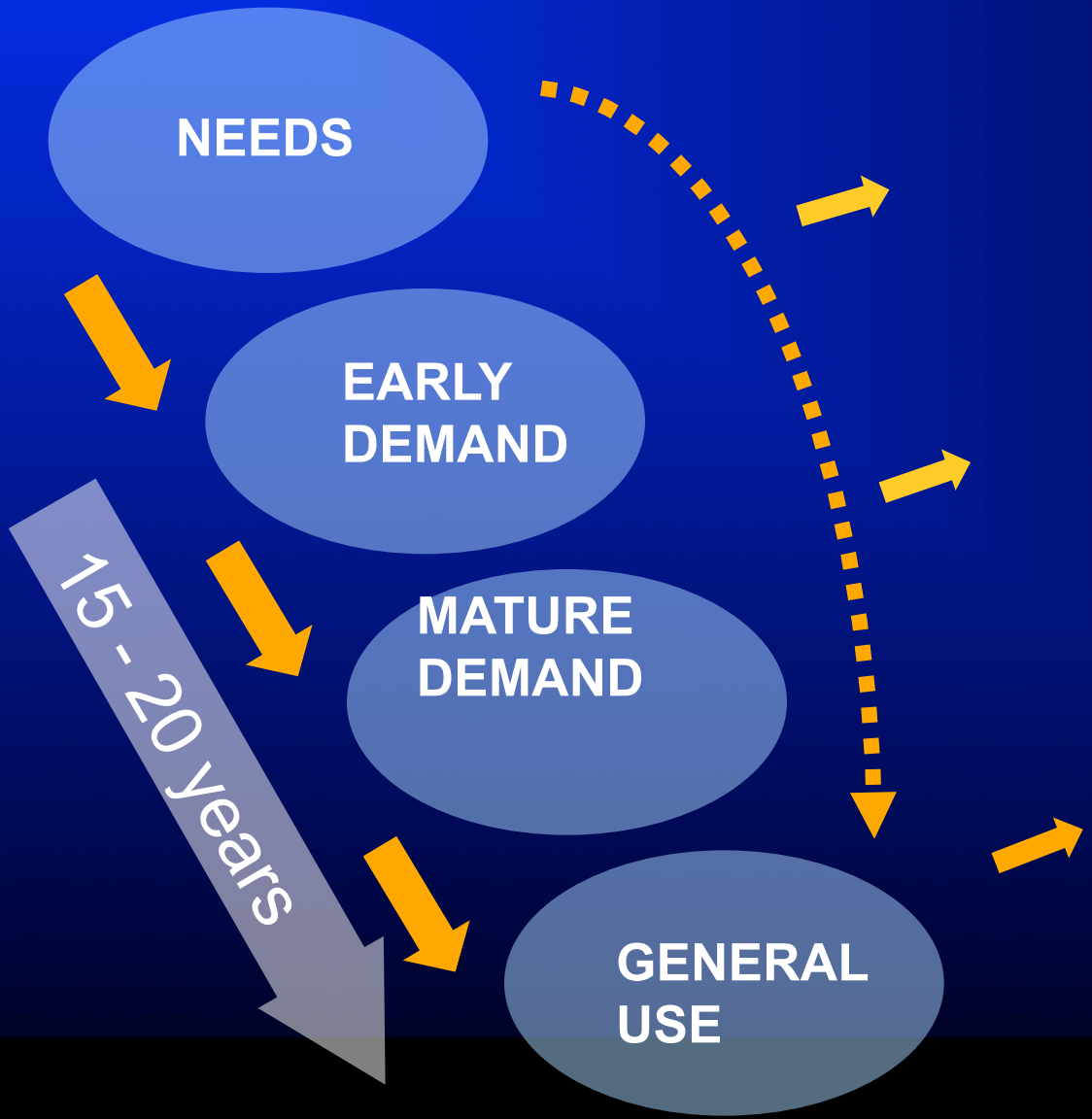
Is Vaccine development less popular than Pharmaceutical drugs?

- 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



Private market

Private market

Public market

Private market

Public market

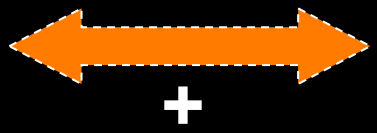
Changing Vaccines Paradigm

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

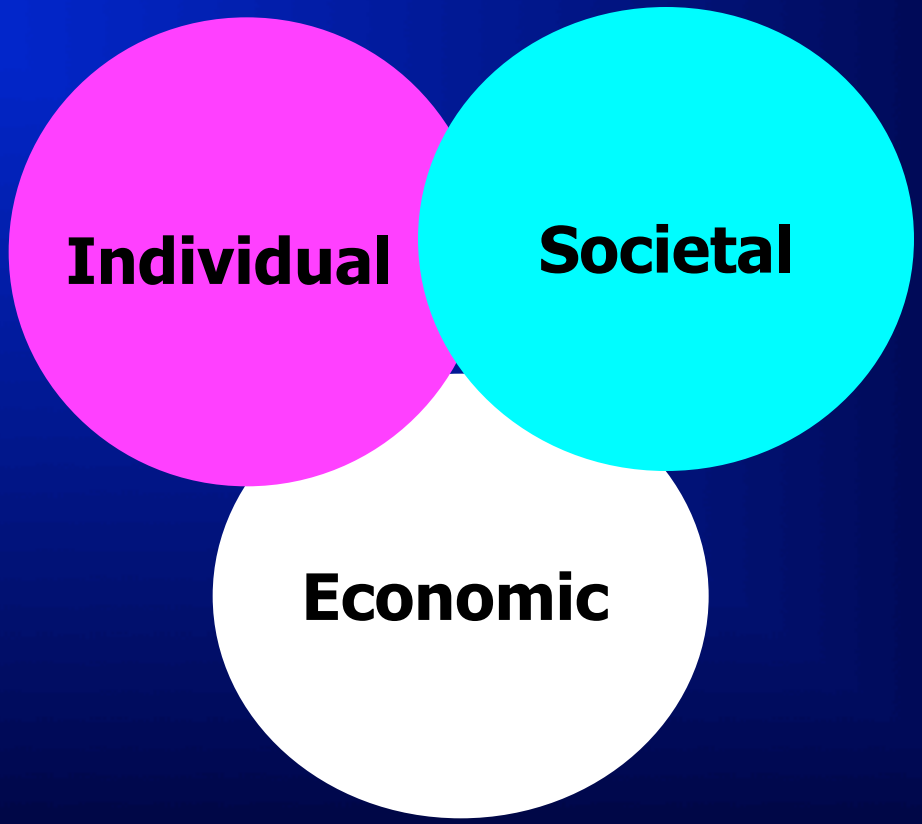
Public  **Private**

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**[1]
- **750,000 children are saved from disability**[1]

. . . due to vaccines

[1]Ehreth J. *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

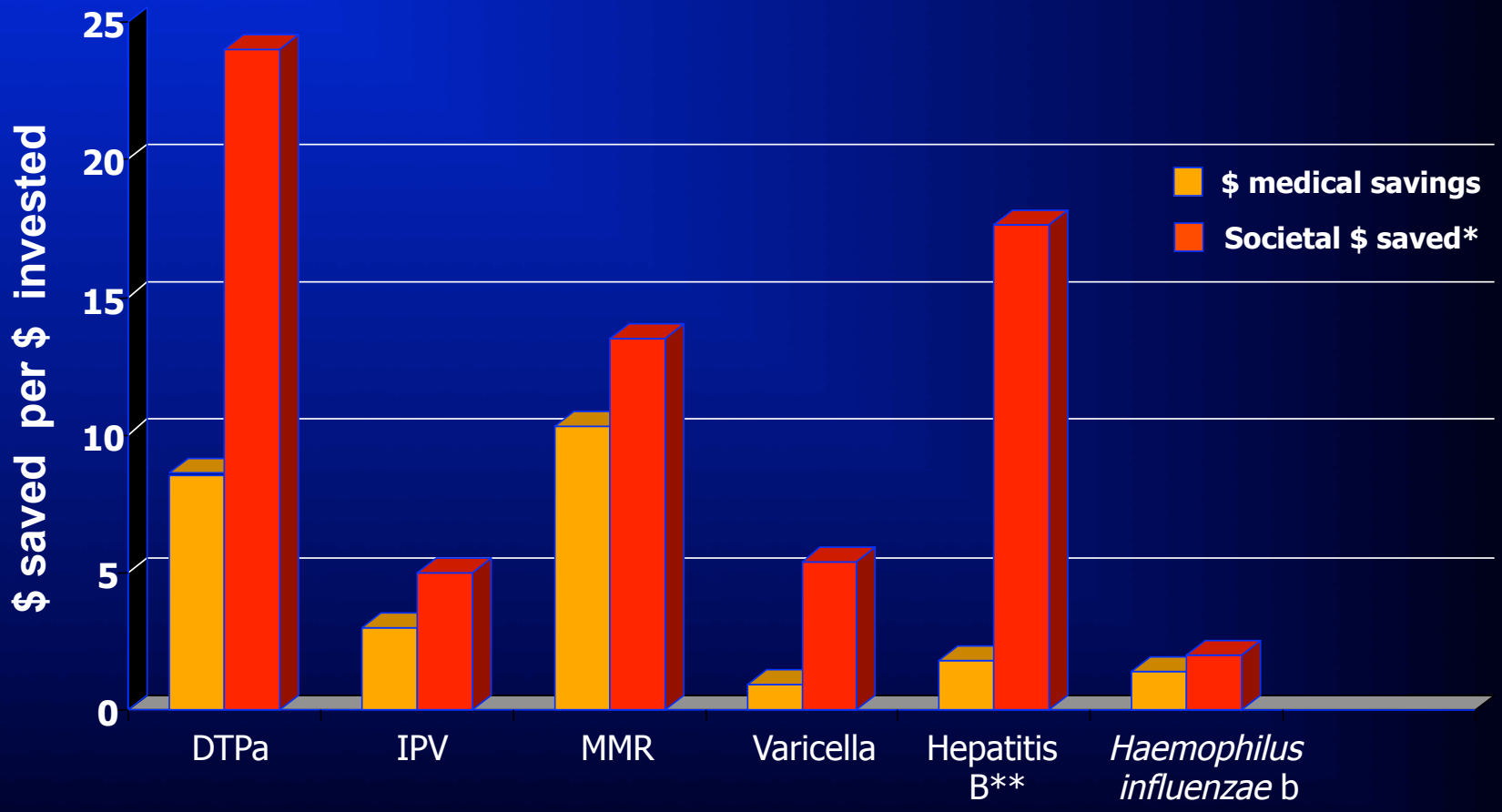
- Before vaccines, parents in the United States could expect that every year:
  - Polio would paralyze 10,000 children
  - Rubella (German measles) would cause birth defects and mental retardation in as many as 20,000 newborns

Philadelphia Vaccine Education Center, http://vaccine.chop.edu

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)

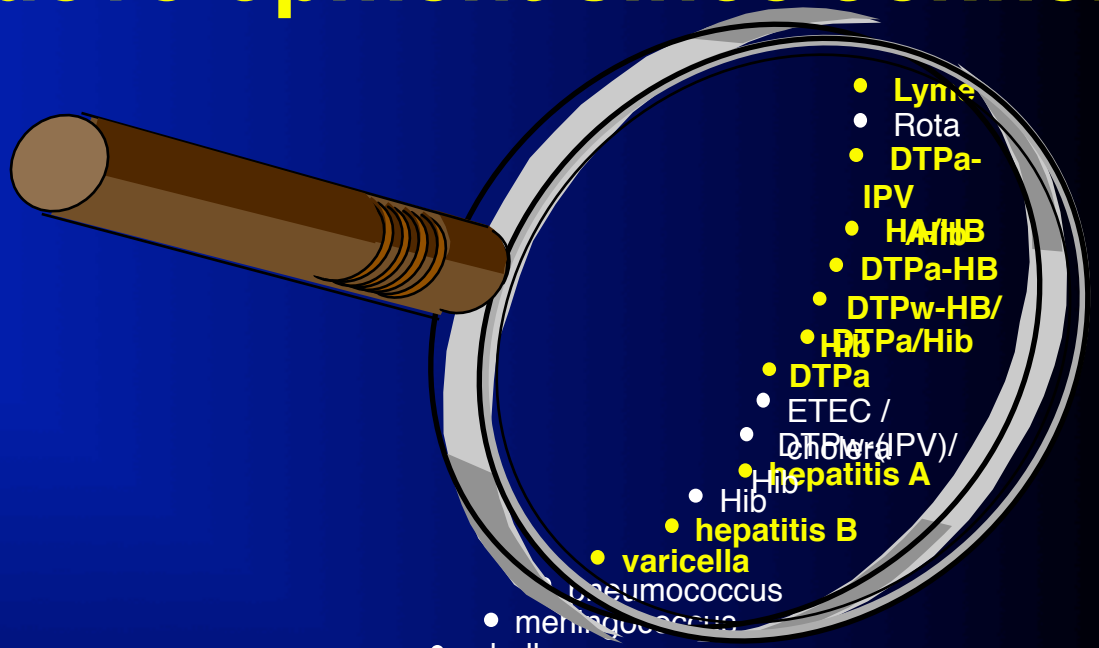


***Includes work loss, deaths and disability**

****Perinatal/infant**

[1]Centres for Disease Control and Prevention 2002

Vaccine development since Jenner



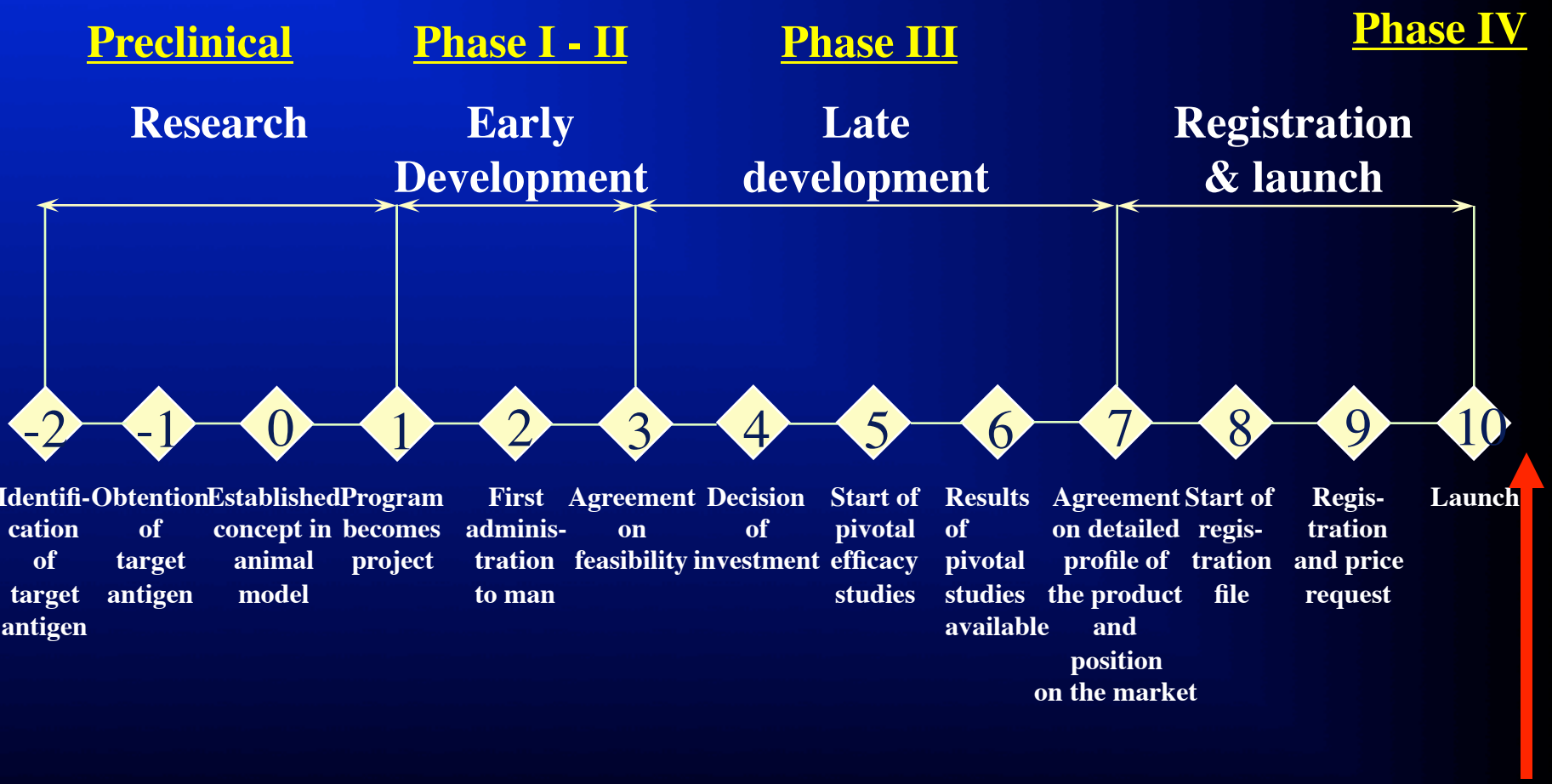
New Advances in the Vaccine Field

- 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



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 (eg 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 its unethical to deprive a subject of his routine vaccination to study the new vaccine

Storage and Distribution

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.

Storage and Distribution

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

Frozen

Vaccines that cannot be frozen

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

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

Terms used for Vaccine Trial

- Safety : Is the vaccine safe?
- Reactogenicity : Reaction caused by the vaccine (eg 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

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?

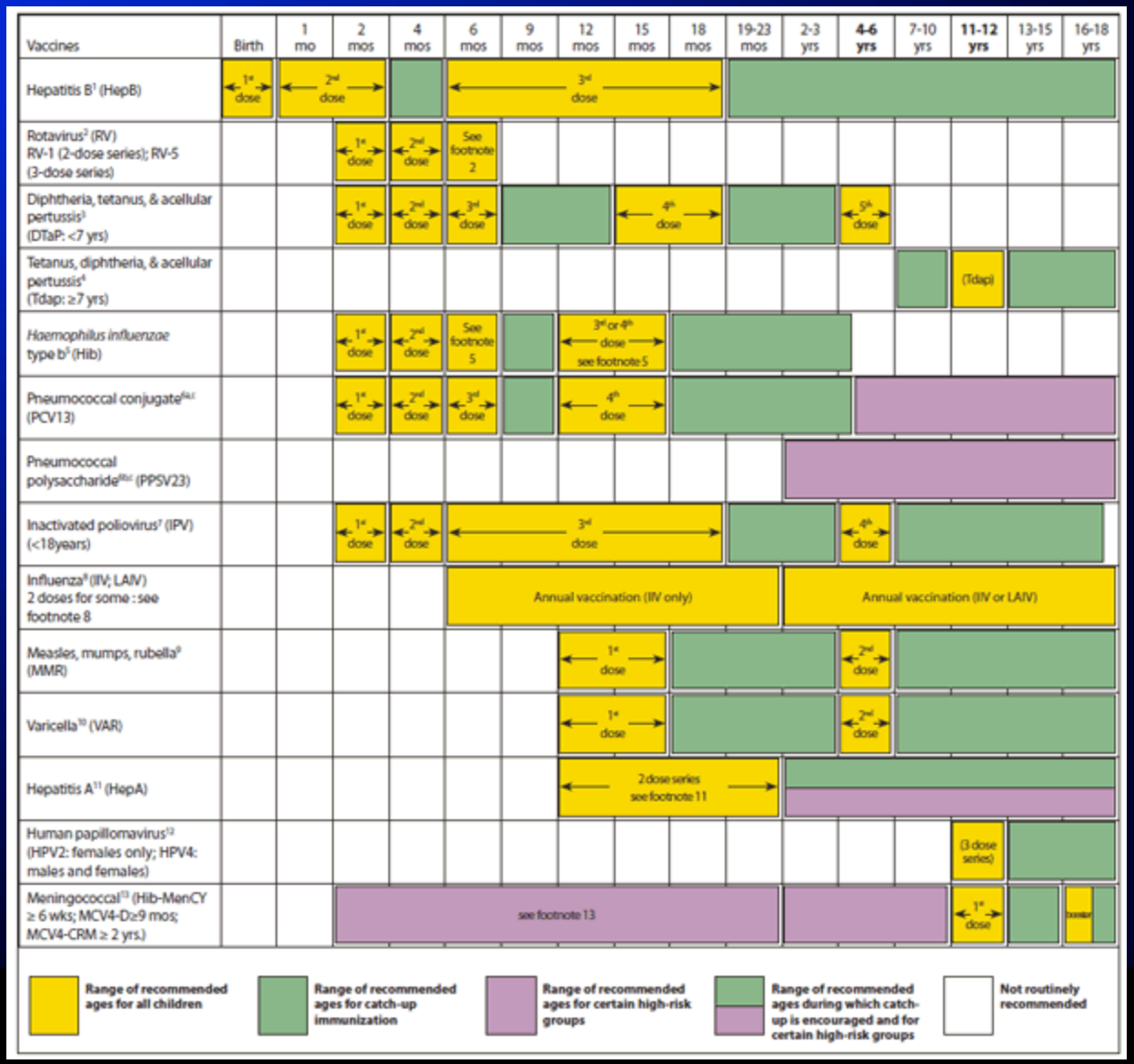
- Need to use indirect markers like immune response instead of efficacy (eg cannot purposely exposed subjects to HIV infection to test for efficacy of HIV vaccine)

ETHICAL CHALLENGES IN VACCINES CLINICAL TRIALS

A/Prof Teoh Yee Leong

MBBS, Master of Medicine (Public Health), FAMS
CEO Singapore Clinical Research Institute

US CDC Vaccination Schedule- majority of vaccines are for infants and children



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 (eg blood taking)
  - Ethics Board is well versed
  - Higher tolerence 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 (eg 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 its unethical to deprive a subject of his routine vaccination to study the new vaccine

Need to co-administered with other vaccines

For persons aged 0 to < 18 years											
		Months								Years	
Vaccination against	**Birth**	1	3	4	5	6	12	15	18	6-7 ^	10-11 ^^
Tuberculosis	BCG										
Hepatitis B	HepB (D1)	HepB (D2)			HepB (D3) #						
Diphtheria, Tetanus, Pertussis			DTaP (D1)	DTaP (D2)	DTaP (D3)				DTaP (B1)		TdaP (B2)
Poliovirus			IPV (D1)	IPV (D2)	IPV (D3)				IPV (B1)		OPV (B2)
Haemophilus influenzae type b			Hib (D1)	Hib (D2)	Hib (D3)				Hib (B1)		
Measles, Mumps, Rubella							MMR (D1)	MMR (D2) ##			
Pneumococcal Disease			PCV (D1)		PCV (D2)		PCV (B1)				
Human Papillomavirus	Recommended for females 9 to 26 years; three doses are required at intervals of 0, 2, 6 months										

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

Deaths in Vaccine Trials

Buenos Aires Herald

Buenos Aires 17°C AccuWeather.com Weather Forecast

Sunday March 23, 2014

Tuesday, January 3, 2012

GSK fined over vaccine trials; 14 babies reported dead

GlaxoSmithKline CEO Andrew Witty.

By Javier Cardenal Taján

BuenosAiresHerald.com staff

GlaxoSmithKline Argentina Laboratories Company was fined 400,000 pesos by Judge Marcelo Aguinsky 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 fro 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 2.3times higher in children who received ProQuad, when compared to those who received MMRII 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 *VariIrix*™ 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*™ + *VariIrix*™ 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

Vaccine 27 (2009) 5936–5941

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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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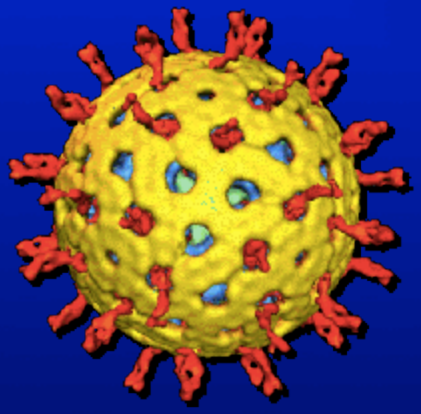
ABSTRACT

This study evaluates the safety and efficacy against severe rotavirus gastroenteritis of the oral live attenuated human rotavirus vaccine RIX4414 (*Rotarix*™) 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.

Group Discussion 4

- Group the participants into 2 groups
- What can you do when the recruitment is behind the timelines?



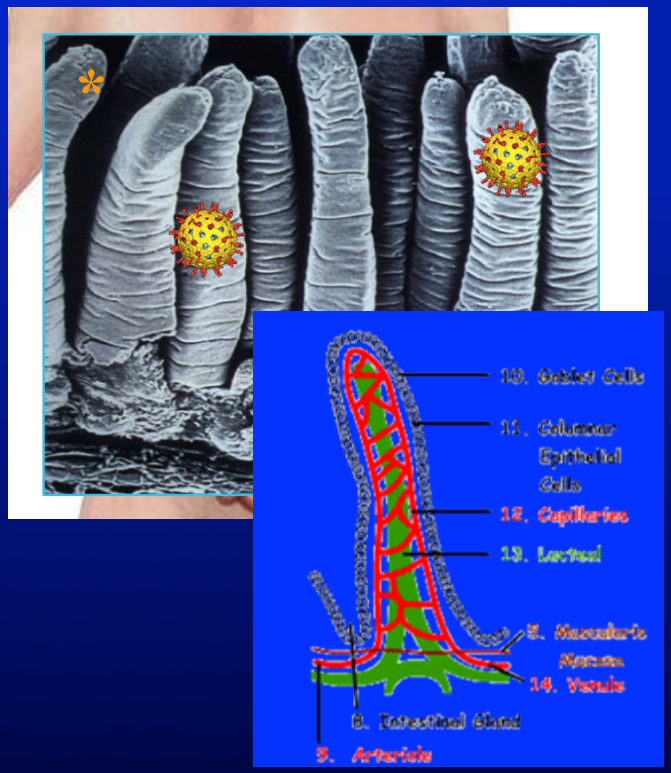
Rotavirus Disease

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

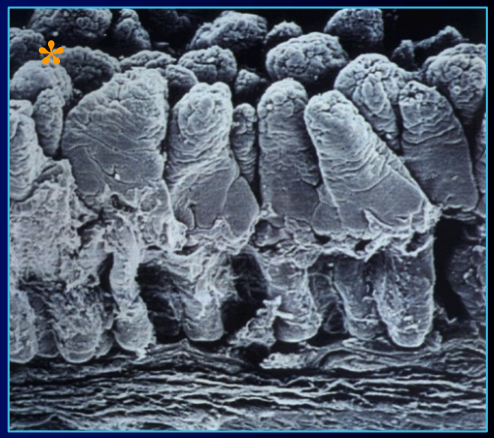
→ **VOMITING AND DIARRHEA**

↓

NSP4 viral enterotoxin

↓

Enteric nervous system activation



*Rotavirus infection in an animal model of infection. Photographs are from an experimentally infected calf. Reproduced with permission from Zuckerman et al, eds. *Principles and Practice of Clinical Virology*. 2nd ed. London: John Wiley & Sons; 1990:182. Micrographs courtesy of Dr. Graham Hall, Berkshire, UK.

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**

Kapikian A and Chanock R. Rotaviruses. In: Fields B et al, editors. Fields Virology, 3rd ed; 1996: p. 1657–1708

Treatment and Prevention

- **Main goals of treatment:**
  - **Control the diarrhea**
  - **Prevent vomiting**
  - **Control other symptoms**
  - **Maintain effective fluid and electrolyt balance with oral re-hydration therap (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**

Kapikian A and Chanock R. Rotaviruses. In: Fields B et al, editors. Fields Virology, 3rd ed; 1996: p. 1657–1708

Why Singapore?

Population: 3.8 million

Area: 620 sq. km

Annual births: 40,000

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

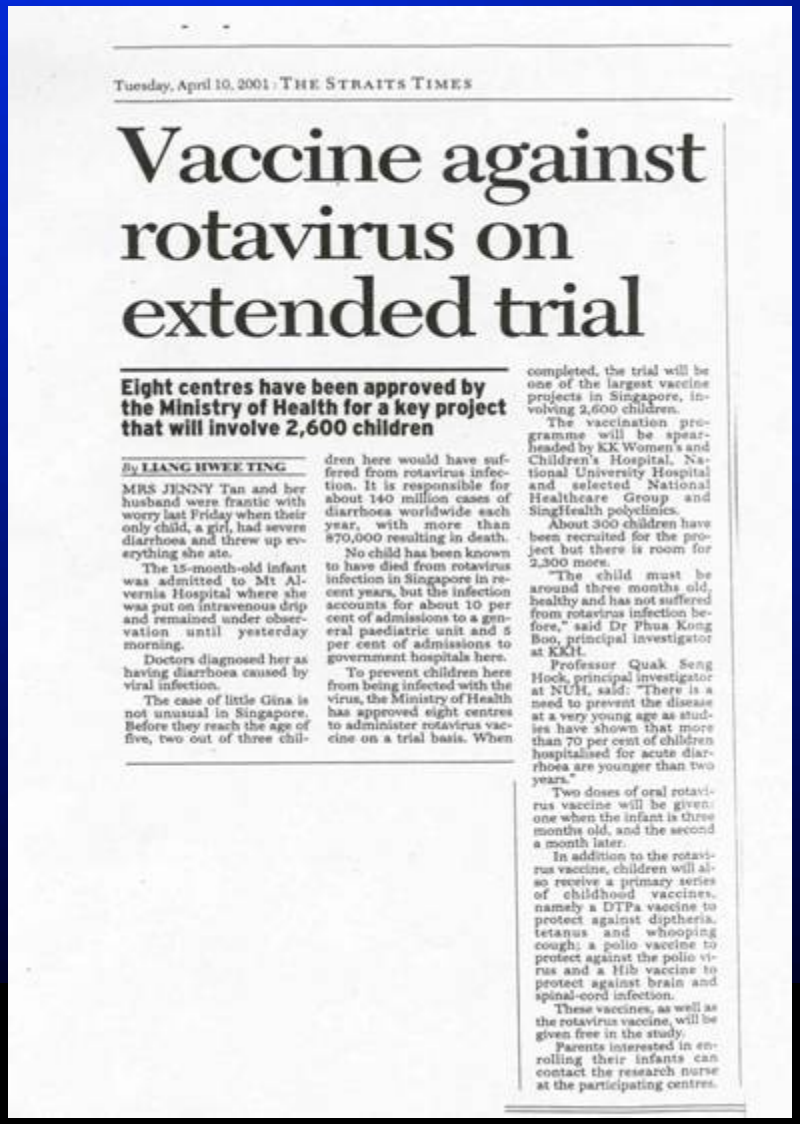

Polyclinics
SingHealth


07.04.16:38

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.

Newspaper Report



Tuesday, April 10, 2001 · THE STRAITS TIMES

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 HWEE 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 15-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 vaccine 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 300 children have been recruited for the project but there is room for 2,300 more.

"The child must be around three months old, healthy and has not suffered from rotavirus infection before," said Dr Phua Kong Boo, principal investigator at KKH.

Professor Quak Seng Hock, principal investigator at NUH, 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 younger than two years."

Two doses of oral rotavirus vaccine will be 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 childhood vaccines, namely a DTPa vaccine to protect against diptheria, tetanus and whooping cough; a polio vaccine to protect against the polio virus and a Hib vaccine to protect against brain and spinal-cord 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.

确保不会感染急性肠胃炎

两千多婴孩将接受轮状病毒防疫注射

本地每年有约10%的孩童，因严重腹泻而必须留医治疗。一般受感染的婴孩大多能在两个星期内完全康复。不过，每年却有约5%的婴孩因严重腹泻、呕吐，以致脱水而最终死亡。

何文欣 • 报道

2640名3个月及4个月大的本地婴孩，将在下来的两年里，陆续参与轮状病毒（rotavirus）免疫试验计划，以确保不会轻易受到这种病毒的感染而导致急性肠胃炎。

这个由国大医院、竹脚妇幼医院及全岛所有综合诊所展开的轮状病毒免疫试验计划，于去年12月间展开，到目前为止，已有300名婴孩接受了轮状病毒的免疫。

医学数据显示，轮状病毒是导致孩童患上急性肠胃炎的罪魁祸首。孩童患上肠胃炎以致腹泻、呕吐及发高烧，其实是非常普遍的。

本地每年就有约10%的孩童因严重腹泻而必须留医治疗。

在这当中，超过70%是两岁以下的孩童，并以6至11个月大的婴孩居多。一般受感染的婴孩大多能在两个星期内完全康复。不过，每年却有约5%的婴孩因严重腹泻、呕吐，以致脱水而最终死亡。

本地儿科医生希望，待免疫试验计划的研究和调查工作完成后，由药剂公司Glaxo-SmithKline开发的轮状病毒疫苗，功效若能获得肯定与批准，将能帮助减低本地孩童感染轮状病毒的可能性。

国大医院儿科肠胃病学顾问郭承福副教授受访时说，轮状病毒的疫苗是口服疫苗，参与计划的婴孩必须在3、4、5、9、12及18个月大时服用疫苗，以完成整个免疫过程。

在接受轮状病毒口服疫苗的同时，参与计划的婴孩也将接受其他如预防百日咳、破伤风、白喉等例常疫苗注射。

郭承福说，我国目前并没有任何预防轮状病毒的疫苗，因此，如果有很多婴孩因为感染轮状病毒导致腹泻和呕吐而必须留院治疗，撒开医药费用不谈，对父母造成的不便是可想而知。

他说："轮状病毒免疫试验计划是由卫生部所批准的一项全岛性计划，如果能证实轮状病毒疫苗的功效和安全，对新加坡的孩童来说将是好事。

"如果疫苗证实有效，就算是孩子在服用了疫苗后仍然感染肠胃炎，病情也将是较轻微的。"

我国是全球展开轮状病毒免疫试验计划的第7地区，欧洲多个国家、美国、拉丁美洲等地区也都展开这个试验计划。

参与这个试验计划的婴孩都是没有感染过轮状病毒的健康婴孩，除了已服用了疫苗的300名婴孩，国大医院、竹脚妇幼医院和综合诊所也呼吁有兴趣的家长，让自己的孩子参与计划。医生会在为孩子进行检查后，才让孩子服用疫苗。

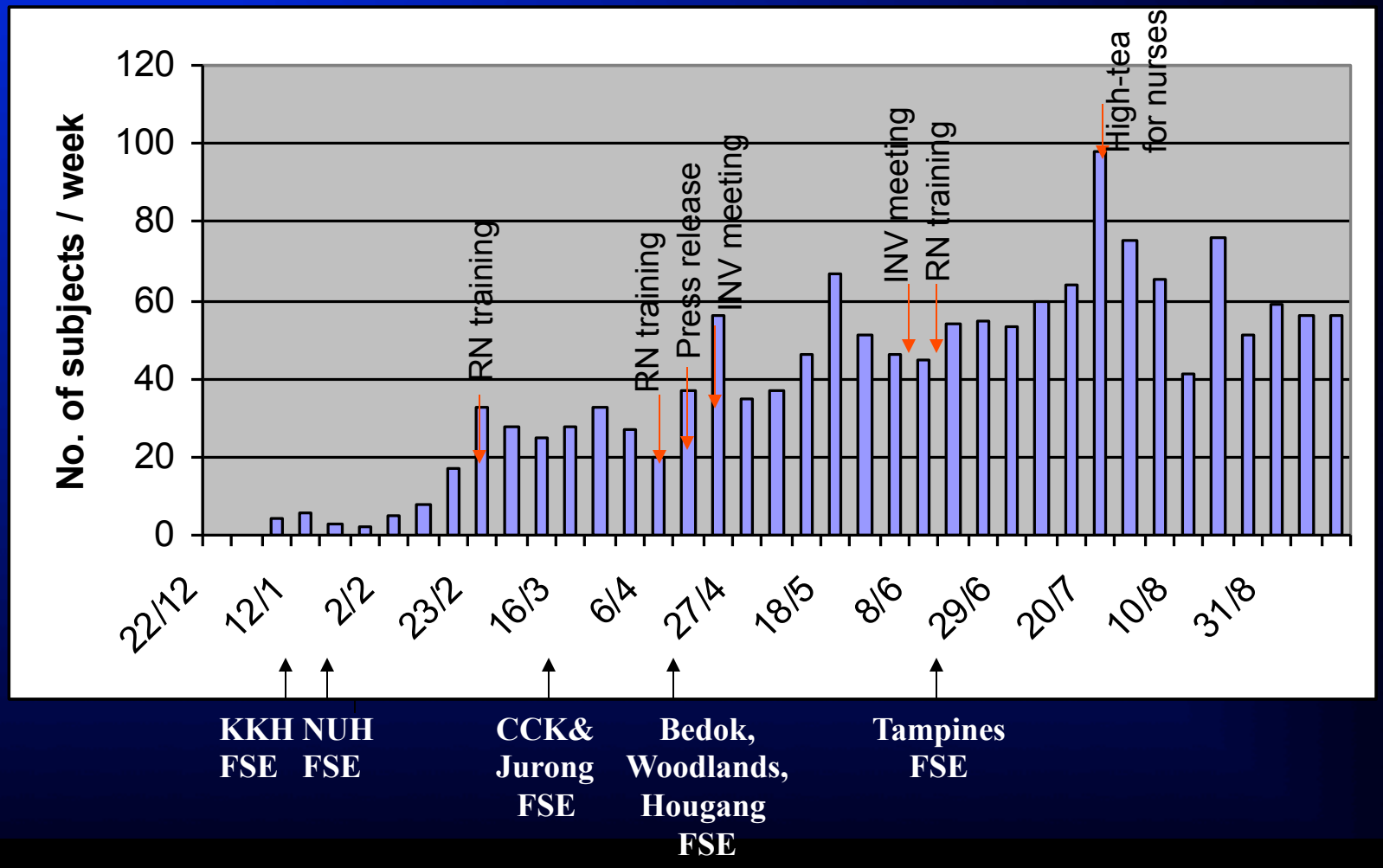
各医院和综合诊所负责护士

有意为自己孩子接受注射的家长，可联络以下医院和综合诊所的负责护士：

☆竹脚妇幼医院	Amy Tay	95557169
☆国大医院	Liew Yoong Pyng	7724451 / 94357300
☆联盟港综合诊所	Joyce Kan	8925349
☆兀兰综合诊所	Fong Li-Er	3697022
☆裕廊综合诊所	Lee Cheng Liang	5630755
☆后港综合诊所	Chin Teng Fong	4898090
☆勿洛综合诊所	Fiona Wong	2436757
☆淡滨尼综合诊所	Yap Siew Yoon	7879607

合办课程15年以来成绩最优秀

Weekly Recruitment for All 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.

Centre 2

SGH Bacteriology lab & NUH lab

SGH lab is ISO 9001 certified lab.

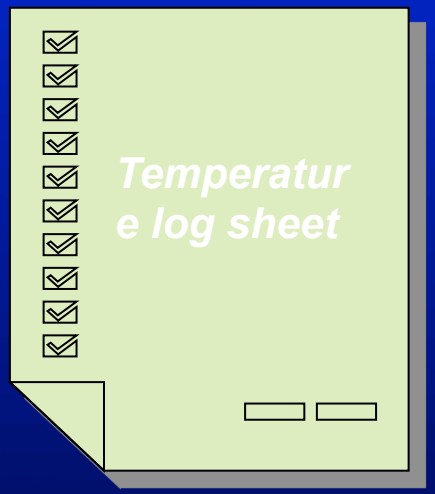
This is Where GE Stool sample being Tested for Rota & Other bacteria.

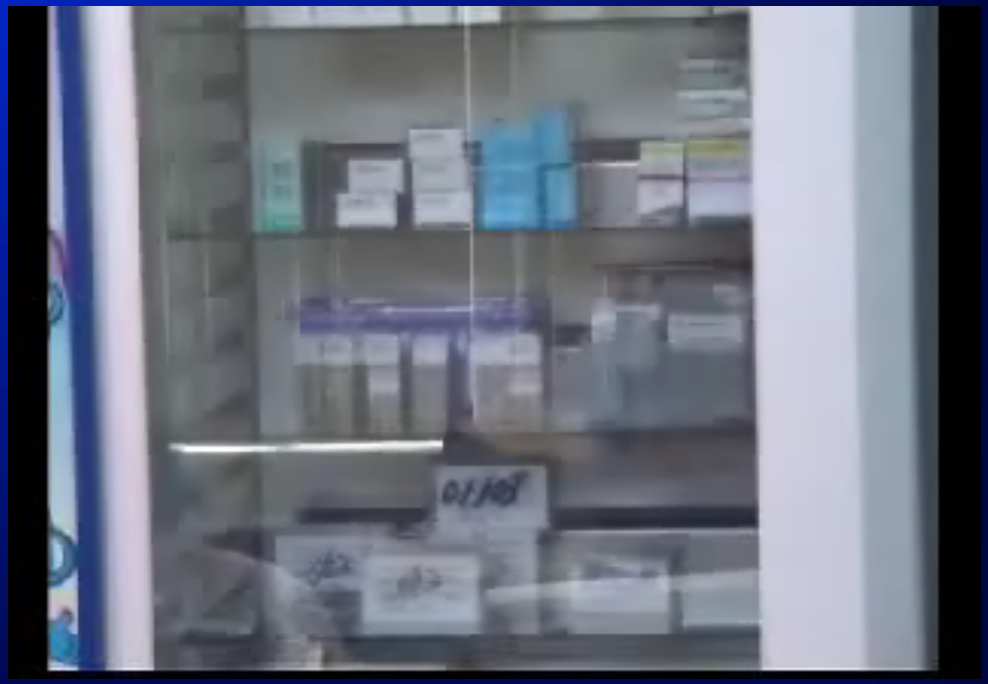
Dispatch rider for stool samples collection

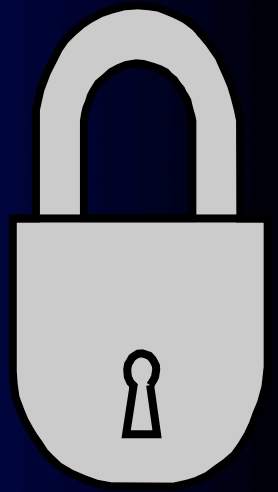
Be careful, Shariff!

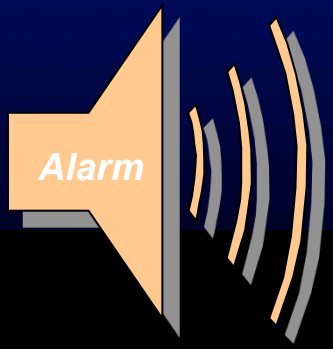
Safety first!

Vaccine storage in clinic



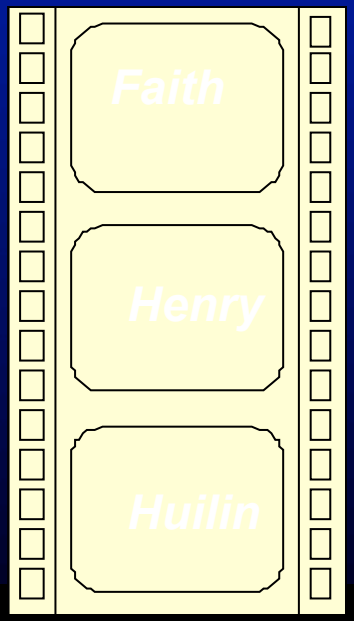






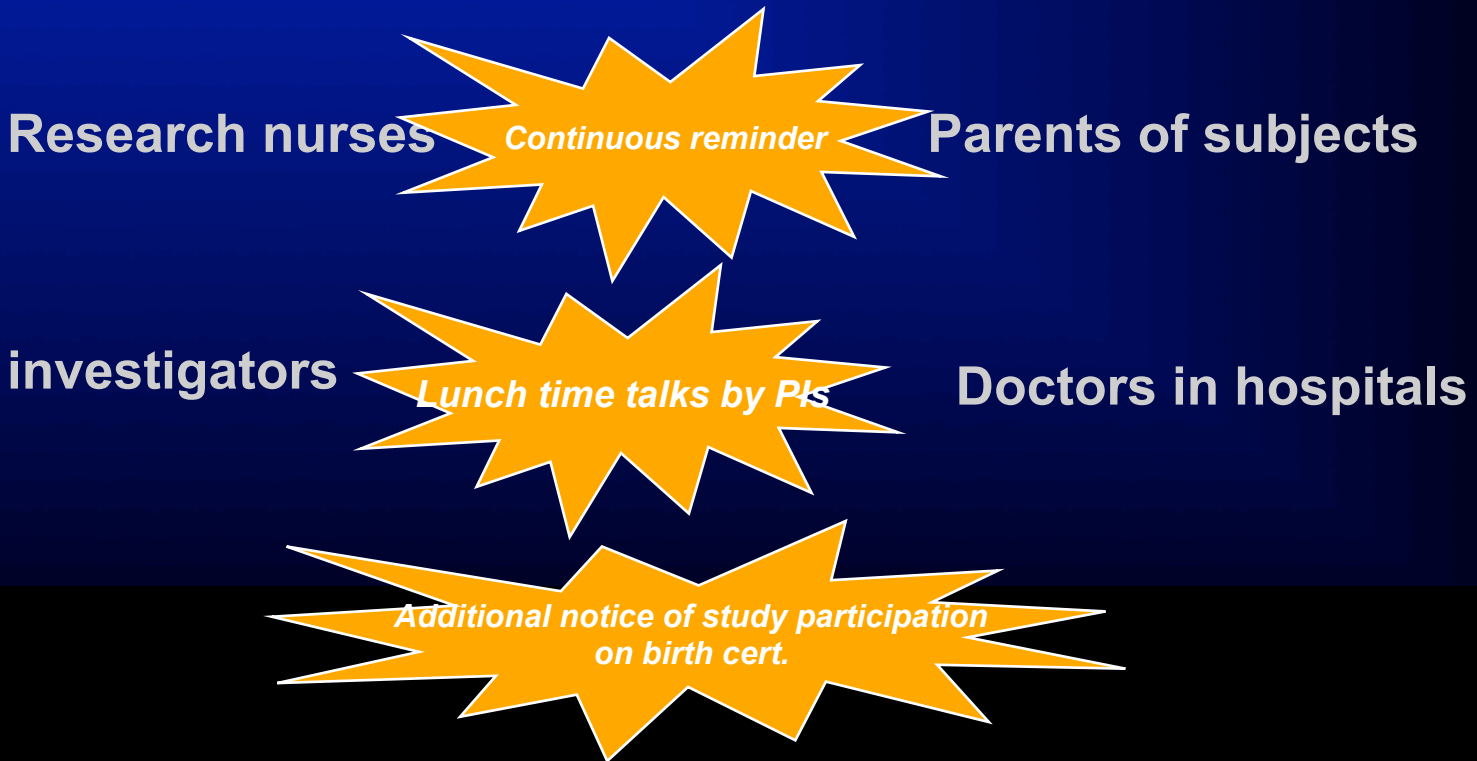
At Zuellig warehouse,

Its very cold here !



After first IS was reported….

- Reinforcements made



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

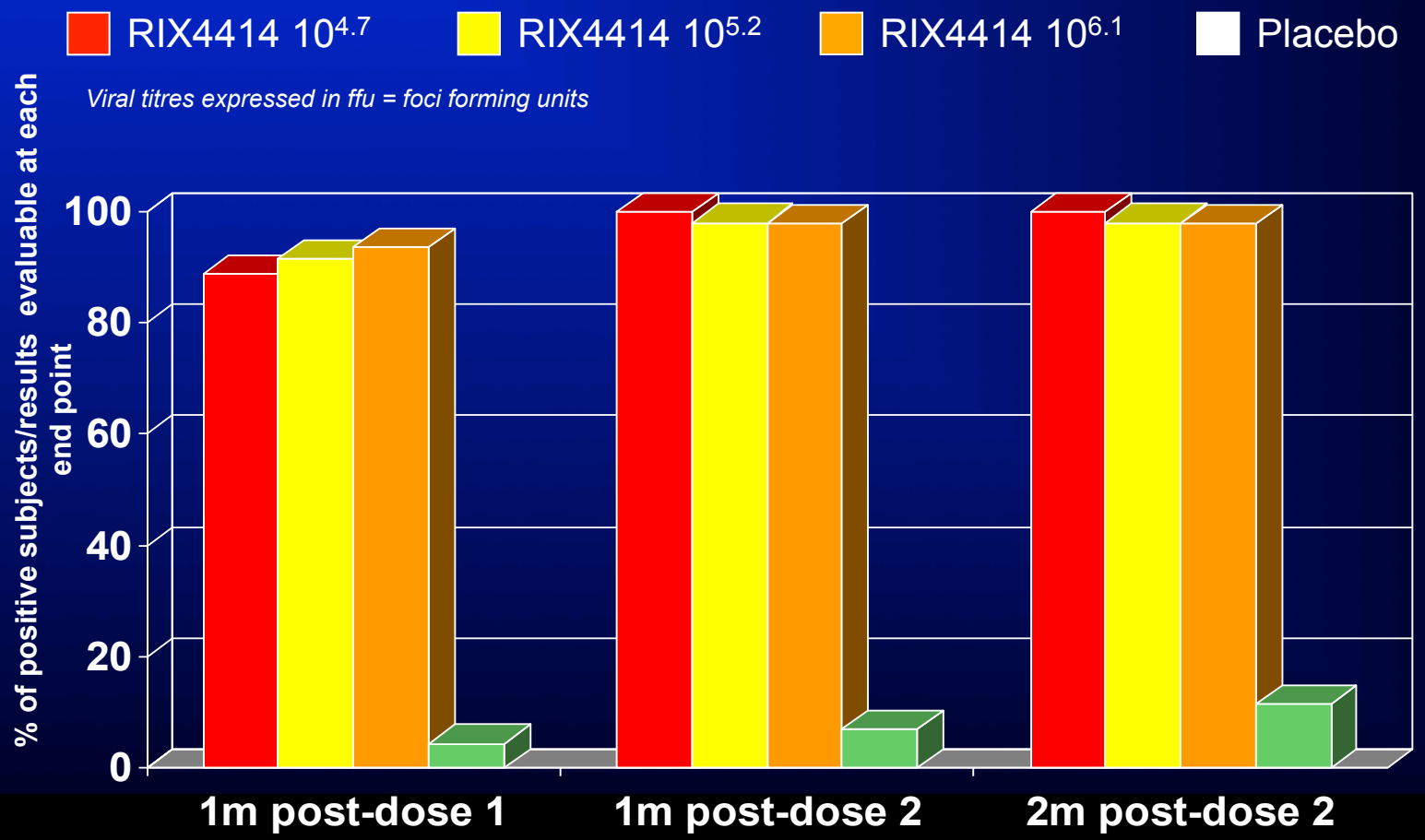
Study 007 – Singapore

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

Vaccine take

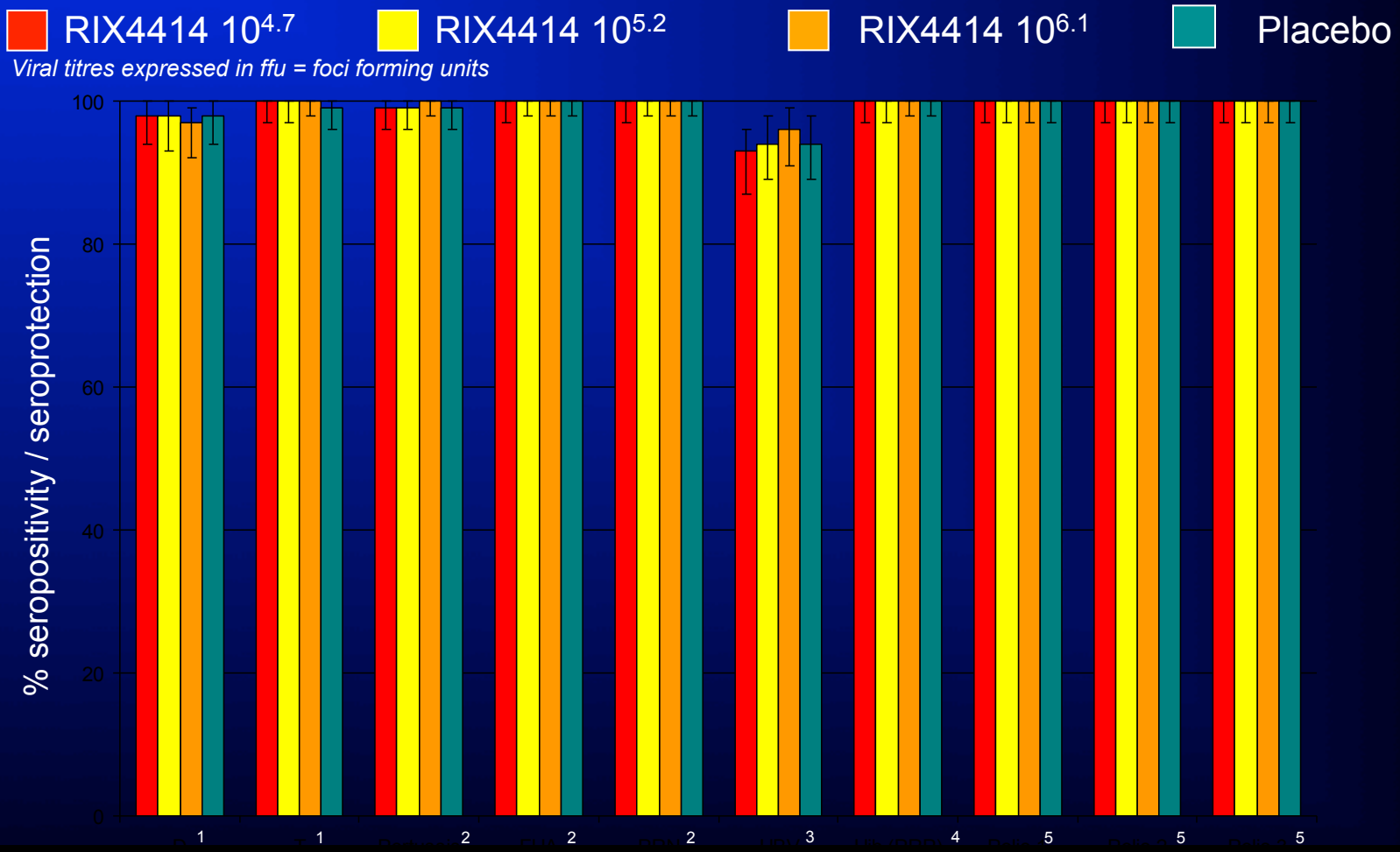
% Vaccine take per groups



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

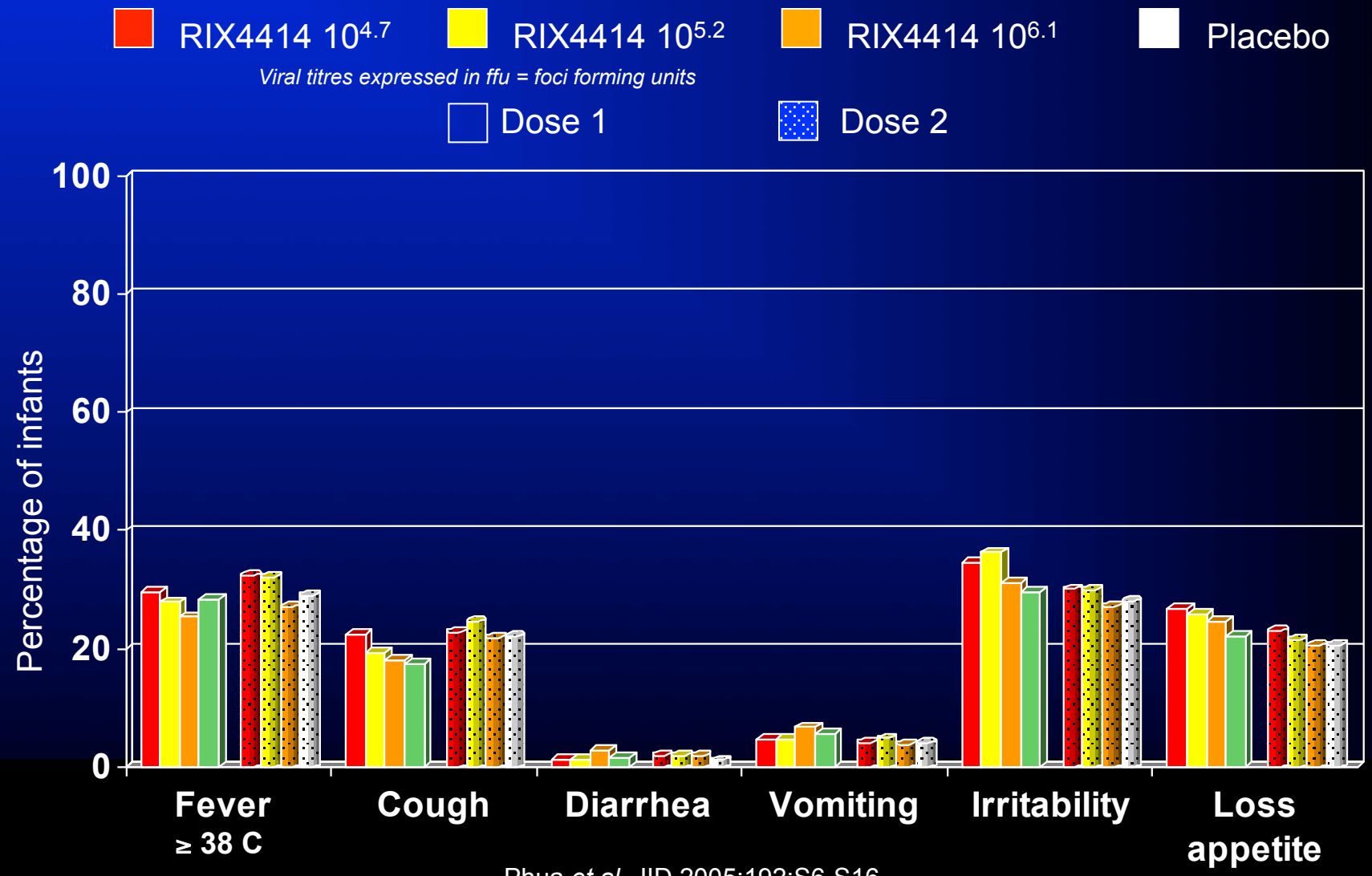


[1] ELISA, cut off at 0.1UI/mL [2] ELISA, cut off at 5 EL.U/mL [3] AUSAB, Abbott Laboratories cut off at 10mIU/mL
[4] ELISA, cut off at 0.15 µg/mL [5] Virus microneutralization cut off titer ≥8

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

Reactogenicity

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



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

AMK	622
BBK	611
CCK	867
HGG	774
JRG	664
TPY	524
WDL	739
YSH	518
KKH	774
Mt. E	111
NUH	338

6,542

End date of Recruitment: 31st Aug 2005

Vaccine Approval in Singapore, Oct 2005

BUSINESS TIMES NOVEMBER 8, 2005

TOP STORIES 3

Glaxo: S'pore's HSA can do robust review

Health Sciences Authority has potential to be Asia's equivalent of the US FDA, it says

By CHEN HUIFEN

[SINGAPORE] GlaxoSmithKline (GSK) reckons Singapore's Health Sciences Authority has the potential to become the Asian equivalent of the US Food and Drug Administration, after

9,000 subjects over four years, Singapore also accounted for more than 30 per cent of the data submitted for approval documentation in various countries.

"What we are beginning to see is that countries outside of the US and Europe are capable of conducting clinical trials to the highest international standard," said Phua Kong Kao, senior consultant in paediatrics at

two sites in Asia that has approved GSK's Rotarix, a vaccine to counter rotavirus gastroenteritis which causes severe diarrhea in children. The Philippine authorities approved it earlier, using Mexico's approval as a reference. As the vaccine has not been evaluated or approved in the US or Europe, using Singapore as a reference site for Asia could help accelerate market availability of the vaccine.

- 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

28 - Metro Ahad - Sunday, September 10, 2006
Rotavirus Is Dangerous

Rotavirus berbahaya

Penyebab utama masalah cirit-birit dan muntah kanak-kanak bawah lima tahun

>>Oleh Norlaila Hamima Jamaluddin
norlaila@hmetro.com.my

NAMA rotavirus mungkin kurang dikenali tetapi ia adalah penyebab utama masalah cirit-birit dan muntah di kalangan kanak-kanak di bawah lima tahun yang memaksa mereka dimasukkan ke hospital.

Dalam tempoh lima tahun pertama hidup mereka, dianggarkan hampir setiap kanak-kanak mengalami masalah cirit-birit akibat jangkitan rotavirus sekurang-kurangnya sekali dengan satu daripada 65 kes akan dimasukkan ke hospital.

Walaupun ada yang menganggap cirit-birit dan muntah adalah perkara biasa tetapi ia tidak boleh dipandang ringan kerana satu daripada 293 kanak-kanak yang dimasukkan ke hospital akibat masalah ini meninggal dunia kerana lewat diberikan rawatan.

Setiap tahun rotavirus menyebabkan 125 juta kes gastroenteritis (keradangan usus mengakibatkan individu dijangkiti muntah dan cirit-birit), 25 juta dirujukkan ke klinik dan dua juta ditahan di hospital. Daripada jumlah ini 440,000 pesakit meninggal dunia. Ini bermakna seorang kanak-kanak menemui maut setiap minit akibat muntah dan cirit-birit.

Di negara kita senarionya juga tidak banyak berbeza. Rotavirus menjadi penyebab utama masalah muntah, cirit-birit dan demam kanak-kanak di Malaysia. Ia juga menyebabkan seorang daripada 61 kanak-kanak di bawah usia lima tahun yang dijangkiti terpaksa dimasukkan ke hospital dengan 37 kes dirujuk sebagai pesakit luar.

Rotavirus ada di sekeliling kita dan tersebar dengan cepat melalui kitaran najis ke mulut. Apabila dijangkiti, seorang kanak-kanak biasanya akan demam, muntah dan cirit-birit sehingga boleh membawa maut akibat kehilangan terlalu banyak air dari badan.

Rotavirus amat mudah berjangkit dan boleh hidup beberapa hari sehingga seminggu di atas permukaan sebarang objek sehingga ia mendapat perumah baru (menjangkiti orang lain). Masalah muntah dan cirit-birit akibat rotavirus adalah jauh lebih tinggi berbanding jangkitan bakteria lain seperti Escherichia coli (E. coli).

Dianggarkan hampir 50 peratus kes cirit-birit kanak-kanak di negara kita akibat jangkitan rotavirus dan satu pertiga daripada 23,000 kes perlu dimasukkan ke hospital.

Menurut Perunding Paediatrik Penyakit Berjangkit Fakulti Perubatan Nasional, Universiti Mexico, Dr Raul Velasquez, rotavirus ada di mana-mana di seluruh dunia dan golongan paling berisiko ialah bayi terutama yang berumur antara enam hingga 24 bulan.

Katanya, bayi yang dijangkiti akan mengalami demam, muntah dan cirit-birit antara 10 hingga 20 kali sehari. Ini adalah kerana rius kerana ia menyebabkan dehidrasi (kekurangan air) dan boleh membawa maut.

FAKTA
cirit-birit antara 10 hingga 20 kali sehari

Rotavirus bukan saja membebankan si kecil tetapi pada masa sama turut menjejaskan produktiviti ibu bapa yang terpaksa mengambil cuti dan memerlukan banyak belanja perubatan setiap kali anak mendapat jangkitan.

Bagaimana mengenali jangkitan rotavirus?

Cirit-birit akibat rotavirus biasanya berlaku selama tiga hingga sembilan hari. Bagaimanapun ia boleh berlanjutan sehingga tiga minggu. Dalam tempoh ini pesakit kanak-kanak boleh mengalami gejala demam, cirit-birit dan muntah pada bila-bila masa.

Gejala jangkitan yang utama ialah:

- Muntah (96 peratus)
- Cirit birit (antara 10 hingga 20 kali sehari)
- Demam (77 peratus)
- Sakit perut

Seperti diterangkan di atas, virus ini mempunyai daya ketahanan yang tinggi. Ia boleh hidup beberapa jam di atas tangan manusia dan beberapa hari di atas permukaan keras yang tidak sesuai untuk membiak. Bahkan ia boleh kekal stabil dalam najis manusia sehingga seminggu.

Malangnya amalan kebersihan seperti kerap mencuci tangan, meningkatkan tahap kebersihan dan penjagaan kesihatan masih tidak dapat membendung masalah jangkitan rotavirus kerana kanak-kanak di negara maju pun turut mengalami masalah gastroenteritis.

Masalah lebih tinggi di kalangan kanak-kanak yang dihantar ke pusat jagaan harian. Virus boleh tersebar melalui sentuhan dengan individu dijangkiti dan permukaan atau objek yang dihinggapi virus serta pengambilan makanan atau minuman tercemar. Malah penjaga yang tidak mencuci tangan dengan bersih selepas menukar lampin bayi juga adalah antara cara penyebaran virus kepada bayi lain.

Kajian yang dijalankan di Mexico mendapati kebanyakan bayi mula mendapat jangkitan pada umur kurang daripada dua bulan yang dipanggil jangkitan primer. Ia menyebabkan 50 peratus bayi jatuh sakit dan 30 peratus mengalami masalah kesihatan serius.

"Jangkitan rotavirus boleh menjadi serius apabila kanak-kanak mula mengalami masalah kekurangan air. Pada ketika ini, badan mereka menjadi amat lemah dan sistem pertahanan badan masih belum mampu melindungi pesakit daripada jangkitan" katanya pada pelancaran vaksin Rotarix anjuran GlaxoSmithKline Pharmaceutical Sdn Bhd.

Setakat ini, tiada rawatan yang boleh menentang rotavirus. Rawatan yang ada hanyalah untuk mengurangkan gejala jangkitan seperti demam dan memberikan air sama ada secara oral atau intravena (suntikan ke dalam salur darah).

Namun masalah yang membebankan si kecil dan ibu bapa ini boleh dibendung melalui pengambilan vaksin untuk kanak-kanak di bawah enam bulan. Ia boleh diambil pada usia seawal enam minggu dan untuk mendapat perlindungan sepenuhnya setiap bayi memerlukan dua dos vaksin yang diambil secara oral (makan).

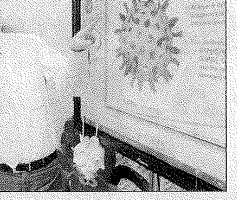
Menurut Pengarah Bahagian Penyelidikan dan Pembangunan Klinikal Dan Hal Ehwal Perubatan, GlaxoSmithKline Singapura dan Malaysia, Dr Teoh Yee Leong, dos kedua perlu diambil dalam jarak sekurang-kurang nya empat minggu atau ketika berumur 24 bulan bersama vaksin polio.

Bagaimanapun dos pertama vaksin ini boleh diberi ketika bayi berumur dua atau tiga bulan diikuti dos kedua pada usia lima bulan. Pada usia inilah bayi paling berisiko tinggi mendapat jangkitan.

Vaksin ini berfungsi merangsang badan untuk meniru tindak balas imunisasi terhadap jangkitan rotavirus semula jadi. Kajian yang dijalankan ke atas 60,000 bayi di Eropah, Amerika Utara, Amerika Latin dan Asia mendapati ia mampu mengurangkan kadar kemasukan ke hospital sehingga 85 peratus.

Malah ibu bapa juga tidak perlu risau kerana ia selamat dan tidak bertindak balas dengan vaksin lain. Bahkan ia juga melindungi bayi daripada jangkitan jenis rotavirus lain sepanjang hayat.

"Bagaimanapun ini bukan bermakna kebersihan itu tidak penting. Aspek kebersihan masih perlu diteruskan dan vaksin memberi perlindungan tambahan kepada bayi. Bagi orang dewasa, jangkitan rotavirus tidak akan memberi kesan kerana badan kita sudah mempunyai ketahanan sebab pernah dijangkiti ketika kecil tetapi kita berkemungkinan menyebarkan virus kepada anak yang boleh membahayakan nyawanya," katanya.

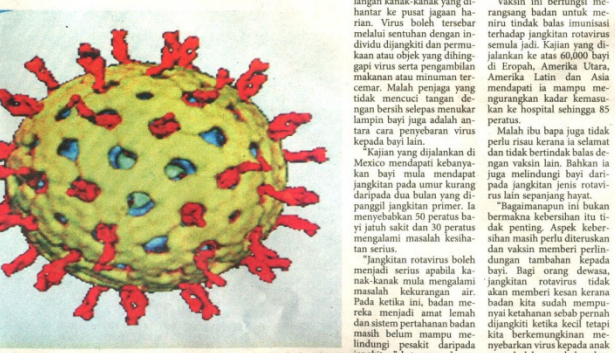


> Dr Raul Velaques
Perunding Paediatrik Penyakit Berjangkit Fakulti Perubatan Nasional, Universiti Mexico.

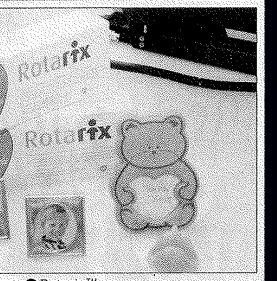
"Jangkitan rotavirus boleh menjadi serius apabila kanak-kanak mula mengalami masalah kekurangan air. Pada ketika ini, badan mereka menjadi amat lemah dan sistem pertahanan badan masih belum mampu melindungi pesakit"

"Bagi orang dewasa, jangkitan rotavirus tidak akan memberi kesan kerana badan kita sudah mempunyai ketahanan sebab pernah dijangkiti ketika kecil"

> Dr Teoh Yee Leong
Pengarah Bahagian Penyelidikan dan Pembangunan Klinikal Dan Hal Ehwal Perubatan, GlaxoSmithKline Singapura dan Malaysia.



ROTAVIRUS... jangkitannya menyebabkan 25 juta kes dirujukkan ke klinik dan dua juta lagi ditahan di hospital.

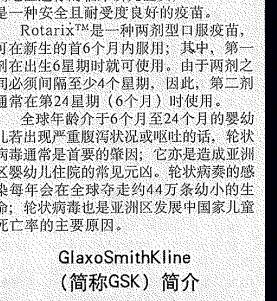


●Dr.Raul与Teoh推介Rotarix™。

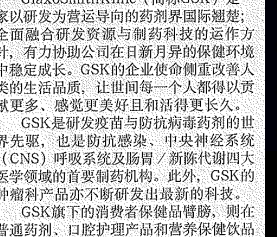
●Rotarix™。

大马婴儿有了防御轮状病毒最新护障

（吉隆坡23日讯）如今，有了防御轮状病毒（rotavirus）之强悍护障的马来西亚婴儿，可以安然挥别此毫无征兆的夺命性感染病。由国际制药钜子GlaxoSmithKline制药公司（以下简称GSK）出品的Rotarix™，是誉沦为高风险群的新生儿（未满六个月）研发的最新两剂型口服疫苗。



●Dr.Raul。



●Dr.Teoh。

全球统计数字显示，所有因急性肠胃炎而住院的未满5岁病童中，半数的起因是轮状病毒感染；后者更会令6至24个月大的新生儿发生严重的腹泻和呕吐现像。

"本地的调查结果发现，在5岁以下的幼童中，每61人中就有1人因为轮状病毒疾病而住院留医；此外，每37人中，则有1人因轮状病毒而到门诊就医。"GSK马新区临床研发与医疗事务部总监Dr.Teoh Yee Leong说明。医疗单位的门诊与住院部每年总共处理约2万3千宗的轮状病毒病例，其中三份之一必须住院留医。

"轮状病毒可谓无所下在，而年幼的新生婴儿则是受感染的最高风险群。不幸被缠上的新生儿除了发烧和呕吐之外，每天还可能出现10至20次的腹泻；轮状病毒型肠胃炎可能随时严重恶化，并且造成脱水现像。"墨西哥国家大学（National University of Mexico）医学院研究所教授兼小儿感染科医主Dr.Raul Valazquez解释。

"轮状病毒造成的腹泻问题，通常会拖延3到9天，但是也有可能会持续至3个星期；因此，小病患的家长不得不向公司请假以照顾纤弱无助的心肝宝贝。"Dr.Raul说。"新疫苗的面世不但让家长们感到宽心，而且也大幅度降低了新生儿的住院率。"他指出。

"Rotarix™的面市，不但为马来西亚新生儿带来了新的健康保障，也替我们奠下足以自豪的重大成就。"Dr.Teoh表示。"基于轮状病毒的夺命天性，可以周全保护婴幼儿的疫苗绝对是家长们引须常盼的护儿佳音。"他补充。

"Rotarix™是医学界的突破佐进展；基于单靠频密洗手或改善卫生条件，并无法有效预防传染力极高的轮状病毒肠胃炎，因此，疫苗是最周全的防御途径。"Dr.Raul解释。

"我们医学院的调查结果显示，Rotarix™也把因轮状病毒而住院的个案降低了85%。"Dr.Raul补充。

Rotarix™的功效在于刺激人体产主感染轮状病毒时的免疫反应，进而制造防御未来感染中度至严重轮状病毒肠胃炎的护障能力。

已经在欧洲、北美洲、拉丁美洲和亚洲地区进行的临床研究证实，Rotarix™是一种安全且耐受度良好的疫苗。

Rotarix™是一种两剂型口服疫苗，可在新生的首6个月内服用；其中，第一剂在出生6星期时就可使用。由于两剂之间必须间隔至少4个星期，因此，第二剂通常在第24星期（6个月）时使用。

全球年龄介于6个月至24个月的婴幼儿若出现严重腹泻状况或呕吐的话，轮状病毒通常是首要的肇因；它亦是造成亚洲区婴幼儿住院的常见元凶。轮状病赛的感染每年会在全球夺走约44万条幼小的生命；轮状病毒也是亚洲区发展中国家儿童死亡率的主要原因。

GlaxoSmithKline（简称GSK）简介

GlaxoSmithKline（简称GSK）是一家以研发为营运导向的药剂界国际翘楚；全面融合研发资源与制药科技的运作方针，有力协助公司在日新月异的保健环境中稳定成长。GSK的企业使命侧重改善人类的生活品质，让世间每一个人都得以贡献更多、感觉更美好且和活得更长久。

GSK是研发疫苗与防抗病毒药剂的世界先驱，也是防抗感染、中央神经系统（CNS）呼吸系统及肠胃／新陈代谢四大医学领域的首要制药机构。此外，GSK的肿瘤科产品亦不断研发出最新的科技。

GSK旗下的消费者保健品髂腋，则在普通药剂、口腔护理产品和营养保健饮品领域稳占市场领袖的位置。

Post Marketing Surveillance - Inturssusception

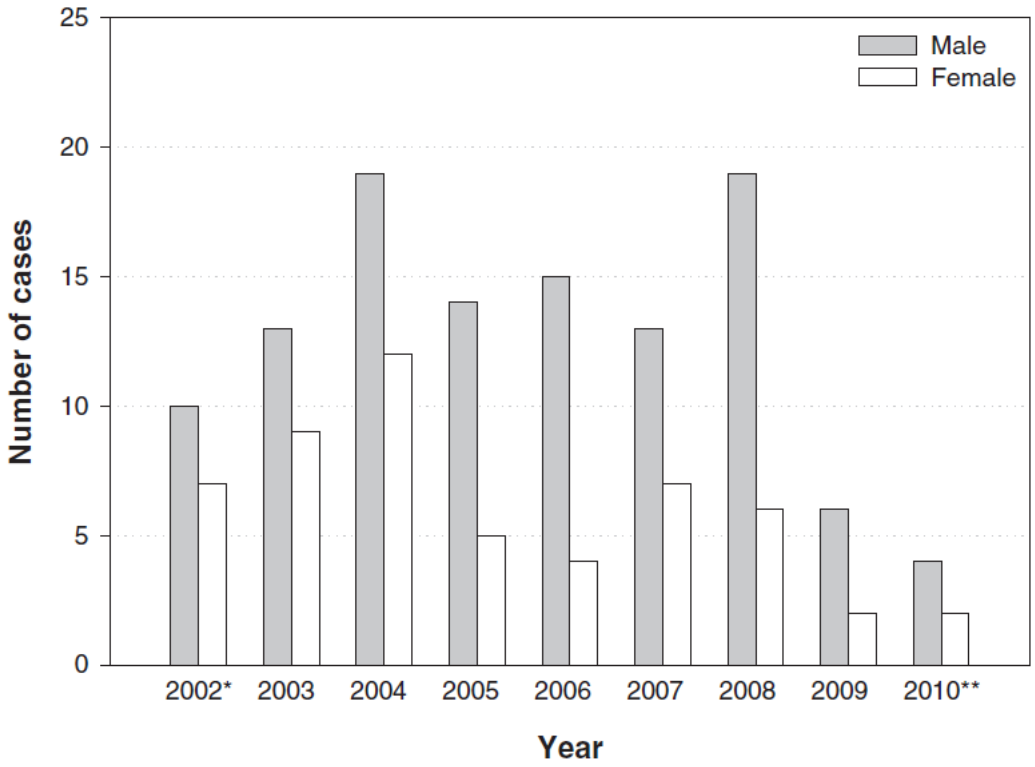


Figure 3 Distribution of IS cases by gender (Total number of cases N=167). *Data collected from May to December - 2002. **Data collected from January to June - 2010.

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

	N subjects with severe RV GE			
	Vaccinees n=9,009	Placebo n=8,858	Vaccine efficacy (95% CI)	*P-value*
Clinical	12	77	84.7 (71.7 - 92.4)	*< 0.001*
Vesikari score ≥11	11	71	84.8 (71.1 – 92.7)	*< 0.001*

ATP efficacy cohort

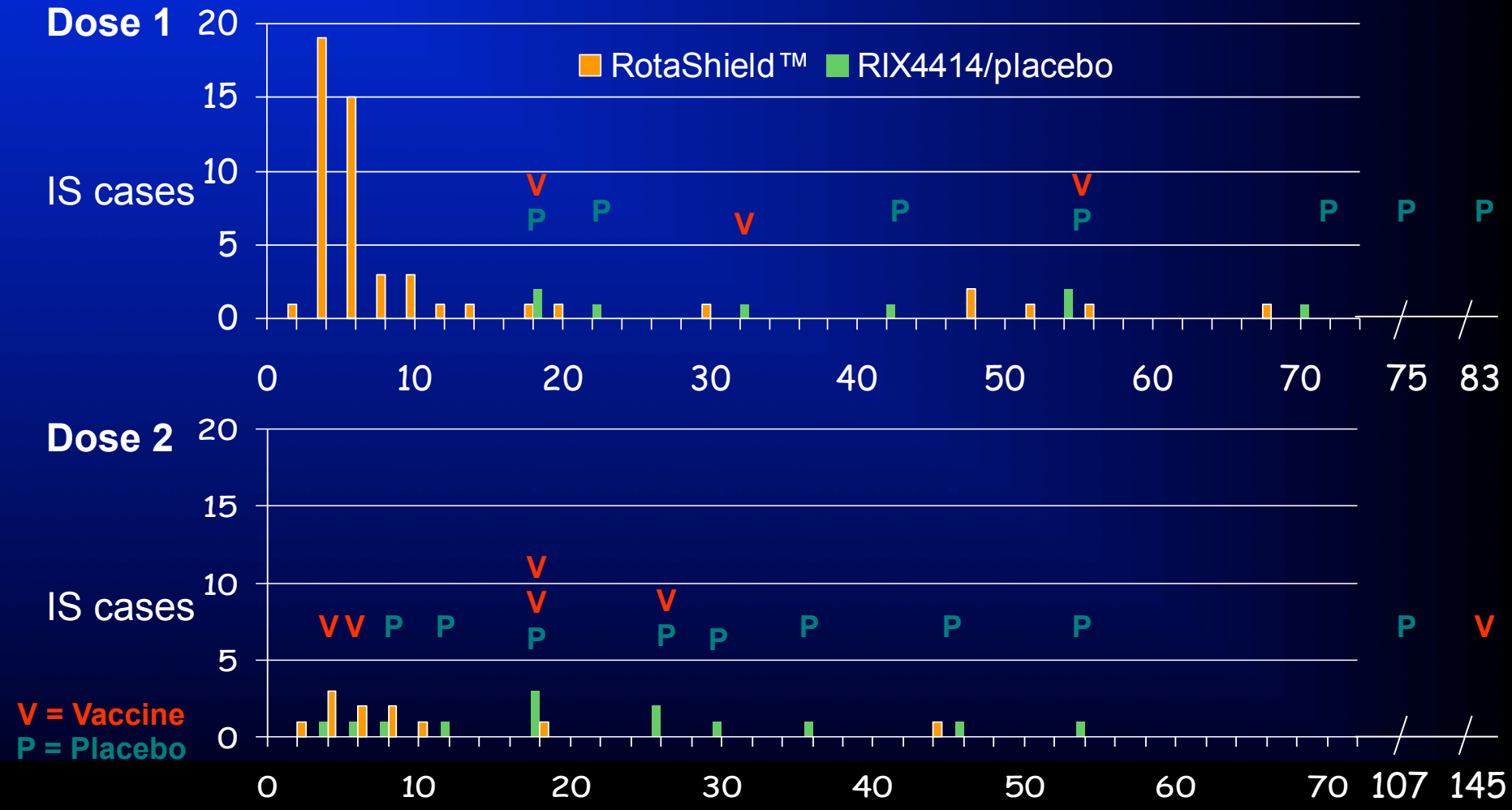
Ruiz-Palacios G. et al N. Engl. J. Med. 2006; 354: 11-22

Human RV strain and IS risk

- No evidence linking wild-type human rotavirus to IS
  - US epidemiology refutes link[1,2]
- Anedoctal reports of RV detection with cases of IS (Japan)
- No link between RV infection seasonality and IS [1,2]

[1]Rennels *et al*, Pediatr Infect Dis J 1998 17 924–925, [2]Chang EJ *et al* PIDJ 2002

Occurrence of Definite IS Cases Compared to RotaShield™-Associated Cases[1]



Vesikari T *et al*. ESPID 2005, abstract 31

[1] Murphy TV *et al*, N Engl J Med, 2001.

IS Surveillance 0 to 31 days and post each dose

(ATP Safety cohort)	Vaccine group N=31,673	Placebo group N=31,552
Total IS Cases		
Total 0 → 31 days[1]	**6**	**7**
0 → 31 days post dose 1	**1**	**2**
0 → 31 days post dose 2	**5**	**5**

Differential Risk = -0.32/10.000 vaccines (95% CI: -2.91 - 2.18)

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

[1]O'Ryan M., abstract, ICAAC, 2004, Washington, USA

Pivotal Phase III Study 023 – Safety

IS Surveillance
0 to 31 days and 0 to 100 days

(ATP Safety cohort)

	Vaccine group N=31,673	Placebo group N=31,552
Total IS Cases		
0 → 31 days[1]	**6**	**7**

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[2]	**9**	**16**

Differential Risk = -2.23/10 000 vaccines (95% CI: -5.70 - 0.94)

Relative Risk = 0.56 (95% CI: 0.25 - 1.24)

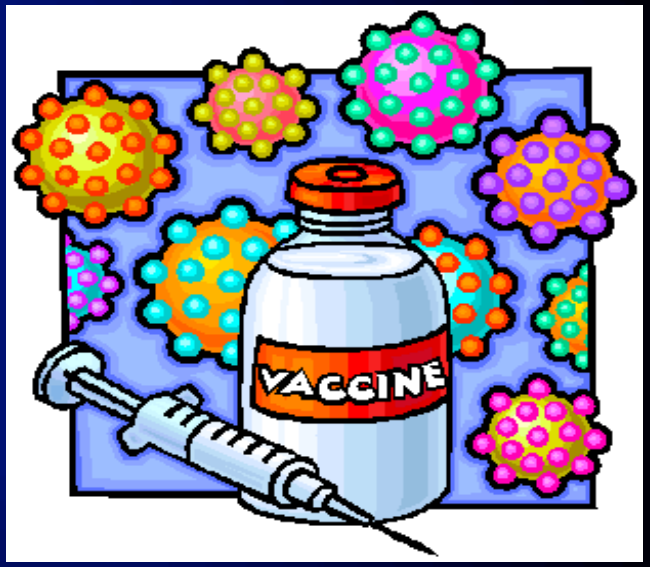
[1]O'Ryan M., abstract, ICAAC, 2004, Washington, USA
[2]Vesikari T., abstract, ESPID, 2005, Valencia, Spain

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

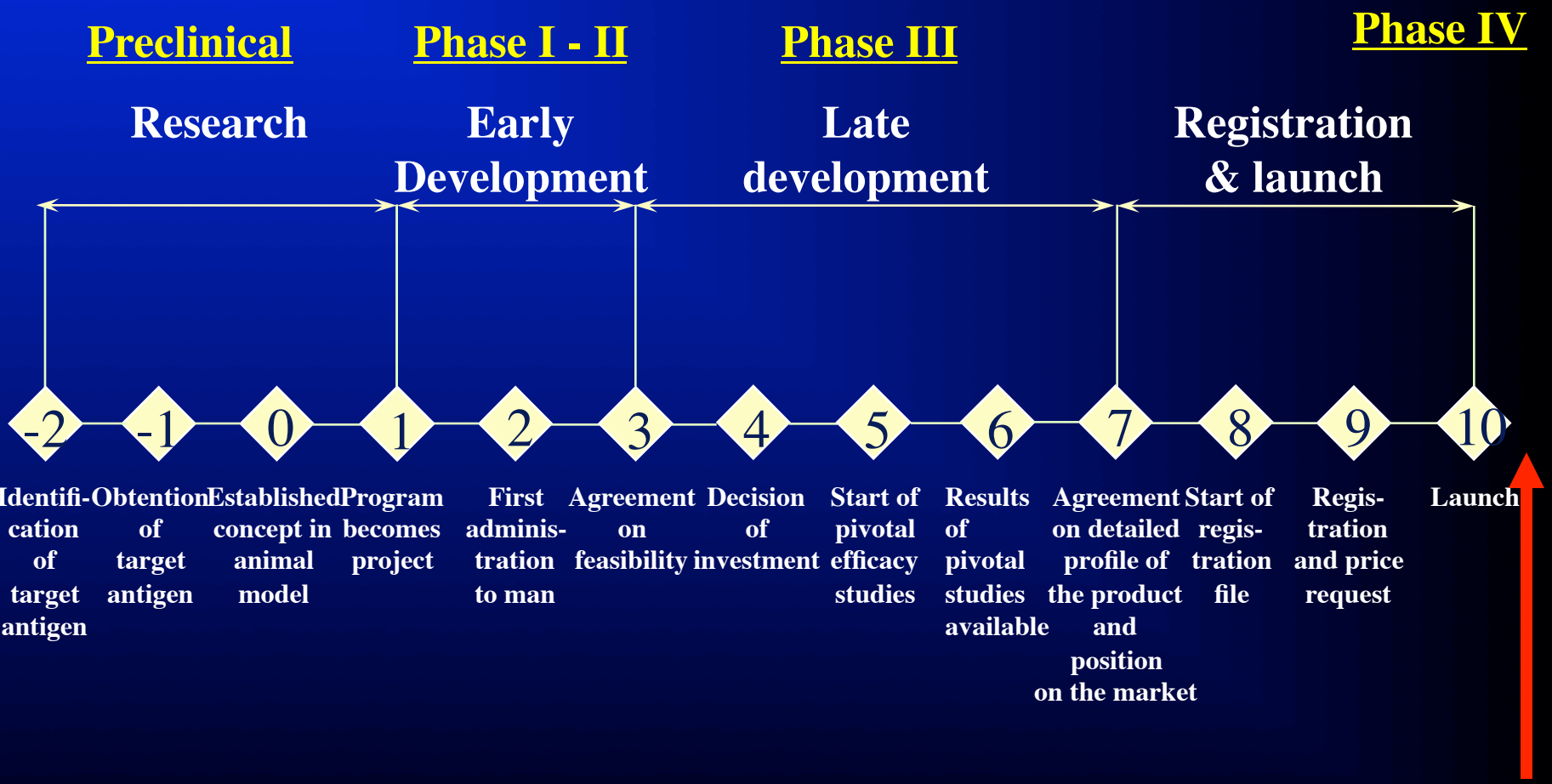


Group Discussion 5

- 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?

4 phases in the development of a Drug



Thank You