Clinical Trials at HKU

- Conducted on patient subjects
- Study sites include hospital and out-patient departments
- Phase 1 drug trials were mainly cancer treatments prior to the establishment of Phase 1 CTC
<table>
<thead>
<tr>
<th>Phase</th>
<th>Primary Goal</th>
<th>Dose</th>
<th>Subject Type</th>
<th>Typical number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Testing of drug on healthy volunteers for dose-ranging</td>
<td>Often subtherapeutic, with ascending doses</td>
<td>Healthy volunteers, Patients</td>
<td>20–100</td>
</tr>
<tr>
<td>Phase II</td>
<td>Testing of drug on patients to assess efficacy and safety</td>
<td>Therapeutic dose</td>
<td>Patients</td>
<td>100-300</td>
</tr>
<tr>
<td>Phase III</td>
<td>Testing of drug on patients to assess efficacy, effectiveness and safety</td>
<td>Therapeutic dose</td>
<td>Patients</td>
<td>1000-2000</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Postmarketing surveillance – watching drug use in public, evaluating different dosages or schedules of administration, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.</td>
<td>Therapeutic dose</td>
<td>Patients (anyone seeking treatment)</td>
<td></td>
</tr>
</tbody>
</table>

Sources: [https://en.wikipedia.org/wiki/Phases_of_clinical_research#Phase_I](https://en.wikipedia.org/wiki/Phases_of_clinical_research#Phase_I)  
HKU Clinical Trials Centre (2003) General Research Ethics Information and Definitions for Investigators and IRB Members
### Number of trials reviewed by HKU HA/ HKW IRB

*(before the establishment of Phase 1 CTC in 2014)*

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 Drug Trials</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Phase II to IV Drug Trials</td>
<td>72</td>
<td>78</td>
<td>66</td>
<td>94</td>
<td>310</td>
</tr>
</tbody>
</table>
Initiatives in establishing Phase 1 Clinical Trial Centres

- In 2011, the Government of the Hong Kong SAR announced the initiative to establish two Phase 1 Clinical Trial Centres ("CTCs") in the two teaching hospitals of the Hospital Authority (HA).
- HA formed a Workgroup in 2011 for developing research oversight mechanism of Phase 1 Clinical Trials.
- In 2012, consultancy commissioned by HA in collaboration with HKU and CUHK on the operation of the Phase I Clinical Trial Centres.
Key areas covered by Consultancy

- Structure and relationships of stakeholders – Food & Health Bureau (FHB), Department of Health (DoH), Hospital Authority (HA), and the two medical faculties/teaching hospitals (HKU/QMH and CUHK/PWH) and their research ethics committees

- Laboratory facilities

- Facilities for medical emergencies

- Insurance
Consultancy’s Recommendations

• Acknowledged both medical faculties/teaching hospitals had vast experiences in conducting all phases of clinical trials.

• Modifications are required for handling of First In Human (FIH) and First in Patients (FIP) Phase 1 clinical trials:
  o Create a Joint Scientific Committee (JSC) for assessment of pre-clinical, clinical and scientific validity of trials
  o Project specific Data Safety Monitoring Board (DSMB) for evaluating clinical, laboratory and safety data
Expansion of scopes of Phase 1 Drug Trials
(following the establishment of Phase 1 CTC in 2014)

- FIP Cancer treatment
- Hepatitis virus infection treatment
- Bioequivalence drug in healthy subjects
- Healthy subjects pharmacokinetics study
- Influenza vaccine

Both healthy volunteers and patients undergoing treatment may be involved in Phase I Clinical Trials.
Organizational Relationships between Stakeholders
Establishment of Phase 1 Panel and Joint Scientific Committee (JSC)
Establishment of Joint Scientific Committee (JSC)

- JSC is governed by the Consortium on Harmonization of Institutional Requirements for Clinical Research (CHAIR)

- JSC performs scientific evaluations of all phase 1 clinical trials on new chemical or biological drugs not registered in Hong Kong (referred as investigational medicinal products (IMPs))
Guidelines on Oversight of Phase 1 Clinical Trials

IRB SOP

JSC SOP

Phase 1 Guideline
## JSC Members – by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
</tr>
<tr>
<td>France</td>
<td>1</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>13</td>
</tr>
<tr>
<td>Japan</td>
<td>1</td>
</tr>
<tr>
<td>New Zealand</td>
<td>2</td>
</tr>
<tr>
<td>Singapore</td>
<td>2</td>
</tr>
<tr>
<td>South Korea</td>
<td>1</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1</td>
</tr>
<tr>
<td>United Kingdom (UK)</td>
<td>8</td>
</tr>
<tr>
<td>United States of America (USA)</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
</tr>
<tr>
<td>JSC Members – Diversity of Specialties</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Biostatistics, statistical analysis</td>
<td></td>
</tr>
<tr>
<td>Cancer medicine</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td></td>
</tr>
<tr>
<td>Clinical oncology</td>
<td></td>
</tr>
<tr>
<td>Clinical pharmacology, pharmacogenetics</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Lung cancer, head and neck cancer</td>
<td></td>
</tr>
<tr>
<td>Genomic instability, drug resistance</td>
<td></td>
</tr>
<tr>
<td>Haematology</td>
<td></td>
</tr>
<tr>
<td>Immunology, Allergy</td>
<td></td>
</tr>
<tr>
<td>Immunology/Rheumatology</td>
<td></td>
</tr>
<tr>
<td>Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma and hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Pharmacy</td>
<td></td>
</tr>
<tr>
<td>Psychological medicine</td>
<td></td>
</tr>
<tr>
<td>Rheumatology</td>
<td></td>
</tr>
</tbody>
</table>
Ethics & Scientific Review Mechanism

- IRB Phase 1 Panel
- Joint Scientific Committee
- Scientific Opinions by emails
- Scientific Documents by emails
- Application
- Mean 8.5 weeks
- Ethical Approval / Opinions after meeting
- 5 to 12 weeks
- Principal Investigator

Scientific Opinions by emails in 2 weeks
Process of evaluation of a Phase 1 ClinicalTrial Application (1)

- IRB invites 1 JSC member as the Lead Reviewer and recommends 2 other members to the Lead Reviewer for forming a Scientific Review Panel (SRP).
- The Lead Reviewer shall not be an employee of the PI’s employing institution.
- Upon formation of a SRP, IRB provides to each scientific reviewer an evaluation package by email.
Process of evaluation of a Phase 1 Clinical Trial Application (2)

- The scientific evaluation package includes:
  - A. A completed ethics review application form;
  - B. A trial protocol;
  - C. An investigator’s brochure and/or other documents detailing the nature, properties, pre-clinical data, if available, human data about the IMP;
  - PI’s curriculum vitae; and
  - A scientific reviewer’s Declaration of Interest (DOI) Form

- Each scientific reviewer shall sign and return the DOI Form to the IRB before making any recommendation or expressing any opinion

- The Lead Reviewer shall provide recommendations to IRB or request for additional information or clarification, on behalf of the SRP

- An honorarium will be provided to each of the 3 scientific reviewers upon completion of review
Scientific Evaluations by JSC

- IMP’s risk
- IMP’s formulation & dosing route
- Scientific basis for subject selection
- Starting dose (for FIH trials)
- Dose escalation scheme (for ascending dose trials)
- Dosing schedule
- Stopping rules
Ethical Assessments by Phase 1 Panel

- Aim of study
- Hypothesis
- Outcome measures
- Inclusion criteria
- Exclusion criteria
- Sample size
- Subjects recruitment
- Protection of vulnerable subjects
- Study design
- Handling and storage of personal data
- Licensed use of test article
- Interventions / procedures required and by whom
- Biological samples stored for future use
- Potential risk arising from study
- Anticipated benefits to study subjects
- Information and consent
- Data and safety monitoring
- Source of funding
- Resources implication and conflict of interest
- Financial costs and payment to subjects
- Indemnity and insurance
Phase 1 Panel’s Ethical Review

Panel adopts international ethical guidelines:
ICH GCP
Declaration of Helsinki
Principal Investigator’s Presentation

whether or not there would be any perceived harm to the subjects,
Ethical Considerations

- **Subject Selection Justification**
- **Informed Consent**: study purposes; potential benefits & risks; subjects’ rights & responsibilities; personal data protection; compensation & costs
- **Payment to Subjects**: expenses, time and lifestyle restrictions
- **Investigators & Study Team**
Process of evaluation of a Phase 1 Clinical Trial Application (3)

• The IRB performs an ethical review of a study by a Phase 1 Panel Review in meeting
• IRB’s Phase 1 Panel has a minimum of 5 members, including scientific and non-scientific members, and in both genders.
• The IRB shall consider the SRP’s recommendations as well as its own ethics evaluation
• The PI has to present the study to the Phase 1 Panel
• HKU/HA HKW IRB has reviewed phase 1 clinical trials since May 2014
Safety Monitoring and Continuous Oversight

- Serious adverse events (SAEs) have to be reported to IRB by the study team within 48 hours of awareness of the event.
- SAEs have to be reported to the Sponsor and the local regulatory authority.
- IRB will perform continuous oversight of each approved phase 1 clinical trial by:
  - A. Regular continuing review;
  - B. Review of amendments and changes;
  - C. Review of new information;
  - D. Review of deviations and compliance incidents;
  - E. Review of safety reports; and
  - F. Final review.
The Way Forward

• In November 2015, HA has commissioned a consultancy service for review of research ethics oversight and scientific evaluation mechanism of Phase 1 clinical trials

• The consultancy is expected to complete their report in 2016
Thank you

Chairman and Secretariat Staff

Institutional Review Board (IRB)