Method and Clinical Trial Design

Dr Vishal Goyal
Drugs for Neglected Diseases initiative
New Delhi, India
Challenges in Methodology and Trial Design

- Regulatory aspects
- Methodology
- Study Design
- Human Resources
- Capacity building
- Logistics issues
Regulatory Review Process

- New Drug Advisory Committee

- Technical Review Committee (TRC) - shall review the recommendations provided by SEC on applications of clinical trials and new drugs after thorough evaluation. Under Chairmanship of DGHS

- Apex Committee - will send their recommendations/opinions after review of proposal sent by TRC
  Under Chairmanship of Secretary, Health and Family Welfare
Stakeholders involved in Regulatory Approval

- Directorate General of Health Services
- Department of Health Research
- National Vector Borne Disease Control Program
- Drug Controller General of India
- ICMR (Health Ministry Screening Committee)

Proposal submitted to:
- Directorate General of Health Services
- Department of Health Research
- National Vector Borne Disease Control Program
- Drug Controller General of India
- ICMR (Health Ministry Screening Committee)

Responsible for submission of application to authorities:
- National Vector Borne Disease Control Program
- Drug Controller General of India
- ICMR (Health Ministry Screening Committee)

Timelines:
- 3-6 months

Principal Investigator:
- Ethics Committee
- Scientific Advisory Committee

ALL APPROVALS OBTAINED
Regulatory Challenges – Recent Changes

- Dec 2016 - Accreditation of Ethic Committee mandatory from 1st Jan 2018
- March 2016 - Academic research conduct with EC approval, NO DCGI approval required
- July 2015 - Audio Video consenting
- Dec 2014 - SAE reporting and Timelines
- Jan 2014 – CT to be done at sites with their own Institutional Ethic Committee
- Feb 2013 - Requirements and Guidelines for registration of Ethics Committee
- Jan 2013 – Compensation in case of injury/death during CT
2. In the Drugs and Cosmetics Rules, 1945, (hereinafter referred to as the said rules), in rule 122 DA, after sub-rule (3), before the *Explanation*, the following shall be inserted, namely:—

“(4) No permission for conduct of clinical trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration or new dose or new dosage form where,—

(a) the trial is approved by the Ethics Committee; and
(b) subject to the provisions of sub-rule 5, the data generated is not intended for submission to licensing authority.

“(5) The Ethics Committee shall however inform the licensing authority about the cases approved by it and also about cases where there could be an overlap between the clinical trial for academic and regulatory purposes and where the said authority does not convey its comments to the Ethics Committee within a period of thirty days from the date of receipt of communication from the Ethics Committee, it shall be presumed that no permission from the licensing authority is required.”.
In the Drugs and Cosmetics Rules, 1945, in Schedule Y,—

(i) in paragraph 2 under the heading “CLINICAL TRIAL”, in sub-paragraph (4) relating to “Informed Consent”, after clause (iii), the following shall be inserted, namely:—

“(iv) An audio - video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record;

Provided that in case of clinical trial of anti-HIV and anti-Leperosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.”;
SAE Reporting Timelines

**Investigator** (within 24hrs of occurrence)

**Sponsor / Investigator** (within 14 calendar days after analysis of SAE)

- **Head of Institution**
- **DCGI**

**Chairman Ethics committee** (within 30 calendar days after due analysis)

In case of **Death**

**Expert Committee (formed by DCGI)** (Order within 105 days of occurrence of SAE)

**DCGI** (Recommendation within 150 days of occurrence of SAE)

**Sponsor** (within 30 days of DCGI receipt compensation to subject)
CT to be conducted at sites with own Ethics Committee

The DTAB after deliberations recommended that the clause may be amended as under:

“The clinical trials of new drugs are required to be conducted at the trial sites, which have their own Ethics Committees. The trial shall be initiated only after the permission has been granted by the Licensing Authority under clause (b) of rule 21, and the approval granted by the Ethics Committee of the institute where trial is proposed to be conducted. The Bioequivalence or bioavailability studies of drugs same area and registered with the said licensing authority. In the case of a multicentric clinical trial, where protocol version is the same at all trial sites, the Ethics Committee(s) of respective sites should accord their approval and accept responsibility for the study at the trial site prior to the initiation of the trial. The Licensing Authority shall be duly informed of the approval of the respective Ethics Committee(s) as prescribed in Appendix VIII”.
Regulatory Challenges
GSR No 53(E) dt 30 Jan 2013

- Insertion of Rule 122 DAB: Compensation in case of injury or death during Clinical trial
- Injury to the trial subject – Free medical management as long as required
- Trial related injury – Medical cost + Compensation
- Trial related death; Compensation to nominee
- Cost of compensation to be borne by sponsor
Compensation Amount - Trial related SAE of Death

Compensation = \( \frac{B \times F \times R}{99.37} \)

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factor</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 65 yrs</td>
<td>4</td>
<td>32 lacs (45000 Euro)</td>
</tr>
<tr>
<td>&lt; 16 yrs</td>
<td>4</td>
<td>73.59 Lacs (100,000 Euro)</td>
</tr>
<tr>
<td>&gt; 65 yrs</td>
<td>0.5</td>
<td>4 Lacs (6000 Euro)</td>
</tr>
<tr>
<td>&lt; 16 yrs</td>
<td>0.5</td>
<td>9 Lacs (12000 Euro)</td>
</tr>
</tbody>
</table>
Methodology Challenges

Screening of patients

• Informed Consent

• Diagnosis

• Primary VL vs relapse

• rK39 vs parasitological confirmation by tissue aspiration (Bone marrow or Splenic tissue aspiration)

• PKDL – probable vs confirmed

• Clinical examination/microscopy and/or qPCR

• Laboratory screening – Back Up Lab

• Timely reporting
Study Design

• Randomised Controlled Trials
  • Placebo – Yes / No
  • Comparator – Yes / No

• Safety and *Efficacy* – Controlled set up

• Safety and *Effectiveness* – Community trials – Real life conditions field study – Evidence for policy Change
  • Amendment of protocol
  • Children vs adults (recruitment only at District Hospital under supervision of pediatrician)

• Observational studies
Diagnostic and Outcome

- VL - rK39, clinical or parasitological (bone marrow or splenic tissue aspiration)

- PKDL – clinical examination, microscopy, qPCR

- End of treatment test and screening diagnosis

- End of Follow Up test vs diagnosis
Treatment period

• Treatment of outpatient basis vs hospitalized
  • Difficult to hospitalize/retain patient for long duration treatment
  • PHC vs District hospital

• Assessment visits
Follow Up

• 6 month vs 12 month FU

• Discharge cards

• Doctors/Health Educator – All information of patients (address, telephone number etc)

• Health Educator team – active follow up
  • Telephonic contact
  • Home visits
Limited Resource Settings
Human Resource and commitment – Study team

- HR - Lack of qualified and experienced medical and paramedical staff
- Motivation and retention of study staff
- Transfer of trained staff by MoH
- Monitor based at site for initial few months – supervision for documentation and training
- Lack of commitment and financial incentive to study team
- Sometimes, lack of sufficient knowledge of the research community and of its understanding of/expectations from research
Documentation

- Paper based CRF vs eCRF
- Source documentation
- Investigator commitment
- Completion of CRF
- Availability of reports
- Drug accountability

- Data entry/ data management
Capacity Building

• Laboratory infrastructure upgradation
  • Microscopes
  • Hematology analyser
  • Biochemistry machine
  • Tissue aspiration
  • Reagents supply
  • Renovation of KA wards
• Trainings to MoH staff for diagnostic procedures and drug administration
• Pharmacovigilance trainings – safety reporting
## TRAININGS - GCP

<table>
<thead>
<tr>
<th>Dates</th>
<th>Training</th>
<th>Venue</th>
<th>Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>07-10 Dec 2011</td>
<td>MSF Team Training on implementation study protocol and GCP, informed consent process and safety reporting</td>
<td>Hajipur, Vaishali, Bihar</td>
<td>42</td>
</tr>
<tr>
<td>30 - 31st Jan 2012</td>
<td>Allopathic doctors and AYUSH medical professional of PHCs of Saran District</td>
<td>ANM Training school, Chappra, Saran, Bihar</td>
<td>75</td>
</tr>
<tr>
<td>09-10 April 2012</td>
<td>Allopathic doctors and AYUSH medical professional of PHCs of Vaishali District</td>
<td>Sadar hospital, Hajipur, Vaishali, Bihar</td>
<td>49</td>
</tr>
<tr>
<td>24-25 May 2012</td>
<td>Good Clinical Practice (GCP) Training organised by DNDi and conducted by Quintiles for PHC and MSF team</td>
<td>Saran (24 May) and Vaishali (25 May), Bihar</td>
<td>42 + 38</td>
</tr>
<tr>
<td>30 Aug 2013</td>
<td>Refresher Training on pilot study</td>
<td>ANM Training school, Chappra, Saran, Bihar</td>
<td>40</td>
</tr>
</tbody>
</table>
## TRAININGS – Laboratory

<table>
<thead>
<tr>
<th>Dates</th>
<th>Training</th>
<th>Venue</th>
<th>Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 26 July 2012</td>
<td>Haemocue (Hemoglobin estimation) Training to Lab technicians and MOIC</td>
<td>Chhapra Sadar Hospital, Saran, Bihar</td>
<td>06</td>
</tr>
<tr>
<td>2 27 July 2012</td>
<td>Haemocue Training to Lab technicians and MOIC</td>
<td>PHC Dariyapur, Saran, Bihar</td>
<td>07</td>
</tr>
<tr>
<td>3 04 Dec 2012</td>
<td>Haemocue Training to Lab technicians and MOIC</td>
<td>PHC Baniyapur, Saran, Bihar</td>
<td>05</td>
</tr>
<tr>
<td>4 23 Aug 2012</td>
<td>Reflotron Installation (Biochemistry analyser) and training to Pathologist, lab technician, MOIC</td>
<td>Chhapra Sadar Hospital, Saran</td>
<td>05</td>
</tr>
<tr>
<td>5 27 July 2012</td>
<td>Haemocue Training to Lab technicians and MOIC</td>
<td>PHC Maraurah, Saran, Bihar</td>
<td>06</td>
</tr>
</tbody>
</table>
Logistics Issues

- Importation of study drugs
- Cold chain - ILR, refrigerator
- Batch Recall
- Shelf life of drugs, diagnostics and reagents
- Regular supply of Laboratory reagents
- Transport of Lab samples from Primary Health centre to District hospital
- Drug destruction
Garoul PHC
IEC Activity
Mahnar PHC
Phase 1 clinical trials

- Regulatory/ Ethics/Operational challenges
- First in Humans study?

Highs –
- Cost effective
- India centric population
- Qualified medical doctors/CRO expertise

Lows –
- Regulatory uncertainty
Conclusion

• Challenging

• Feasible with consideration of field requirements

• Useful to develop standardised guidelines
## Approvals – pilot study

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Concerned Authority</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Technical Advisory Committee of NVBDCP under Chairmanship of DGHS approved the project</td>
<td>08 Aug 2011</td>
</tr>
<tr>
<td>2</td>
<td>NVBDCP approval letter</td>
<td>22\textsuperscript{nd} Sep 2011</td>
</tr>
<tr>
<td>3</td>
<td>MoU signed b/w State health society Bihar &amp; DNDi</td>
<td>21 Nov 2011</td>
</tr>
<tr>
<td>4</td>
<td>Health Ministry Screening Committee</td>
<td>23 March 2012</td>
</tr>
<tr>
<td>5</td>
<td>DCGI approval</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RMRI EC approval</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>LSHTM EC Approval</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MSF ERB review</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CTRI Registration</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NVBDCP Meeting under Chairmanship DGHS rolling out combination treatments in additional districts</td>
<td>13 August 2013</td>
</tr>
<tr>
<td>11</td>
<td>Steering Committee meeting under Chairmanship Dr SD Seth- Advisor Clinical Trials Registry ICMR- Proceed to step 2</td>
<td>10 Dec 2013</td>
</tr>
<tr>
<td>12</td>
<td>Policy Change - Adoption of SDA and Combination treatments for VL</td>
<td>Aug 2014</td>
</tr>
<tr>
<td>13</td>
<td>Presentation to NVBDCP experts for KA elimination</td>
<td>Sep 2014</td>
</tr>
</tbody>
</table>

Thank you!