Human Infection Challenge Studies: Ethical Dilemma and Africa’s readiness

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OVERVIEW

My experience

• Worked in
  • South Africa
  • Zambia
  • Uganda
  • Nigeria
  • Tanzania
  • Ethiopia
  • Kenya

• PI, Monitor, Auditor, Filed Coordinator

Geneva micrococktail

<table>
<thead>
<tr>
<th>Probe</th>
<th>Enzymatic target</th>
<th>Dosage</th>
<th>Usual therapeutic dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>CYP1A2</td>
<td>50 mg</td>
<td>100 mg in a usual cup of coffee</td>
</tr>
<tr>
<td>Bupropion</td>
<td>CYP2B6</td>
<td>20 mg</td>
<td>150-300 mg/day</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>CYP2C9</td>
<td>10 mg</td>
<td>150-200 mg/day</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>CYP2C19</td>
<td>10 mg</td>
<td>40-80 mg/day</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>CYP2D6</td>
<td>10 mg</td>
<td>75-100 mg/day</td>
</tr>
<tr>
<td>Midazolam</td>
<td>CYP3A4</td>
<td>1 mg</td>
<td>7.5-15 mg/day</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>P-glycoprotein</td>
<td>25 mg</td>
<td>120-180 mg/day</td>
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</tbody>
</table>

Drug Safety
https://doi.org/10.1007/s40256-020-00983-8

Safety of the Geneva Cocktail, a Cytochrome P450 and P-Glycoprotein Phenotyping Cocktail, in Healthy Volunteers from Three Different Geographic Origins

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KEY CONSIDERATIONS

• Health Awareness of the Community

• Human and Infrastructure capability

• IRB and regulatory oversight

• Obtaining informed consent

• Culture and belief systems
• Challenge studies have a long history > 100 yrs
  • Smallpox
  • Yellow fever
  • Malaria
  • Typhoid
  • Cholera
  • Influenza

• Africa has been on “human challenge studies” for centuries
  • Use of unapproved “treatments” including traditional medicine
  • Use of drugs that are not tested on the population
Introduction

• Deliberate infection --- intuitively unethical

• Intentional infection ---- can be ethically acceptable

• High levels of uncertainty -- infection, disease and sequelae

  • Minimize harm and preserve public trust in research
Introduction

• Limited experience globally and in Africa
• Most guidelines, national policies do not address human challenge studies
• Need specialized facilities
• Need close monitoring
• Supportive treatment and critical care
• Highest scientific and ethical standards
Benefits of challenge studies

- Fewer participants
- Accelerate development and faster than field trials
- Used to compare the efficacy of multiple candidates
- Interepidemic or interpandemic periods
- Cheaper
Most IRBs have limited experience on HCS
Emphasis on safety information
Significant experience in designing, reviewing and conducting human challenge studies
Expert review (specialized independent committee)
Emphasis when involving health care workers or self-experimentation
During the study
- Check on any complaints
- Control processes, including protective equipment for staff
- Regular consultation --- in light of new data
Informed consent process

- Challenges and controversies
  - Poverty (inducement), literacy, access to health care .......
- In African context decision-making is often communitarian
  - Involving consultations with family/community members
  - Elders of the community are usually involved
- Understand the cultures and beliefs of the communities
- All important even if complex information should be conveyed
- Consent should be revisited throughout the study
Risk-benefit assessment

- Challenging and complex process
  - Potential risks and anticipated benefits Vs true risks and benefits

- Communities Vs Individual
  - The benefit of having vaccines introduced first
  - Participants, society, third-party contacts

- Obtaining the maximum amount of scientific knowledge per individual challenged
  - Collecting additional samples during challenge trials
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Risk-benefit assessment

• Close monitoring, early diagnosis
• Specific treatments
• Long-term follow-up
• Compensation for any study-related harms
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Trust

• Public
• Expert groups
• Consultation: Timely, in-depth and updated information, before, during and afterwards
• Responding to community concerns
• Maximizing transparency
• Zoom out to see social justice
Summary

Adhere to standard research ethics requirements

Decision to undertake Infection Challenge Studies

Needs major regulatory policy change

Do we have the Resource/facility?

Do we have qualified team?

Do we have qualified IRBs/RBs?
• Key criteria for the ethical acceptability of COVID-19 human challenge studies (WHO)
• Research Ethics in Africa: A Resource for Research Ethics committees (Mariana Kruger ■ Paul Ndebele ■ Lyn Horn)