Intervention Study (Clinical Trial)

Mayfong Mayxay M.D., Ph.D. (Trop Med)

GFMER - WHO - UNFPA - LAO PDR
Training Course in Reproductive Health Research
Vientiane, 22 October 2009
Risk or intervention?

No

Observational study

Control?

Yes

Analytical study

Start with “cause” or “effect”?

Yes

Cause → Effect

Cohort study

No

Descriptive study

→

Clinical descriptive

- Cross-sectional

- Longitudinal

Cause ← Effect

Case-control study

Yes

Experimental/intervention study or clinical trial

Randomized controlled trial (RCT) or true experimental study

Non RCT or Quasi-experimental study

Pre-experimental study

Cause / Effect

Cross-sectional study
What Are Clinical Trials?

• Research studies involving people
• Try to answer scientific questions and find better ways to prevent, diagnose, or treat disease
• Follow somewhat the pattern of observational studies
Why Are Clinical Trials Important?

• Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat disease

• The more people take part, the faster we can:
  - Answer critical research questions
  - Find better treatments and ways to prevent disease
Intervention Study/Clinical Trial

- Cohort
- Intervention / manipulation
- Follow up
- Measurement of intervention

3 sub-types:
- Randomized controlled trial (RCT)
- Non RCT
- Pre-experimental
Randomized controlled trial (RCT)

- Randomization
- Intervention
- Control
- Gold standard for studying intervention in a clinical setting
Non-randomized controlled trial (NRCT)

• No randomization (patients can select)
• Intervention
• Control
Pre-experimental study

- Intervention
- No control
- No randomization
What Are the Different Types of Clinical Trials?

- Treatment
- Prevention
- Early detection/screening
- Diagnostic
- Quality of life/supportive care
Treatment Trials

• What new treatments can help people with a particular disease?
• What is the most effective treatment for people with that disease?
Clinical trials  To determine whether or not there are differences between the effects of treatments

Treatments A and B

- purpose
- difficulties
- knowledge
  - Previous studies
  - publications
  - data bases
  - theory

- Analysis method
  - $\mu_A \neq \mu_B$
  - $\mu_A = \mu_B$
Clinical Trial Phases

Phase 1 trials
- How does the agent (drug) affect the human body?
- What dosage is safe?

Phase 2 trials
Does the agent or intervention have an effect on the disease?

Phase 3 trials
- Is the new agent or intervention (or new use of a treatment) better than the standard?
- Participants have an equal chance to be assigned to one of two or more groups
Participants have an equal chance to be assigned to one of two or more groups:

• One gets the most widely accepted treatment (standard treatment)

• The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than the standard treatment
Randomization

Control Group

Investigational Group

Randomization
Why is Randomization Important?

• So all groups are as alike as possible
• Provides the best way to prove the effectiveness of a new agent or intervention
Placebos are almost never used:

• Placebos are used only when no standard treatment exists

• Patients are told of this possibility before deciding to take part
Difficulties and ethics:

- Patients
  - availability
  - inclusion and exclusion criteria
  - willingness to participate
  - presentation rates
  - compliance
  - how many?

- Data
  - measures of effects
  - adverse effects
  - influence of other factors
  - **random variation of effects between people**
  - bias
    - allocation bias
    - assessment bias
    - analysis

- Cost
Is treatment A better than treatment B?

<table>
<thead>
<tr>
<th></th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>total</th>
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<tbody>
<tr>
<td>Recovered</td>
<td>17</td>
<td>8</td>
<td>25</td>
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<tr>
<td>No better</td>
<td>3</td>
<td>12</td>
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<tr>
<td>total</td>
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If treatment A is better than treatment B . . .

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Why did these eight recover? Were they younger, stronger, or in a better condition than those who did not recover?
If treatment A is better than treatment B . . .

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Why didn’t these three recover? Were they older, more feeble, or in a worse condition than those who did?
Perhaps treatment A is not better than treatment B? So...

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Could there have been an allocation bias?
Perhaps treatment A is **not** better than treatment B?  So . . .

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Could the results have occurred by chance?
The efficiency and effectiveness and cost of a clinical trial depend on:

- response to each treatment
- influence of other factors such as age, gender or life style
- number of patients
- how patients are selected for the trial
- how patients are allocated to treatments
- type of trial: parallel or crossover
- compliance of patients to treatments
- how data are recorded, analysed and interpreted
Type of trial:

- Parallel
- Cross-over
- Sequential
- Group sequential
- Factorial
Parallel Designs

1. Population
2. Assessment
3. Eligible and willing subjects
4. Allocation
   - Treatment A
   - Treatment B
5. Assessment
6. Data analysis

Exclusions

arm 1

arm 2
Two-period Cross-over designs

POPULATION

Assessment

Eligible and willing subjects

Exclusions

Allocation

First period

Treatment A

Treatment B

Assessment

Second period

Treatment B

Treatment A

Assessment

Data analysis

arm 1

arm 2
Prevention Trials

• Evaluate the effectiveness of ways to reduce the risk of a particular disease
• Enroll healthy people at high risk for developing that disease

• Action studies (“doing something”)
• Agent studies (“taking something”)—also called “chemoprevention studies”
Chemoprevention Trials

- Phase 3 chemoprevention trials compare a promising new agent with either an:
  -- Standard agent
  -- Placebo
Clinical Trial Protocol

• A recipe or blueprint
• Strict scientific guidelines:
  -- Purpose of study
  -- How many people will participate
  -- Who is eligible to participate
  -- How the study will be carried out
  -- What information will be gathered about participants
  -- Endpoints
Benefits of Participation

Possible benefits:

• Patients will receive, at a minimum, the best standard treatment (if one exists)
• If the new treatment or intervention is proven to work, patients may be among the first to benefit
• Patients have a chance to help others and improve patient care
Risks of Participation

Possible risks:

• New treatments or interventions under study are not always better than, or even as good as, standard care

• Even if a new treatment has benefits, it may not work for every patient

• Health insurance and managed care providers do not always cover clinical trials
Patient Protection

- There have, unfortunately, been past abuses in patient protection
- Federal regulations ensure that people are told about the benefits, risks, and purpose of research before they agree to participate
How Are Patients’ Rights Protected?

- Informed consent
- Scientific review
- Institutional review boards (IRBs)
- Data safety and monitoring boards (DSMBs)

RCT: unethical if the intervention is strongly believed to be the best available, whether or not that has been established scientifically by careful design and control studies
Advantages & Disadvantages of Clinical Trial

- **Advantages:**
  - Bias & systematic error can be controlled
  - Intervention, samples, outcome can be controlled

- **Disadvantages:**
  - Ethical problem
  - Very expensive & time consuming
  - Problems related to therapy changes & dropped outs
  - Limited in the possibility to generalize results
An Example of RCT in Laos

A Randomized Clinical Trial of

ORAL ARTESUNATE + MEFLOQUINE (AM)

VERSUS

ORAL DIHYDROARTEMISININ - PIPERAQUINE (ARTEKIN®) (DP)

in the treatment of uncomplicated falciparum malaria in Laos
Why / What study?

* Chloroquine (CQ) & Fansidar (SP): not longer effective in Laos

* In 2000 - 01: Clinical trials of CQ vs SP with 42 days of follow up:

  Treatment failure rate of CQ  = 35 – 80 %
  Treatment failure rate of SP  = 18 – 40 %

(Mayxay et al., 2003; Schwobel et al., 2003; Guthmann et al., 2002)
* In 2002 - 03: Clinical trial of 3 combination treatments with 42 days of follow up:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cure Rate</th>
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<tbody>
<tr>
<td>CQ + SP</td>
<td>= 92 %</td>
</tr>
<tr>
<td>Artesunate + mefloquine</td>
<td>= 100 %</td>
</tr>
<tr>
<td>Artemether - lumefantrine</td>
<td>= 94 - 97 %</td>
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</tbody>
</table>

(Mayxay et al., 2004; Stohrer et al., 2004)
COSTS PER 3 DAYS-TREATMENT COURSE IN ADULTS (in $US)

* Artesunate + mefloquine ~ 3.5

* Artemether - lumefantrine (Coartem®) ~ 2.4

* Dihydroartemisinin - piperaquine (Artekin ®) (DP) ~ 1.2
What combination treatment will be appropriate for Laos?
STUDY PLAN

• What regimen to compare?
  → Artesunate + mefloquine

• How many cases?
  Cure rate for AM ~ 97%
  Power of 80%, Alpha error of 5%
  Significant difference in the treatment success rate of 10%.
  = 200 cases. but ~ 10% lost to follow up = 220 cases!

• Definition to measure end-point?
  This must be defined before the trial

• Is the trial ethical?

• Can the trial be compared with other studies?

• When and where?
Ethical Considerations

- Blood Volume
- Safety monitoring of the patients
- Change of treatment in case of treatment failure
- Informed consent and information sheet
- The patients can withdraw from the trial at any time without negative impact on their treatment
- What to do when the patients develop severe disease?
- Patient information must be kept confidential
- Conflict of interest?
- Ethical review by the external people who are not involved in the trial (Approval from 2 ethical committees are preferable)
- Must be published
RANDOMISATION AND BLINDNESS

- Those who are in the study team must not know the treatment allocation before the patient recruitment
- Randomization: done by people who will not enroll the patients
- Patients are randomized in block of 10
- Treatment code in the envelopes (thick paper)
- The envelopes will be open only when the patients sign informed consents
- Blinded vs Open / Placebo vs Non-placebo?
ARTESUNATE + MEFLOQUINE (AM)

VERSUS

DIHYDROARTEMISININ - PIPERAQUINE (ARTEKIN®) (DP)

FOR

THE TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA IN LAOS:

AN OPEN, RANDOMIZED CLINICAL TRIAL
OBJECTIVES

To determine the efficacy & tolerability of dihydro-artemisinin - piperaquine (Artekin®) in comparison with artesunate + mefloquine in Lao patients with uncomplicated falciparum malaria.

All patients were admitted to the clinic.
Study site - Phalanxay, Savannakhet Province

Study site ~ 605 Km southeast of Vientiane

Phalanxay District Clinic with 10 beds

Study duration: May 20 – Sept 28, 2004
Criteria:

* Informed written consent

* Age $\geq 1$ years & not pregnant

* *P.falciparum* parasitemia $\sim 1,000 - 200,000/\mu L$

* Temperature $\geq 37.5^\circ C$, or fever in previous 3 days

* Likely to complete 42-day follow up

* Did not take full course of antimalarials in previous 3 days

* No signs of severe malaria (WHO; 2000)

* No contraindication or allergy to study drugs
Procedure

Patients’ details, medical history, physical examination

Urine test: CQ, Q, Pyr  Finger prick: parasite count, Hct, PCR

Randomised to:

AM  DP

Follow up daily until parasite clearance, then weekly for 42 days

Assessment using WHO (2002) guidelines: ETF, LTF, ACR

Follow up of patient at home
DPAM. 32.

DPAM. 34

DPAM. 33

DPAM. 32.
TREATMENTS

1. **AM**: D0 = Artesunate 4 mg/kg
   
   D1 = Artesunate 4 mg/kg + Mefloquine 15 mg/kg
   
   D2 = Artesunate 4 mg/kg + Mefloquine 10 mg/kg

2. **DP**: (dihydroartemisinin/piperaquine)
   
   2.1/16.8 mg/kg/day
   
   once daily at hour 0, 24, 48

Drug administration in children
RE-TREATMENT

1. Failure of AM → DP

2. Failure of DP → AM

3. Second failure or severe → ARTESUNATE IV ~ 7 days
<table>
<thead>
<tr>
<th>วันที่</th>
<th>เวลา</th>
<th>ดูมะชูม</th>
<th>ทำมำจำย</th>
<th>ถ้ำกี้</th>
<th>ทำยาย</th>
<th>อาหารหมี่</th>
<th>หายานา</th>
<th>มะยง</th>
<th>หมายเหตุ</th>
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2 - 6 2004
ถ้วยเจ็บมูค
บ.ยัก 13 ปี
DPAM-031
น้ำดี D7
วัชบุค 9/6/04
Outcome measures

Primary

* Cure rate: clinical responses

Secondary

* Parasite clearance time (PCT)

  ‘interval in days between the first treatment dose and the first thick film negative for *P. falciparum* parasites after checking > 200 oil fields’

* Fever clearance time (FCT)

  ‘the time, from onset of treatment, to the first time axillary temperature fell below 37.5 °C and remained below 37.5 °C for 48 hours’

* Gametocytaemia after treatment

* Adverse effects
RESULTS

1,311 febrile patients examined for malaria

565 (43 %) malaria positive

500 (88 %) *P. falciparum* malaria

220 patients enrolled

AM (110)

Completed 42 days-follow up 107 (97 %)

DP (110)

Completed 42 days-follow up 105 (95 %)
## OUTCOMES (Adjusted for re-infection)

<table>
<thead>
<tr>
<th></th>
<th>AM = 110</th>
<th>DP = 110</th>
</tr>
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<tbody>
<tr>
<td><strong>42-day cure rate (%) (95% CI)</strong></td>
<td>99 (94 - 100)</td>
<td>100 (100 - 100)</td>
</tr>
<tr>
<td>Recrudescence</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><em>P. vivax appearance</em></td>
<td>1 (1%)</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>
COMPARISON OF PARASITE CLEARANCE TIMES

PCT - Mean (SD)

Days

AM

DP

$P = 0.14$
COMPARISON OF FEVER CLEARANCE TIMES

Checking body temperature

FCT - Mean (SD)

Hours

0

10

20

30

PM

AM

$P = 0.85$
HAEMATOCRIT CHANGE AFTER TREATMENT

Mean (SD) haematocrit (%)

Days

Artesunate + mefloquine

Dihydroartemisinin-piperaquine
## COMPARISON BETWEEN CHILDREN AND ADULTS

[*Data shown as mean (95% CI) unless indicated*]

<table>
<thead>
<tr>
<th>Variables</th>
<th>Children (≤15 yr)</th>
<th>Adults (&gt; 15 yr)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n = 151 (69%)</td>
<td>n = 69 (31%)</td>
<td></td>
</tr>
<tr>
<td>Adm temp (°C)*</td>
<td>38.4 (38.2 - 38.6)</td>
<td>37.9 (37.5 - 38.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Adm Hct (%)*</td>
<td>33.3 (32.4 - 34.3)</td>
<td>39.4 (37.9 - 41.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCT (days)*</td>
<td>2.07 (2.01 – 2.12)</td>
<td>1.90 (1.80 – 1.90)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FCT (hours)*</td>
<td>24.3 (22.1 – 26.5)</td>
<td>20.2 (17.6 – 22.7)</td>
<td>0.031</td>
</tr>
<tr>
<td>Gametocytaemia after treatment No. (%)</td>
<td>11/151 (7 %)</td>
<td>1/69 (1 %)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
PROPORTION OF PATIENTS WITH AT LEAST ONE PROBABLE RECORDED SIDE-EFFECT

Percentage (%)

AM: 58%
DP: 44%

P = 0.031
PROBABLE SIDE EFFECTS AFTER TREATMENT

- Nightmares
- Insomnia
- Vomiting
- Nausea
- Dizziness
- Headache
- Weakness

* Significant difference between groups ($P < 0.05$)

%
CONCLUSION

DP did not have superior efficacy to AM for the treatment of uncomplicated falciparum malaria in Laos but was associated with fewer adverse effects.