Study design issues in trials among children with MAM

Session 5: Impact Assessment in MAM: Methodological Challenges

International Symposium on Understanding Moderate Malnutrition in Children for Effective Interventions
Vienna, Austria, 26–29 May, 2014

Henrik Friis, MD, PhD, Professor of International Nutrition and Health Dept of Nutrition, Exercise and Sports, University of Copenhagen
hfr@nexs.ku.dk
Research in MAM

- Immediate
- Short-term
- Long-term

MAM

- Body composition
- Development
- Physical activity
- Immunity/Infections
- Education
- Working capacity
- Diabetes/NCD Infections

SAM

- Survival
Study design

- Issues of concern
  - Ethics
  - Scientific
    - Validity
    - Generalizability

- Study design options
  - Non-controlled or non-randomised
  - Randomised, controlled trial
    - Special design
      - Stepped wedge
      - Cluster randomised
      - Factorial

- Examples
Issues of concern - ethics

Study design

- Intervention – potential benefit and harm?
  - Experimental
  - Control

- Methods – pain, risks, inconvenience, etc

- Suboptimal research?
- Lack of research?
Issues of concern - scientific

Study design

- Validity
  - Confounding
  - Bias
    - Information
    - Selection
  Randomisation

- Generalizability?
Generalisability of nutrition trials?

Study design

- Difficult!

- Why?
  - Background status/intake differs – difficult to measure
  - Nutrient deficiencies widespread – co-exist and interact
  - High infectious disease burden – affects metabolism

The effect of the same intervention will differ between individuals and populations
Generalisability of nutrition trials

Conceptual framework

(Friis H, Trop Med Int Health, 2006)
**Explanation of no effect**

(A) No relationship between nutrient and risk?
(B) Intervention not adequate?
(C) Status/intake already adequate?

(Friis H, Trop Med Int Health, 2006)
Effect modification by background intake/status

(A) Large effect if severe deficiency
(B) Moderate effect if moderate deficiency
(C) No effect if no deficiency

(Friis H, Trop Med Int Health, 2006)
Effect modification by other factors

(A) Harmful – due to other factor
(B) Neutral – due to other factor
(C) Beneficial – due to other factor

(Friis H, Trop Med Int Health, 2006)
Options
Study design

❖ Non-controlled or non-randomised

❖ Randomised, controlled trial
  ❖ Special design
    ❖ Stepped wedge
    ❖ Cluster randomised
    ❖ Factorial
Randomised, controlled trial

Study design

- Experimental vs control?

- Existing standard of care – without evidence?
  - Difficult to test its effect
  - Difficult to test a potentially better intervention

- An infinite number of potential diets - which to test?
  - Nutrient dose/form/quality/processing, etc

- Individual allocation difficult
**Stepped wedge**

**Study design**

- Randomised sequential roll-out of intervention

- Underutilised, but useful if
  - prior belief that intervention is better
  - impossible to deliver simultaneously to all

- Disadvantage
  - Information bias, due to lack of blinding
  - When done, often not randomised
Research article

The stepped wedge trial design: a systematic review
Celia A Brown* and Richard J Lilford

Shaded cells represent intervention periods
Blank cells represent control periods
Each cell represents a data collection point

Brown, 2006
Comparison of home-based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial \(^1-^4\)

Michael A Ciliberto, Heidi Sandige, MacDonald J Ndekha, Per Ashorn, André Briand, Heather M Ciliberto, and Mark J Manary

**Experimental design**

This study was a controlled, comparative clinical effectiveness trial of 2 different management strategies for the second phase of treatment of childhood treatment. Randomized assignment to either standard therapy or home-based therapy with RUTF was not possible in this setting because of resource constraints and cultural beliefs, so prospective systematic allocation with the use of a stepped wedge design was used (10). Children receiving standard therapy were recruited at 6 of the 7 NRUs during the first 3 wk of center participation, during which home-based therapy with RUTF was not offered. The 7th participating NRU offered home-based therapy with RUTF at the onset of the study. The first 2 centers began participation in December 2002, and an additional NRU began participation every 3 wk thereafter. After 3 wk of enrollment of only children receiving standard therapy, home-based therapy with RUTF was offered to all eligible children for 8 wk. Thus, children receiving standard therapy were enrolled throughout the duration of the study, but in fewer numbers. Malawi is an agrarian country with a single annual harvest in April, and most cases of childhood malnutrition occur in the preharvest season (December to April), which is when the study was conducted. The stepped wedge design was used to control bias that might be introduced by seasonal variations in the severity or type of childhood malnutrition in this preharvest season.
Cluster randomised trial

Study design

- Clusters rather than individuals are randomised

- Advantage
  - Logistically easier
  - Lower risk of spill-over

- Disadvantage
  - Less efficient control of confounding, due to lower N
  - Individuals in a cluster not independent
    - Overestimates precision, need to adjust
    - More individuals required, ie more costly
Factorial trial
Study design

- Testing two or more interventions simultaneously

- Advantage
  - Possible to test for interactions
  - ie, if effect of one factor depends on the other factors
  - If no interactions, possible to assess the effect of each factor independently, with full statistical power

- Disadvantage
  - Larger sample size required if interactions expected
  - Complicated analysis plan
Factorial trial
Study design

If effects are independent, then marginal comparisons are made
A vs non-A and B vs non-B

If effects are dependent, then inside-the-table-comparisons are made
AB vs 0; A vs 0, AB vs B

(McAlister FA, JAMA, 2003)
Example: the TreatFOOD trial

Background

- Collaboration between U Copenhagen and MSF-DK
  - key people from WFP, WHO, MSF, Epicentre, and other researchers

- Trial implemented with ALIMA in northern Burkina Faso, Yako

- From September 2013 to July 2015
Example: the TreatFOOD trial

Background

❖ Focus on MAM: develop and test effect of new foods

❖ Intervention?
  ❖ Both quality and cost important
    ❖ Can CSB be improved, without increasing cost?
    ❖ Can LNS be cheaper, without losing effect?

❖ Control group?
  ❖ Unsupplemented?
  ❖ CSB+?
2-by-2-by-3 factorial

TreatFOOD

**Matrix**

- CSB
- LNS

**Soy quality**

- Dehulled
- Isolate

**Milk (% mass)**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>8</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatments**

- **A**: CSB+
- **B**: CSB++
- **H**: eeZeeRUSF/PlumpySup?
- **L**: Plumpynut
Outcomes

The TreatFOOD trial

- **Primary outcome:**
  - lean mass increment to 3 months (D2O)

- **Secondary outcomes:**
  - Anthropometry and organometry
    - increase in weight-height Z-score
    - linear growth, including **knee-heel length**
    - thymic size (ultrasound, subgroup)
  - Morbidity
  - Physical activity (accelerometry)
  - Child development
  - Laboratory outcomes:
    - Blood hemoglobin and essential fatty acids
    - Serum ferritin, acute phase proteins, IGF-1
  - Acceptability of and adherence to the products
TreatFood

TreatFood is a 5 year nutritional research project with the overall objective to contribute to improving quality of and access to treatment for children with moderate acute malnutrition (MAM).

The project is a research collaboration between MSF-Denmark and the University of Copenhagen, with ALIMA as the implementing partner of the trial. Read more about the treatFOOD project.

36 million children worldwide suffer from moderate acute malnutrition (MAM).

Read more facts about malnutrition...
Example: the ARTFood trial
Nutrition trial among adult HIV patients

- Delayed intervention?
- Justifiable, if
  - Equipoise?
  - Mortality not an issue?

(Olsen, Abdissa et al, BMJ, 2014)
Weight increment during supplementation
Weight decline after supplementation
- Due to considerable fat loss
- Despite a continued lean mass increase
Presence of virus at 3 months modified the effect

(Olsen, Abdissa et al, BMJ, 2014)
Conclusions

- Need for cost-effective interventions
- Requires randomised trials, maybe special design
- Choice of control poses scientific and ethical concerns
- Can unsupplemented control groups be justified, and under what conditions?
Thanks!

... and to:

Treatfood:
Bernardette Chicon, Ann-Sophie Iuel-Brockdorff, Christian Fabiansen, Charles Yameogo,
MSF-DK and ALIMA

Artfood:
Mette Frahm Olsen, Alemseged Abdissa, Daniel Yilma, Tsinuel Girma, Markos Tesfaye

Kim Fleischer Michaelsen, Pernille Kæstel, Christian Mølgaard, Åse Bengaard, Jonathan Wells, Søren Brage