Phase III Clinical Trial

Randomization, Blinding and Baseline Assessment

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Statistics Core, Department of Medicine

Subgroup analysis and other (mis)uses of baseline data in clinical trials. The Lancet, 2000 355: 1064-1069


AN1792 immunization reduces Aβ plaque burden and preserves cognitive function in APP transgenic mice.

Plan a Clinical Research

Problem formulation
What is the hypothesis?

Study design
Type of study? Comparison or estimation? interventions? Outcomes?
For whom?
When for how long?
Sample size?
case report forms, database, procedures, timelines
contingency plans? early stopping?

Analysis plan
AN1792 vaccine clinical trial in Alzheimer’s disease

Hypothesis: An1792 immunization will reduce the development or progression of amyloid plaques and prevent the expected cognitive decline

Type of study: This is a randomized (4:1) placebo-controlled double blind clinical study

For whom: patients from 28 centers in US and Europe with mild to moderate AD

Interventions and sample size: IM AN1792 (300 patients) vs saline (72 patients) at 0, 1, 3, 6, 9 and 12 months

Outcome: safety, tolerability (primary) cognitive outcomes (secondary)

The trial stopped after 6% of vaccine recipients developed meningoencephalitis
Problem formulation
(What is the hypothesis)

- Null hypothesis:
  No difference between An1792 immunization and placebo
- Alternative hypothesis:
  There is difference between An1792 immunization and placebo

Express in terms of endpoints

- Null hypothesis:
  no difference in change of total brain volume from baseline to 12 month between An1792 immunization and placebo
- Alternative hypothesis:
  An1792 immunization would have slower rate of reduction of whole brain volume than placebo.
  An1792 immunization would have a 30% slower rate of reduction of whole brain volume than placebo.
Study Population
(For Whom)

Subset of the general population determined by the eligibility criteria

General population

Eligibility criteria

Study population

Enrollment

Study sample

Observed
N=372
Patients randomly assigned to study treatment

N=299
AN1792(QS-21)

N=300
Received at least one injection

N=223 (74.3%)
Completed study

N=77 (25.7%)
Prematurely withdrawn

N=73
Placebo

N=72
Received at least one injection

N=53 (73.6%)
Completed study

N=19 (26.4%)
Prematurely withdrawn
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Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥ 1:2200 at any time after injection 1.
Study Design
(comparison? Estimation?)

Uncontrolled (no comparison group)

Controlled
- Before/after
- Historical
- Concurrent, not randomized
- Randomized
Problems

- Uncontrolled trials: potential to provide a very distorted view of therapy.
- Before and after:
  - Historical controls: patient selection? Experimental environment?
  - Concurrent nonrandomized controls: bias in treatment assignment.
Comparing Treatments

Fundamental principle
- Groups must be alike in all important aspects and only differ in the intervention each group receives

Tools: Randomization and Blinding
Comparing Treatments

Randomization
- Each participant has the same chance of receiving any of the interventions under study
- Purposes (Fisher, 1935)
  1. To guard against any use of judgment or systematic arrangements leading to one treatment getting pots with poor soil, i.e., to avoid bias.
     (Allocation is carried out using a chance mechanism so that neither the participant nor the investigator will know in advance which will be assigned)
  2. To provide a basis for standard methods of statistical analysis such as significance tests

Blinding
- Avoidance of conscious or subconscious influence
- Unbiased evaluation of outcomes
Why does randomization work?
Table 1 Patient demographics, baseline characteristics, and medications

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Patients were considered antibody responders if they had a serum anti-AN1792 IgG (total) titer ≥ 1:2200 at any time after injection 1.
Randomization

- The two groups are comparable at baseline.
- Could do a better job manually matching patients on 12 characteristics listed, but no guarantees for other characteristics.
- Randomization did a good job without being told what the 12 characteristics were.
- Other un-listed characteristics are likely also comparable too.
- Chance assignment could create some imbalances, but statistical methods account for this properly.
Methods of Randomizations
(Preparing the randomization list)

Simple randomization (with table of random digits 0-9)

- 2 treatments: A=0-4, B=5-9
- 3 treatments: A=1-3, B=4-6, C=7-9
- 4 treatments: A=1-2, B=3-4, C=5-6, D=7-8

- Advantage: completely unpredictable
- Disadvantage?
Methods of Randomizations
(Preparing the randomization list)

Random permuted blocks (with table of random digits 0-9)

■ 2 treatments
  blocks of 2 pts: AB=0-4, BA=5-9
  blocks of 4 pts: AABB=1, BBAA=4
  ABAB=2, BABA=5
  ABBA=3, BAAB=6

■ Advantage?
■ Disadvantage?
Methods of Randomizations
(Preparing the randomization list)

Random permuted blocks

- Better with reasonable large block size
- One can also vary the block size at random from one block to the next
- Not to inform PI that blocking is used, especially they should not know the block size
Stratified randomization

- If unfortunately, important risk factor is not balanced between groups
  - Cast doubt on correct randomization
  - Affect credibility of treatment comparison
  - Loss of statistical power

- We wish treatment groups to be similar regards certain relevant patient characteristics.
Stratified randomization

What factor to stratify by?

How?
- Random permuted blocks within strata

Balancing for institution:
- institutions differ in patient selection and experimental environment.

disadvantage: over-stratification, especially in small sample size

One should quite confident about a factor’s potential impact on outcome before including it in stratification.
Unequal randomization

- Gaining greater experience and insight into the new treatment. (e.g., standard vs new/low doses vs new/high dose)
- Expecting higher dropout in one treatment
- Disadvantage?
Non-randomized Trials May Be Appropriate

- Early studies of new and untried therapies
- Uncontrolled early phase studies where the standard is relatively ineffective
- Ethical concerns
- Truly dramatic response
Summary
Randomization

1. Randomization "tends" to produce comparable groups
2. Treatment assignment is unpredictable
3. Randomization produces valid statistical tests
4. Randomization should be simple and foolproof, only stratifying by centers and predictive factors.
5. Reports should state the detailed randomization method (e.g., stratification)
Disadvantages of Randomized Control Clinical Trial

1. Generalizability?
   - Participants studied may not represent general study population.

2. Recruitment
   - Hard

3. Acceptability of Randomization Process
   - Some physicians will refuse
   - Some participants will refuse

4. Administrative Complexity
Blinding

Potential bias if without blinding
from the patient
from the treatment team
from the evaluator

The value of placebo control:
Many patients could be effectively treated by placebo.
Blinding

Other considerations:

- Ethics: double blind should not result in an harm or undue risk to a patient
- Practically
- Avoidance of bias: how serious the bias might be without blinding
- Compromise: partial blinding can be sufficient?
Baseline data

What are the uses of baseline data?
Baseline data

- characterize the study participants, and comparability of treatment groups
- use as the stratifying factors in randomization
- use as covariates in the analysis of treatment effects on outcomes
- use to define subgroup analysis
Baseline data table

- Use as an overall description of study subjects than a comparison of treatment group.

Q: What to include in the tables?

A: Baseline factors thought to be associated with the primary outcome.
Baseline table in randomized trials

- significance test for group difference?
- any difference is either due to chance or flawed randomization
- statistical analysis can not correct for flawed randomization
- A significant imbalance will not matter if a factor does not predict outcomes
- a non-significant imbalance is important if the factor is a strong predictor
Significance tests in Baseline table

Senn S. (1994) Testing for baseline balance in clinical trials, Statistics in Medicine, 13, 1715-1726:

this practice is philosophically unsound, of no practical value and potentially misleading
Covariate adjustment:

- should emphasize unadjusted analysis
- adjust for baseline values of the outcome is recommended.
- Other pre declared factors are OK to included
- adjustment based on model selection should be secondary analysis. (investigators bias?)
- adjust for imbalanced baseline variables? For peace of mind?
Subgroup analysis:

- intellectually important
- results are generally overused and over-interpreted.
- use statistical test for interactions, however, it generally lacks of power
- Recommendation: exploratory analysis (don’t do it, or at least don’t believe it).
AN1792 vaccine clinical trial in Alzheimer’s disease:

- Based on MRI data, a sample size of 75 patients per group would provide 78% power to detect a 30% change in rate of reduction of whole brain volume (placebo vs active).
- Based on phase I data, approximately 25% of patients would develop serum anti-AN1792 titers of $\geq 1:2,200$ (defined as antibody responders).
- To achieve approximately 75 antibody responders, 300 patients were planned for enrollment into the active group and 75 patients for the placebo group.
Alzheimer’s disease: vaccine responders vs placebo

Table 5 Effect of AN1792(QS-21) or placebo on neuropsychological test battery measures in the efficacy-evaluable population

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Data Analysis

- In this study $59/300 = 0.2 = p$ subjects in the vaccine group are responders.
- Let $y_0$ be the outcome of the placebo group and $y_1$ be the outcome of the vaccine.
- $y_1 = p \cdot y_{1r} + (1-p) \cdot y_{1n}$
- $y_{1r}$ = average outcome of responders in the vaccine group.
- $y_{1n}$ = average outcome of non-responders in the vaccine group.
Data analysis

Because of randomization, we expect about 20% of the subjects in the placebo would have responded to the vaccine if they had vaccine, and 80% would have been non-responders.

\[ y_0 = p \cdot y_{0r} + (1-p) \cdot y_{0n} \]

- \( y_{0r} \): average outcome of responders in the placebo group
- \( y_{0n} \): average outcome of non-responders in the placebo group
## Data Analysis

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Data analysis: Method A

- Intention-to-treat analysis: compare subjects according to their treatment assignments. I.e., compare all subjects in the vaccine group with all subjects in the placebo:
  
  Compare $y_1$ vs $y_0$,

- Randomization makes two groups comparable.

- It’s the standard analysis for randomized clinical trials.
Data analysis: Method B

- Compare responders to placebo:
  - Compare $y_{1r}$ vs $y_0$
- Assumption $y_{0r}=y_{0n}$; responders and non-responders behave similarly if given placebo
- It may not be a good assumption, for example, we observed different APOE allele frequency distribution between responders and non-responders in the vaccine group.
Data analysis: Method C

- Compare responders in the vaccine group to responders in the placebo group.
  - Compare $y_{1r}$ vs $y_{0r}$
  - Assumption: randomization makes the responders in two groups comparable
  - $y_{1} - y_{0} = [p*y_{1r} + (1-p)*y_{1n}] - [p*y_{0r} + (1-p)*y_{0n}] = p*(y_{1r} - y_{0r}) + (1-p)*(y_{1n} - y_{0n})$
  - If assume $y_{1n} = y_{0n}$; non-responders in the vaccine group behave similarly to non-responders in the placebo group.
  - $y_{1r} - y_{0r} = (y_{1} - y_{0})/p$
Data analysis: BSI

Ventricular volume boundary shift integral (BSI) is a measure of cerebral atrophy.

Contrary to the trial hypothesis, mean BSI is found to be greater for all vaccine recipients and in vaccine responder subgroup.

The investigators speculated that some of the reduction in cerebral volume may have been due to removal of amyloid from brain parenchyma.

<table>
<thead>
<tr>
<th></th>
<th>responder</th>
<th>Non-responder</th>
<th>all</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine</strong></td>
<td>1.10 0.75</td>
<td></td>
<td>0.64 0.55</td>
</tr>
<tr>
<td>(n=45)</td>
<td></td>
<td></td>
<td>(n=228)</td>
</tr>
<tr>
<td><strong>placebo</strong></td>
<td></td>
<td></td>
<td>0.48 0.40</td>
</tr>
<tr>
<td>(n=56)</td>
<td></td>
<td></td>
<td>(n=228)</td>
</tr>
</tbody>
</table>
Data Analysis: estimate of vaccine effect in BSI example

- **Method A:**
  - Vaccine-placebo = 0.64 - 0.48 = 0.16

- **Method B:**
  - Vaccine responder-placebo = 1.10 - 0.48 = 0.62

- **Method C:**
  - \[ P = 20\% = \frac{59}{300} \]
  - \[ 0.64 = p \cdot y_{1r} + (1-p) \cdot y_{1n} \] \hspace{1cm} (1)
  - \[ 0.48 = p \cdot y_{0r} + (1-p) \cdot y_{0n} \] \hspace{1cm} (2)
  - Assume \( y_{1n} = y_{0n} \)
  - (1)-(2) => 0.64 - 0.48 = 0.16 = \[ p \cdot (y_{1r} - y_{0r}) = 0.2 \cdot (y_{1r} - y_{0r}) \]
  - Vaccine responder – placebo responder = \( y_{1r} - y_{0r} = \frac{0.16}{0.2} = 0.80 \)
Summary:

- **Method A** (intention to treat analysis) is always a valid analysis under randomized design (it gives a correct average effect).

- **Method B** relies on the assumption that responders and non-responders behave similarly if given placebo (APOE distributions are different between responders and non-responders).

- **Method C** relies on the assumption that outcome of non-responders is not affected by where they receive vaccine or placebo. (18 cases of meningocencephalitis: 13 vaccine responders + 5 vaccine non-responders + 0 placebo.)
Questions and comments?