Historical Controls for Clinical Trials

Contemplation on Use in Drug Development

FDA Small Clinical Trials Course
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The views expressed are those of the author, and do not necessarily represent an official FDA position
What Is a Clinical Trial?

• Study as a part of drug development (for present discussion)

• Use of drug in an investigational manner

• Key objective
  ➢ Answering a specific question(s)
  ➢ As a sufficiently clear conclusion

• Statistical comparison is often the process that leads to a conclusion
  ➢ Thus statistical principles are important
A Perspective on the Statistical Result

• Analysis commonly produces:
  ➢ An estimate of the size of the difference between two groups on some measure
  ➢ A p-value attached to that difference

• P-value is an indicator of robustness of the between group difference
  ➢ In light of the range of patients in the groups (between patient differences)
  ➢ Small p-value indicates that the between group difference is not likely to be play of chance
Statistical Results and Study Conclusions

- Small p-value: Conclude that at the time outcome was measured the two groups are different
- Either the groups were not ‘the same’ from the very beginning, or something happened during the study to make them not ‘the same’
- To conclude the treatment was the cause, we need to conclude that the ‘from the very beginning’ possibility is not applicable
- RANDOMIZATION is the easy way to support that belief
What does Randomization Do?

- Promotes making the groups comparable in all prognostic factors that were measured
- Permits us to believe the groups are comparable in all the unknown & unmeasured prognostic factors

Thus, supports assumption that the groups were comparable at the very beginning
Value of Randomization

• Based on assumption of initial comparability:
  ➢ All of the observed difference occurred after study entry and randomization.
• In a well designed and conducted study:
  ➢ The only known difference between groups is the treatment given.

• Thus we conclude there is a cause and effect relationship between treatment and the observed difference
What IS a Historical Control Trial

- A clinical trial intended to support a comparative conclusion regarding the treatment
- The comparator to the treated group is not a concurrent separate group of patients
  - The comparison is between two different ‘times’
- Non-randomization does not equal Historical Control
  - Concurrent case-control study
  - Concurrent groups non-randomized study
- Absence of placebo does not equal Historical Control
  - Dose comparison study
Types of Historical Control

• Prior patients with same disorder
  ➢ From an observational study
    ▶ Prospective natural history study
    ▶ Medical chart data from clinical care
  ➢ Control group from a prior randomized investigational study
Types of Historical Control

• “Patient as Own Control”
  ➢ Comparison to patient’s baseline
  ➢ Depends on historical knowledge for projecting what patient’s outcome would be had the intervention not been given
    ➢ Natural history knowledge

• Patient as own control using repetitive cross-over
  ➢ Special circumstances to be feasible
  ➢ Special type of non-randomized study
A Key Aspect of Clinical Trials (again)

- Same for both historically controlled, and non-historically controlled trials

- Study intended for comparative conclusion
- Conclusion directed by statistical analysis
  - Statistical result alone implies only that the data of the two groups are not likely from the same ‘population’
Key Question with Historical Controls

• Data are intended to support the conclusion that the Tx caused the study-end difference
  ➢ Only if can rule out the possibility that the study-end difference was not caused by differences present between the two groups at study-start
  ➢ Requires believing there are no meaningful differences in prognostic factors, known or unknown
    ❖ No randomization step to support that belief

• Are the two sets of patients comparable?
  ➢ What justifies that belief?
Causes of Potential for Differences Between Groups Separated in Time

- Changes in diagnostic criteria
- Differences in population with the disease
  - Prognostic factor distribution
  - Especially unknown prognostic factors
  - Differences in phenotype composition
- Differences in concomitant standards of care
Causes of Potential for Differences Between Groups (2)

- Differences in performing assessments that measure the endpoint
- Differences in subjective portions of assessment procedure
  - In patient or physician actions or judgment between clinical care setting and prospective, interventional clinical trial
- Missing data in historical records
  - May bias apparent outcome
- Other data quality problems
Factors that Strengthen Historical Controls: Outcome and Endpoint Related

• Large treatment effect

• Difficult to bias outcome assessment
  ➢ Incontrovertible event
  ➢ Accurately ascertained event
  ➢ Reliably ascertained
  ➢ Not alterable by other therapy or management choices
Stronger Historical Controls: Patient Related Factors

- Little phenotype variability

- Known prognostic factors account for much of existing variability in patient’s clinical course
  - No unknown significant prognostic factors
Stronger Historical Controls: Data Source Factors

• Less time between when historical data are obtained and the interventional trial
  ➢ Less time for changes in concomitant care, etc.

• Use of control groups from prior clinical trials of similar design
  ➢ Better documentation of eligibility criteria, on study management, endpoint assessment, baseline factors measured

• Large, broad-based historical datasets
  ➢ Especially relative to total size of patient population and size of treatment study
Stronger Historical Controls: Some Patient as Own Control Designs

- Repetitive cross-over design
  - Patient measure pre-Tx as patient’s own control
  - Rapid onset of effect, rapid loss of effect, repeat
  - Patient as own control shown repeatable
Historical Control Examples – Successful Use

• Gaucher Disease
  ➢ Hepatomegaly

• Transfusion-induced Iron Overload
  ➢ Serum ferritin

• Pompe Disease
  ➢ Mortality
Historical Control Examples – Misleading

- Acute MI
  - Mortality
  - Antiarrhythmics in CAST

- Massive Middle Cerebral Artery Infarction
  - Mortality
  - Tx: Decompressive hemicraniotomy
Malignant Middle Cerebral Artery Stroke

- Massive edema
  - Cerebral herniation
  - Death and disability

- Decompression by craniotomy
# Malignant Middle Cerebral Artery Stroke

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<td>Survival (%)</td>
<td>75%</td>
<td>22%</td>
<td>78%</td>
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Challenge Questions
Question 1

• Question:

• Historical control studies all perform a statistical comparison of outcomes in a group of drug-treated patients to a different group of patients who did not receive the drug treatment.

• (True / False)
Question 1

- Answer:
- False
- Any study that makes or implies a comparison of data not from two concurrent groups (i.e. uses data collected at two separate times) is an historically controlled study.
Question 2

• Question:

• Historically controlled studies are always an invalid basis for reaching conclusions about drug effect.

• (True/False)
Question 2

• Answer:

• False.

• Under certain circumstances, which are not usual, an historically controlled study can be a sound basis for conclusions.
Question 3

• Question:
• Which factors strengthen an historically controlled comparison?

➢ A) Small time period between collection of the historical data and conduct of the treatment trial
➢ B) Large, broad-based historical dataset
➢ C) Wide disease variation without distinct phenotypes
➢ D) Use of a continuous scale measurement as the outcome
➢ E) Large treatment effect of new drug treatment
Question 3

• Answer:

• A, B, E

- Short difference in time between datasets
- Large, broad historical dataset
- Large treatment effect