

Historical Controls for Clinical Trials

Contemplation on Use in Drug Development

FDA Small Clinical Trials Course
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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

	VISTA registry	DESTINY (surgery)
n	32	17
Survival (n)	23	14
Survival (%)	72%	88%

Malignant Middle Cerebral Artery Stroke

	VISTA registry	DESTINY (surgery)	DESTINY (medical)
n	32	17	15
Survival (n)	23	14	7
Survival (%)	72%	88%	47%

Malignant Middle Cerebral Artery Stroke

	DECIMAL surgery	DECIMAL medical	HAMLET surgery	HAMLET medical
n	20	18	32	32
Survival (n)	15	4	25	13
Survival (%)	75%	22%	78%	40%

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