Secondary Analysis of Clinical Trials Data – A Biostatistician’s Experience

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In clinical trials, numerous data collection activities and resources were invested.

Rich data from clinical trials provide unique, cost-effective opportunities for the secondary data analyses.

Secondary analyses of clinical trials data are common and strongly encouraged.

- Can advance medical science or improve patient care.
Increasing Opportunities for Secondary Analysis of Data

- The data sharing enforced by NIH policy for NIH-funded clinical trials
- NIH R21 funding to support secondary data analysis
- Clinical trial data from pharmaceutical companies can be requested through ClinicalStudyDataRequest.com
- The International Committee of Medical Journal Editors (ICMJE) proposes to require authors to share others the de-identified individual data for the clinical trial results presented in the article Taichman DB et al. Sharing Clinical Trial Data. JAMA 2016;315:467-8.
Use of Secondary Data Analysis

- To assess predictors for treatment responses
- Subgroups analyses of treatment efficacy or safety
- To describe natural history of disease (use control arm data)
- To perform patient-level meta-analysis
- To plan for new similar clinical trial (sample size, primary outcome, duration of follow-up)
- To develop and test new hypotheses
- To develop new statistical methodologies
Challenges of Secondary Analysis

- Large and complicated data
  - Modifications in data forms and protocol
  - Data from sub-study and ancillary study
  - Different versions of data
  - Outcome measures from different sources
- Biostatistician may not be familiar to data and study protocol
- Clinical investigators may not be aware of complexity of data
Comparison of Age-related Macular Degeneration Treatments Trials (CATT)

- NIH-funded trial to compare two drugs and two dosing regimens for their relative efficacy and safety of treatment of neovascular AMD with:
  1) Lucentis® on a fixed schedule (every 4 weeks)
  2) Avastin® on a fixed schedule (every 4 weeks)
  3) Lucentis® on a variable* dosing schedule
  4) Avastin® on a variable* dosing schedule
CATT Design

Baseline (N=1185)  Year 1  Year 2

Lucentis Monthly

Avastin Monthly

Lucentis PRN

Avastin PRN

Retreat if fluid on OCT or other signs of active CNV

Primary Endpoint

Final visit

(Columns: Months)

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
CATT Primary Results

- Lucentis and Avastin are equivalent on their efficacy when treated Monthly or PRN.

CATT Research Group. NEJM 2011;364:1897-908
Secondary Analysis of CATT Data

- Published 30+ secondary papers from CATT data in top ophthalmology journals
- Most papers were led by CATT Investigators and Data Coordinating Center (DCC)
- Biostatisticians in DCC performed all statistical analyses supported by original grant and a R21 grant
- Most of the findings from the secondary analyses were verified by the other similar trials in other countries
- CATT is a good example of secondary data analyses of a large NIH-funded trial
Topics of CATT Secondary Analyses

- Baseline predictors of vision outcomes
- Risk factors of morphological outcomes
- Associations of morphological outcomes and vision outcomes
- Phenotype and genotype association
- Genetic factors for association with treatment response
- Incidence and risk factors of late AMD in the fellow eye
- Papers from additional grading of new features in OCT images or fundus photographs
Case #1: Good Use of CATT data

- There are 3 effective anti-VEGF agents (Lucentis, Avastin, Eyelea) for treating neovascular AMD.
- When a patient seems not respond to an anti-VEGF drug, clinicians attempt to switch to another anti-VEGF drug (in particular Eyelea).
- MANY uncontrolled studies have investigated the effect of switching from Avastin or Lucentis to Eyelea and concluded benefits from switching on vision and morphological outcome.
## Case #1: Switching Effect in Non-controlled Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>VA change after switching</th>
<th>Retinal Thickness Change after switching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yonekawa et al (2013)</td>
<td>132</td>
<td>Gained 3 Letters (p=0.25)</td>
<td>Decreased 30 u (p&lt;0.0001)</td>
</tr>
<tr>
<td>Cho et al (2013)</td>
<td>353</td>
<td>Loss 2 letters (p=0.49)</td>
<td>Decreased 21 u (p=0.008)</td>
</tr>
<tr>
<td>Eadie et al (2014)</td>
<td>111</td>
<td>Loss 1 letter (p=0.84)</td>
<td>Decreased 52 u (p=0.001)</td>
</tr>
<tr>
<td>Ehlken et al (2014)</td>
<td>114</td>
<td>gained 3 letters (p&lt;0.0001)</td>
<td>Decreased 66 u (p=0.008)</td>
</tr>
<tr>
<td>Moisseiev et al (2015)</td>
<td>114</td>
<td>Loss 2 letters (p&gt;0.05)</td>
<td>Decrease 22 u (p=0.003)</td>
</tr>
</tbody>
</table>
Case #1: Good Use of CATT data

- Can we believe benefits are really from switching?
- Without a parallel control group, can the improvements in vision or morphological outcome due to the natural change of the disease or the phenomenon of regression to mean?
- What happen if these eyes continued to be treated using the same drug without switching?
Case #1: Good Use of CATT data

- Secondary data analysis of CATT data from the patients who were randomized to monthly treatment may help to show the effect of continuous treatment of the same drug.

- Use the same “switching” criteria that most papers used:
  - Already received 3 monthly anti-VEGF treatment (i.e., baseline, week 4, week 8)
  - VA 20/40 or worse at week 12
  - No more than 5 letters gain from baseline
  - Persistent fluid at the foveal center
Case #1: Good Use of CATT data

- Total 126 patients met the “switching” criteria at week 12
- The VA change from week 12 at 1 year is 2.8 letters (p=0.050)
- The thickness change from week 12 at 1 year is -52 um (p<0.0001)

Case #1: Good Use of CATT data

- The primary limitations of switching studies are:
  - Lack of a control group of similar patients who were not switched
  - The implicit assumption that outcome would not change with continuing use of the same drug

- Our secondary analysis demonstrated the importance of a control group
Case #2: Meta-Analysis of Safety Data

- In CATT, we found the SAE rate was higher in patients treated with Avastin than Lucentis (adjusted RR=1.28; \( P=0.009 \))

- The 5 similar Lucentis-Avastin trials in other countries did not find increased risk of SAE associated with Avastin

- The individual patient-level meta-analysis was proposed to compare the SAE between Avastin and Lucentis to account for the possible unbalance in baseline characteristics between two drugs
Case #2: Meta-Analysis of Safety Data

- We made the data request to every study Chair or DCC PI for:
  - demographic and medical history (9 variables), drug group, dosing regimen, follow-up length
  - SAE information (MedDRA code, days since enrollment)
- Several requests to receive the data from 4 studies
- In one study, we could not obtain the patient-level data even after all possible approaches (emails, FedEx, face-to-face meeting with PI)
Case #2: Meta-Analysis of Safety Data

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAMD</td>
<td>1.34 (0.79, 2.28)</td>
</tr>
<tr>
<td>CATT</td>
<td>1.28 (1.06, 1.55)</td>
</tr>
<tr>
<td>GEFAL</td>
<td>1.15 (0.67, 1.98)</td>
</tr>
<tr>
<td>IVAN</td>
<td>1.04 (0.76, 1.42)</td>
</tr>
<tr>
<td>LUCAS</td>
<td>0.57 (0.35, 0.91)</td>
</tr>
<tr>
<td>MANTA</td>
<td>1.34 (0.71, 2.54)</td>
</tr>
</tbody>
</table>

Overall (I^2=52%, P=0.06) 1.09 (0.88, 1.35)

Relative Risk (log scale)
Case #2: Meta-Analysis of Safety Data

What we learned from this meta-analysis of 6 Lucentis-Avastin studies are:

- Took much more time than expected to receive data
- Many communications are needed
- Data are collected and coded in different ways across studies
- Some inconsistencies between the final data received and published data
Case #3: Inappropriate Use of CATT data

- CATT data were made public available at https://rt4.cceb.med.upenn.edu/catt/catt_index.php

- In 2015 Annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), a group of non-CATT investigators presented results from a secondary analysis of CATT data

- The number of anti-VEGF injections were negatively associated with incidence of geographic atrophy
Case #3: Inappropriate Use of CATT data

- Their results contradict to our previous CATT results: patients in monthly groups had higher rate of developing geographic atrophy than patient in PRN groups

Grunwald JE, Ophthalmology 2014;121:150-61
Case #3: Inappropriate Use of CATT Data

- We found the secondary analyses were done inappropriately
  - Evaluating the association of post-treatment variable (total number of injections) with outcome is problematic
  - Mis-interpreted results
  - Not aware of the sub-study data

- One day before ARVO poster presentation, the first-author shared the results with CATT Study Chair

- In the end, the first-author did not show up for the poster
Recommendation

- Check with DCC to find whether the secondary data analyses have been done or in progress
- Biostatistician should work closely with clinicians to develop scientific questions for the secondary analysis meaningful
- Clear definition of inclusion/exclusion criteria and key outcomes
- Biostatistician should replicate numbers for key outcomes published in main papers before working on proposed secondary analyses
Cautions in Secondary Analysis

- Subgroup analysis in clinical trials – fun to look at, but don’t believe it
- Unconfirmed subgroup analyses can lead to premature translation to practice with subsequent harm to patient
- Results from secondary analysis should wait for the confirmation by the adequately powered trial.
- Results may not represent the general population as restricted by the study eligibility criteria.
Conclusions

- Enormous opportunities for secondary analyses of clinical trials data
- Biostatistician should work closely with clinicians for developing secondary analysis plan and perform careful statistical analysis
- Appropriate secondary analyses may provide useful information for clinical research and clinical care
NEI/NIH, DHHS grants: U10 EY017823; U10 EY017825; U10 EY017826; U10 EY017828, and R21EY023689