Central Statistical Monitoring of Clinical Trials

Marc Buyse, ScD

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Embedding statistics in science and society will pave the route to a data informed future, and statisticians must lead this charge.

Marie Davidian and Thomas A. Louis

6 APRIL 2012 VOL 336 SCIENCE www.sciencemag.org
The second European Stroke Prevention Study (ESPS2, 1997) accrued 7,040 patients, of which 438 (!) were fabricated using historical data at one center.
THE ROLE OF BIOSTATISTICS IN THE PREVENTION, DETECTION AND TREATMENT OF FRAUD IN CLINICAL TRIALS†

MARC BUYSE¹*, STEPHEN L. GEORGE², STEPHEN EVANS³, NANCY L. GELLER⁴, JONAS RANSTAM⁵, BRUNO SCHERRER⁶, EMMANUEL LESAFFRE⁷, GORDON MURRAY⁸, LUTZ EDLER⁹, JANE HUTTON¹⁰, THEODORE COLTON¹¹, PETER LACHENBRUCH¹² AND BABU L. VERMA¹³

for the
ISCB SUBCOMMITTEE ON FRAUD
Statistical detection of fraud

Number of citations of paper on fraud over time
Statistical detection of fraud

Number of citations of paper on fraud over time
Are these data real? Statistical methods for the detection of data fabrication in clinical trials

Sanaa Al-Marzouki, Stephen Evans, Tom Marshall, Ian Roberts
Are these data real? Statistical methods for the detection of data fabrication in clinical trials

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**Table 4** $\chi^2$ value (with P value) for the final digit at the baseline

<table>
<thead>
<tr>
<th></th>
<th>$\chi^2_{test}$ (P value)</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>46 (5x10^{-7})</td>
<td>9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>48 (3x10^{-7})</td>
<td>9</td>
</tr>
<tr>
<td>Energy</td>
<td>16 (0.064)</td>
<td>9</td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>154 (2x10^{-28})</td>
<td>9</td>
</tr>
<tr>
<td>Complex carbohydrate</td>
<td>135 (1.4x10^{-24})</td>
<td>9</td>
</tr>
</tbody>
</table>
Are these data real? Statistical methods for the detection of data fabrication in clinical trials

Sanaa Al-Marzouki, Stephen Evans, Tom Marshall, Ian Roberts

**Table 3** $\chi^2$ value (with P value) for the final digit at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>1053 ($6 \times 10^{-221}$)</td>
<td>1522 (U)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>642 ($2 \times 10^{-132}$)</td>
<td>963 ($2 \times 10^{-201}$)</td>
</tr>
<tr>
<td>Energy</td>
<td>2151 (U)</td>
<td>2630 (U)</td>
</tr>
<tr>
<td>Total carbohydrates</td>
<td>207 ($1 \times 10^{-39}$)</td>
<td>927 ($7 \times 10^{-194}$)</td>
</tr>
<tr>
<td>Complex carbohydrates</td>
<td>231 ($1 \times 10^{-44}$)</td>
<td>939 ($3 \times 10^{-196}$)</td>
</tr>
</tbody>
</table>

* U means that the P value is too small for calculation.
Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study

Takahisa Sawada1*, Hiroyuki Yamada1, Bjoern Dahlof2, and Hiroaki Matsubara1
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See page 2417 for the commentary on this article (doi:10.1093/eurheartj/ehp336)

Aims

The objective was to assess the add-on effect of valsartan on top of the conventional treatment for high-risk hypertension in terms of the morbidity and mortality.

Methods and results

The KYOTO HEART Study was a multicentre, prospective randomised open-label trial (PROBDESC) designed and the primary endpoint was a composite of fatal and non-fatal cardiovascular events (diabetes.gov NCT00149527).

A total of 1501 Japanese patients (41% female, mean 66 years) with uncontrolled hypertension were randomised to either valsartan add-on or non-ARB treatment. Median follow-up period was 5.3 years. In both groups, blood pressure at baseline was 157/88 and 127/76 mmHg at the end of study. Compared with non-ARB arm, valsartan add-on arm had fewer primary endpoints (2% vs. 15%; HR 0.14, 95% CI 0.03–0.71, P = 0.0029).

Conclusion

Valsartan adds-on treatment to improve blood pressure control produces more cardiovascular events than conventional non-ARB treatment in high-risk hypertensive patients in Japan. These benefits cannot be entirely explained by a difference in blood pressure control.

Keywords

High-risk hypertension • Angiotensin receptor blockers • Cardiovascular mortality • morbidity • Valsartan

Introduction

Cardiovascular disease is the leading cause of mortality worldwide. Hypertension is the most common cause of primary heart disease and heart failure in Japan. Leading causes of cardiovascular disease is still more prevalent in Japan than in Western countries. The percentage of cerebral infarction is two to three times greater than in white people, and stroke is the most common cause of death according to the National Vital Statistics Report.

The renin–angiotensin system (RAS) plays a major role in the homeostasis of blood pressure, electrolytes, and fluid balance. However, dysregulation of RAS contributes to the development of hypertension and cardiovascular organ damage. Numerous trials have investigated the benefits of ACEi, e.g. The Heart Outcomes Prevention Evaluation (HOPE) Study reported that ACEi inhibitors significantly reduced mortality, myocardial infarction, and stroke in high-risk patients. Another important study in this case with ARB, was the Losartan Intervention for Endpoint reduction (LIFE) trial in patients with hypertension. In the LIFE trial, losartan based therapy prevented more cardiovascular morbidity and death, in particular stroke, than standard-based regimen despite similar blood pressure control. There are now numerous studies showing beneficial effects of RAS blockers on cardiovascular outcomes, in particular with ARB, in various stages of the CV continuum. However, these studies have included as maximum a few percent of Asian patients in general and even less Japanese in particular.

Cardiovascular disease incidence in Japan differs from those in Western countries. CAD mortality is three times that in the USA, and cerebrovascular disease mortality is also three times higher than in the USA. The dietary habits in Japan differ from...
Importance of fraud

FDA under pressure to clamp down on clinical trial fraud

By Kirsty Barnes, 25-Jul-2006

Related topics: Clinical Development, Phase I-II, Phase III-IV, Regulatory affairs

The US Food and Drug Administration (FDA) has outlined a series of imminent changes to the way it evaluates clinical trials in an attempt to clamp down on fraud.

The move comes in the wake of an ongoing government investigation into serious allegations that the FDA approved French firm Avenits's antibiotic drug Ketek despite unresolved questions about the drug's safety and efficacy, with full knowledge that some of the clinical data submitted to support the drug's approval was fraudulent.
FDA’s requirement to ensure data quality

100% (manual) source data verification!
Central Data Management / On-site Monitoring
100% (manual) source data verification!

Typical phase III clinical trial

- 100 centers
- 10 patients / center
- 10 visits / patient
- 100 data items / visit

→ $10^6$ data items to check (hospital files vs. case report form)
What proportion of the total budget of a clinical trial is spent on “100% source data verification”?

- < 1%
- 1 – 5%
- 5 – 10%
- 10 – 20%
- > 20%

What proportion of the total budget of a clinical trial is spent on “100% source data verification”?

- < 1%
- 1 – 5%
- 5 – 10%
- > 15%
- > 20%

Cost of a typical phase III clinical trial : 100 M$
Cost of source data verification : 15 M$

What proportion of clinical data items are corrected during the course of a trial?

- < 1%
- 1 – 5%
- 5 – 10%
- 10 – 20%
- > 20%
What proportion of clinical data items that are corrected during the course of a trial?

- < 1%
- < 5%
- 5 – 10%
- 10 – 20%
- > 20%

Source: Medidata (J. Pines)
Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.
Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

Several publications suggest that certain data anomalies (e.g., fraud, including fabrication of data, and other non-random data distributions) may be more readily detected by centralized monitoring techniques than by on-site monitoring.\textsuperscript{21, 22, 23} It has been suggested that a statistical approach to central monitoring can “help improve the effectiveness of on-site monitoring by prioritizing site visits and by guiding site visits with central statistical data checks,” an approach that is supported by illustrative examples using actual trial datasets.\textsuperscript{24}

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

Notably, the advancement in electronic systems and increasing use of electronic records (i.e., electronic data capture (EDC) systems) facilitate remote access to electronic data and, increasingly, to some source data (see section III.B.2.b for further discussion of access to electronic source data). Additionally, statistical assessments using data submitted on paper CRFs or via EDC may permit timely identification of clinical sites that require additional training, monitoring, or both.

Central Statistical Monitoring

Countries → Centers → Investigator Site staff → Patients

Central Statistical Monitoring Database → Data Managers

Auditors → Investigator Site staff

Visits → Items
Humans vs. Computers

Humans are not good at fabricating data, nor at detecting erroneous data patterns.

Computer algorithms are very good at detecting data patterns (they are also reliable and cheap).
Variable types are automatically determined

- Center, subject, visit identifiers
- Binary
- Categorical
- Numerical (continuous if ≥ 10 distinct values)
- Dates
Uninformative variables are removed

- Tables without patient identifiers
- Auxiliary variables (database management)
- Variables with too many missing values
- Variables with no variability
- Variables with too much variability (e.g. mixed units)
For each variable, all relevant statistical tests are selected based on the type of the variable.

The tests compare each center against all other centers.

One $P$-value is generated per center per test.
Tests for numerical variables

- Variables are transformed to have approximate normal distribution

- Non repeated measures
  - Means and variances, using linear mixed effects model to account for between-center variability
  - Outliers

- Repeated measures
  - Within-patient variance
  - Sequence outliers (e.g. 30,32,33,32,55,32)
  - Propagation of values (e.g. 32,32,32,32)
Tests for binary variables

• Non-repeated measures
  – Beta-binomial model to account for between-center variability
  – Binomial model if little between-center variability

• Repeated measures
  – Markov model with two different states (0 and 1)
    • Start 1: State 1 at the beginning of the sequence
    • 1 -> 0: The transition from state 1 to state 0
    • 0 -> 1: The transition from state 0 to state 1
Categorical variables are dichotomized
- e.g. \( x \) having possible values A, B and C:
  3 variables are created
  \( y_1 = 1 \) if \( x = A \), \( y_1 = 0 \) otherwise
  \( y_2 = 1 \) if \( x = B \), \( y_2 = 0 \) otherwise
  \( y_3 = 1 \) if \( x = C \), \( y_3 = 0 \) otherwise

Tests as for binary variables
- single \( P \)-value is calculated as the minimum of the \( P \)-values of all binary tests
- simple correction for multiplicity (Bonferroni)
- e.g. in the example: \( p = \min(p_A, p_B, p_C) \times 3 \)
• $P$-values ($p_{ij}$) form a matrix with as many rows as centers and as many columns as individual tests.

• Typical phase III clinical trial:
  – 100 sites
  – 1000 items to test
  – 10 statistical tests per item
→ $10^6$ $P$-values
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>DZ</th>
<th>EA</th>
<th>EB</th>
<th>EC</th>
<th>ED</th>
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<th>EF</th>
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</tbody>
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P-values
**P-values**

- **Color conventions:**
  - Red: $0 < p < 10^{-5}$
  - Orange: $10^{-5} < p < 10^{-3}$
  - Yellow: $10^{-3} < p < 5 \times 10^{-2}$
  - No color: $5 \times 10^{-2} < p < 1$

- **P-values are signed for directional tests**
• For each test, centers are ranked from most extreme to least extreme $P$-value (e.g. if there are 100 centers, the rank will range between 1 and 100)

• Ranks form a matrix with as many rows as centers and as many columns as tests
<table>
<thead>
<tr>
<th>A</th>
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</tbody>
</table>

*Note: The table represents the ranking of different samples with their scores in various categories.*
• **Color conventions:**
  
  – **Red:** $\text{Rank} \leq 3$
  – **Orange:** $3 < \text{Rank} \leq 5$
  – **Yellow:** $5 < \text{Rank} \leq 10$
  – **No color:** $10 < \text{Rank}$

• **Convention for tied ranks:**
  
  – Mid-ranks used for tied ranks
Center scoring

\[ score_i = \exp \left( \frac{1}{N} \sum_{j=1}^{N} \log p_{ij} \right) \]

- Some tweaking…
  - Tests with extreme \( P \)-values are eliminated
  - Uninformative tests are eliminated
  - \( P \)-values are weighted to account for correlation between tests

- Statistical significance of center scores
  - Estimated using resampling
In summary

Central statistical testing engine

\[
\text{score}_i = \exp\left(\frac{1}{N} \sum_{j=1}^{N} \log p_{ij}\right)
\]

Score \(_i\)

Matrix of \(P\)-values \(p_{ij}\)

Matrix of ranks \(r_{ij}\)
Visual displays

Bubble plot

Circles are proportional to the center size
A statistical approach to central monitoring of data quality in clinical trials

David Venet, Erik Doffagne, Tomasz Burzykowski, François Beckers, Yves Tellier, Eric Genevois-Marlin, Ursula Becker, Valerie Beeg, Veronique Wilson, Catherine Legrand and Marc Buyse
Abnormal Pattern:
No ineligible patients (out of 35 patients in 3 centers) in country X

Interpretation:
The MADRAS score was «pushed» down to make patients eligible.
Visit 1 (baseline)

An example of fraud
An example of fraud

Visit 2 (run-in)
An example of fraud

Visit 3 (run-in)
Visit 4 (run-in)

An example of fraud
An example of fraud

Visit 5 (run-in)
An example of fraud
An example of fraud

Visit 7 (eligibility)

MADRAS score

Frequency

0 10 20 30 40

0 50 100 150
An example of fraud

Visit 7 (eligibility)

Eligible

Ineligible

(MADRAS > 12)
## Continuum from errors to fraud

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<th>Type</th>
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