[Unfulfilled?] Potential of R in Clinical Research

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AGENDA

• What is Clinical Research? (brief intro and terminology)

• What is the potential of R? (in variously regulated environments)

• What needs to be considered for using R in regulated environments?
  • Security breaches (case-study with a Shiny App for bioequivalence)
  • Industry standards (for computerized systems and data deliverables)
  • Audits (how to prove that words meet actions)
**WHAT IS CLINICAL RESEARCH?**

Clinical research is a branch of healthcare science that **determines the safety and effectiveness of drug/device/biologic products** and treatment regimens **intended for human use**.

These may be **used for prevention, treatment, diagnosis or for relieving symptoms of a disease**.
WHAT IS CLINICAL RESEARCH?

Main actors are:

- **Sponsors** (e.g. pharma company that owns the molecule)
- **Subcontractors** (e.g. contract research organizations – CROs)
- **Regulators** (government agencies like FDA and EMA)
**WHAT IS THE POTENTIAL OF R?**

**NB!** Lack of regulations does not mean absence of any standards

**Key points:** Usage of R is an invers function of regulatory scrutiny

Limitations are confused with prohibition
WHAT IS THE POTENTIAL OF R?

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Key points: Usage of R is an invers function of regulatory scrutiny
Limitations are confused with prohibition
CONSIDERATIONS FOR USING R IN REGULATED ENVIRONMENT

• Security breaches
  In most cases security issues are not directly related to R but sometimes they do.

• Industry standards
  • For computerized systems (possibility to use R in principle)
  • For deliverables (electronic submissions to FDA)

• Audits
  Sponsors, government agencies, independent parties.
CASE STUDY

Shiny-app for bioequivalence studies by Andrey Ogurtsov:
statist.shinyapps.io/bioeq_en

FDA defines bioequivalence as:
“the absence of a significant difference in the rate and extent to which the active ingredient … in pharmaceutical equivalents [i.e. generics] becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study”.

CASE STUDY

Shiny-app by Andrey Ogurtsov: statist.shinyapps.io/bioeq_en

Data upload

This app computes main results required for bioequivalence evaluation (standard 2x2x2 crossover design). Your dataset should contain:
subj - randomization number;
seq - sequence (1 - RT, 2 - TR);
prd - period;
drug - test (T) or reference (R) formulation;
time - time of blood sampling;
conc - concentration of analyte.

Demo dataset can be downloaded here (right click - save as...).

Undetectable concentrations for first time points should be entered as 0; for last points - as NA (missed values).
CASE STUDY

Shiny-app by Andrey Ogurtsov: statist.shinyapps.io/bioeq_en

```html
<br>

<table>
<thead>
<tr>
<th>subj</th>
<th>seq</th>
<th>prd</th>
<th>drug</th>
<th>time</th>
<th>conc</th>
<th>subj2</th>
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<td>0.0</td>
<td>1R</td>
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<td>2</td>
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<td>126.0</td>
<td>1R</td>
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<td>R</td>
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</tr>
</tbody>
</table>
```
CASE STUDY

Shiny-app by Andrey Ogurtsov: statist.shinyapps.io/bioeq_en
# CASE STUDY

**Shiny-app by Andrey Ogurtsov: statist.shinyapps.io/bioeq_en**

## Cmax

<table>
<thead>
<tr>
<th>Value</th>
<th>Std.Error</th>
<th>DF</th>
<th>t-value</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>(Intercept)</td>
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<td>0.05</td>
<td>12.00</td>
<td>142.87</td>
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<tr>
<td>drugT</td>
<td>0.06</td>
<td>0.05</td>
<td>12.00</td>
<td>1.27</td>
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<tr>
<td>prd2</td>
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<td>12.00</td>
<td>-1.31</td>
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<tr>
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</table>

## AUC(0-t)

<table>
<thead>
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<th>Value</th>
<th>Std.Error</th>
<th>DF</th>
<th>t-value</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
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<td>12.00</td>
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<td>12.00</td>
<td>0.30</td>
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<tr>
<td>seq2</td>
<td>0.13</td>
<td>0.12</td>
<td>12.00</td>
<td>1.07</td>
</tr>
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</table>

## 90% CI

<table>
<thead>
<tr>
<th>Lower limit of 90% CI, %</th>
<th>T/R ratio, %</th>
<th>Upper limit of 90% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>97.59</td>
<td>106.23</td>
</tr>
<tr>
<td>AUC (0-t)</td>
<td>78.81</td>
<td>98.13</td>
</tr>
</tbody>
</table>
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  Sponsors, government agencies, independent parties.
INDUSTRY STANDARDS

- **Documents collectively referred to as GxP:**
  - 21 CFR Part 11 - Electronic Records; Electronic Signatures
  - Guidance for Industry: Part 11, Electronic Records; Electronic Signatures - Scope and Application
  - 21 CFR Part 58 - Good Laboratory Practice (GLP)
  - 21 CFR Part 312 - Good Clinical Practice (GCP)
  - 21 CFR Part 210 - Current Good Manufacturing Practice (cGMP)
  - ICH E6 - Good Clinical Practice Consolidated Guideline

- **Principal software guidance documents:**
  - General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002)

- **Principal statistical guideline documents:**
  - ICH E9 - Statistical Principles for Clinical Trials
  - Guidance for Industry and FDA Staff - Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (2010)
INDUSTRY STANDARDS

Key points

• Standards do not specify which statistical software can or should be used
• There is a distinct difference between data collection and storage (21 CFR Part 11 - Electronic Records) vs data processing & reporting (General Principles of Software Validation)
• Most standards for computerized systems are already met in established companies
• R installation need to be validated


Revolutionanalytics blog article about R in FDA: [blog.revolutionanalytics.com/2012/06/fda-r-ok.html](http://blog.revolutionanalytics.com/2012/06/fda-r-ok.html)
• FDA expects data to be submitted in electronic ways

• **There are standards developed by CDISC** – Clinical Data Interchange Standards Consortium: CDASH, SDTM, ADaM etc., some of them are adopted by FDA.

• **FDA requires datasets to be sent in .xpt (Transport File) format** originally developed by SAS Institute. This is an open standard now which is already supported in R.

• **CDISC works towards even more platform independent standards based on XML** (e.g. Define.xml file) – a potential for R to develop new tools.
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RECAP

• **R usage varies across different stages of clinical research**
  (inverse function of regulatory requirements)

• **R community has a great potential for developing new tools**
  (interactive vs static reports, helpful for non-programmers, optimization of processes)

• **R is Okay for electronic submissions to FDA**
  (need to overcome misconceptions and implement accordingly)

• **R can gain reputation by covering existing needs & challenges**
  (e.g. better compliance with CDISC standards for electronic submissions)
Q&A SESSION