Use of R in Clinical Trials and Industry-Sponsored Medical Research

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Session Overview

- Brief Background
- Panel Introductions
- Three Presentations
- Announcement
- Q&A
Challenges

- Periodic threads on R-help regarding R and FDA “validation”

- **PERCEPTION** that a certain three-lettered statistical analysis system is the “Gold Standard” and, worse, is perhaps the only one accepted by the FDA *(NOT!)*

- Even MS Excel can be made “21 CFR 11 Compliant”

- However, free (“as in beer”) is not good enough, despite large companies allocating enormous budgets to statistics related IT infrastructure
Challenges (cont.)

- Significant use of R by industry for “pre-clinical” work, but we have not effectively “Crossed the Chasm\(^1\)” to the clinical side of the house

- Substantial internal perception, behavioral, training, documentation, regulatory, legal and management risk aversion related hurdles

- Large corporate entities don’t engage in significant internal process changes unless there is clear benefit to the “bottom line” and even then, behavioral resistance to change is a barrier

\(^1\)Geoffrey A. Moore, “Crossing the Chasm: Marketing and Selling High-Tech Products to Mainstream Customers”, Harper 1991
Reasons to be Optimistic

- Yet, there is increasing industry comfort and use of Open Source operating systems and applications (eg. Linux and OpenOffice)

- Steadily increasing openness on the part of medical industry and regulatory bodies to evaluate the maturity and “value proposition” associated with open source applications

- Over time, current students training with R will move into industry, governmental and other regulatory bodies, planting the “seeds for growth”

- Non-clinical statisticians providing R exposure and training to their clinical colleagues
Reasons to be Optimistic (cont.)

- Presentation by FDA at JSM 2006: *Times ’R’ A Changing: FDA Perspectives on Use of ’Open Source’*

- Increasing use of R within the FDA itself

- Discussions pertaining to formally addressing these issues vis-á-vis R began in earnest at useR! 2006

- Substantial “behind the scenes” work over the past year to make incremental progress on many of these issues on behalf of the R Community

- Hang around - MORE TO COME!!
R for Clinical Trial Reporting: Reproducible Research, Quality and Validation

Frank E. Harrell Jr., Ph.D.
Professor and Chair
Department of Biostatistics
Vanderbilt University School of Medicine
Nashville, TN
Open Source Statistical Software ($OS^3$) in Pharma Development:
A case study with R

Anthony J. Rossini, Sc.D.
Group Head, Modeling and Simulation
Novartis Pharma AG
Basel, Switzerland

David A. James, M.S.
Modeling and Simulation Group
Novartis Pharmaceuticals
Hanover, NJ
Using R: Perspective of a FDA Statistical Reviewer

Mat Soukup, Ph.D.
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, MD
Thanks!!

- Doug Bates
- Dianne Cook
- Frank Harrell, Tony Rossini, David James and Mat Soukup
A key aspect of the CT regulatory framework is 21 CFR 11 with respect to digital signatures, audit trails, etc.

Questions regarding the applicability of 21 CFR 11 to “stand-alone” statistical applications as opposed to databases that acquire, store and manage source electronic records.

However, most decision makers want to see documentation of compliance with “applicable” aspects of the regs.

Efforts to create a guidance document for R began in earnest at useR 2006 in Vienna.
Announcement (cont.)

- “Working Group” began drafting a document with the goal of addressing key issues as they specifically pertain to R

- Marc Schwartz, Frank Harrell and Tony Rossini

- Solicited constructive criticism from multiple parties

- NO changes in procedures were required by R Core!!

- Leverage existing information on development, version control, testing, maintenance, bug reporting/resolution, stable release cycles, updates, documentation, end user support, etc.
Announcement (cont.)

- Document submitted to The R Foundation for approval on June 15, 2007

- Notified of approval by The R Foundation on July 27, 2007

- “R: Regulatory Compliance and Validation Issues A Guidance Document for the Use of R in Regulated Clinical Trial Environments”

- Document is now available on the R Project web site at “Documentation” — > “Certification”

- Direct link: http://www.r-project.org/doc/R-FDA.pdf
Document Scope

- Covers explicitly listed packages from **“Base R”** and the **“Recommended Packages”**

- Does **NOT** cover other CRAN and non-CRAN R packages

- Qualification and Validation

- Software Development Life Cycle (SDLC)

- Specifically addresses 21 CFR 11.10 (a-i) and 11.30 functional requirements
End User Requirements

- The document does not absolve end users from meeting internal requirements for the qualification and validation of R

- End users still must write and maintain applicable SOPs

- 21 CFR 11 is not the only FDA framework applicable to software use (e.g., GxP, etc.)

- We have addressed a notable documentation hurdle, but the burden of implementation and use is still on you
Thanks!!

- Frank Harrell and Tony Rossini
- Reviewers
- Doug Bates
- Martin Mächler
- The R Foundation Board and R Core
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Session Overview
Background
Harrell
Rossini and James
Soukup
Thanks
Announcement
Q and A
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