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!!

Presentation 1

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

Presentation 3

Using R: Perspective of a FDA Statistical ReviewR

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

Announcement

- 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 (eg. G*x*P, 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

Q & A