QUINTILES

R vs. SAS in model based drug development

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UseR!
2009

Overview

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1. Introduction to model based drug development
2. An example
3. Current practice in the pharmaceutical industry
4. Planning how to model the development of a treatment
5. Coding and running the simulations: R vs. SAS
6. (Results of our simulation of a development program)
7. Summary

Model based drug development

QUINTILES

- "Model based drug development " a very fuzzy term. Can mean...
  - using a regression model to explore the dose-effect profile of a treatment (as opposed to comparing results for each dose vs. results from placebo group)
  - modelling the biological mechanism of the treatment– "pharmacometrics"
  - modelling a study or studies
    - simulating pseudo-subjects in a drug development program
      - » (early dose-finding phase IIa -> dose selection phase IIb -> pivotal final phase III)

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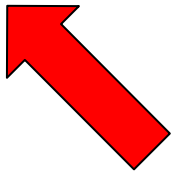

This presentation

An example

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- Challenging program: use model based drug development
  - model/simulate the working of the three phases, automating a mechanism for choosing doses at end of each phase
    - phase IIa -> phase IIb: choose highest safe dose
    - phase IIb -> phase III: choose safe dose with highest model-predicted efficacy
  - little data available about efficacy and safety in humans needing to be treated, so **under a number of possible scenarios**, evaluate
    - probability of finding viable dose
    - probability of finding the best dose (most efficacious dose that is safe)
  - "**scenario**": profile of safety + profile for efficacy across candidate doses of treatment, including zero dose (placebo)

Current practice in the pharma industry?

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- Many large pharmaceutical companies talk of their model based drug development initiatives
  - in most cases this may describe work modelling the mechanism of action of the drug (simulating biology), not clear that it includes modelling a development program (simulating a chain of clinical trials)
- Business Week: “Pfizer, GlaxoSmithKline and others are using simulation...Novartis is far ahead of the rest of the industry” (again unclear what kind of simulation to which Business Week is referring)

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R library MSToolkit simulates single studies and dose selection, such as we are describing here. May become open source.

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Model based drug development: planning

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- Clear and detailed specification
  - In Quintiles: specification is followed independently by originator and by quality-control (QC) statistician
    - two simulation programs produced
    - the two programs produce same or similar outputs
    - Originator used R
    - QC used SAS
  - opportunity to compare R vs. SAS in this work
  - since SAS and R cannot produce simulation of identical random variables, QC of the generation of data is best separate from QC of the processing of those variables
    - 1. QC the generation of random variables
    - 2. share the random data
    - 3. QC the processing of that data in the simulated studies

/Model based drug development: planning

QUINTILES

- /Clear and detailed specification
  - facilitate using same programs for other treatments
    - self-contained functions in R for data generation, simulated analysis, dose selection
    - self-contained macros in SAS
  - rules for selection of doses from a dose-effect curve
    - many simulations -> some unexpected outcomes – rules must cater for these
    - e. g. unsafe dose between two safe doses – assess the higher dose as unsafe?
  - agree how to deal with simulations where development is discontinued mid-program
    - “empty” simulations passed to next stage of simulation?
    - “make up the numbers” by drawing at random from the simulations where the development was not stopped?

Coding

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R vs SAS

- **rv** package in R: nice compact generation of simulated data
  - its objects (=lists) not intended for use in modelling or other complex statistics
- Bulk of code: 972 lines (R) vs. 1323 lines
- Example

```
#simulate a placebo binary var and a group of active-group binary vars
ppe      <- 0.15
pevents<- rvbinom(n=1, size=controls, prob=ppe)
pae      <- max(.01, min(rvnorm(1, mean=activerate, sd=0.0001), 1))
aevents <- rvbinom(n=1, size=actives, prob=pae)
pnon     <- controls - pevents
anon     <- actives - aevents
```

R

```
do d=1 to maxdose;
                    cohort=d;
*** randomly purturb the fixed SAE rate for each simulation ***;
                    rate_sp=max(.01, rand('NORMAL', saerate_dose(d), 0.0001));

                    do pt=1 to ptN;
                                        subjid=d*1000+pt;
                                        dose=1;
                                        sae=rand('BERNULLI', rate_sp);
                                        if sae=0 then sae=2;
                                        output;
                    end;

                    rate_sp=max(.01, rand('NORMAL', saerate_dose(0), 0.0001));
                    do pt=1 to ptN/2;
                                        subjid=pt;
                                        dose=0;
                                        sae=rand('BERNULLI', rate_sp);
                                        if sae=0 then sae=2;
                                        output;
                    end;
end;
```

SAS

/Coding

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R vs SAS

- **rv** package in R: nice compact generation of simulated data
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- Example

```
# simulate fishers exact test for placebo
(AE/death rate 15% vs. the active dose (rate specified)
for specified numbers of subjects
fishersim<-function(activerate=0.15, controls, actives) {
binfish         <- sim.event(activerate=activerate, controls=controls, actives=actives)

binfish$pnon<- controls - binfish$pevents
binfish$anon<- actives - binfish$aevents

rvfish<-rvmapply(function(x, y, a, b)
  fisher.test(
       matrix(c(x, a, y, b), nrow=2), alternative="l"
                                                ),
          x=binfish$pevents,
          a=binfish$pnon,
          y=binfish$aevents,
          b=binfish$anon
                                  )
list(pvalue=rvfish$p.value)
}
```

R

```
proc freq data = IIa noprint ;
  tables dose*sae / nowarn fisher out=IIaSAEfreq(keep=scenario
sim cohort dose sae count where=(sae=1))  ;
  by scenario sim cohort;
  output out = IIaFish(keep=scenario sim cohort xpl_fish) exact ;
run;
```

SAS

/Coding

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R vs SAS

- Readability?
  - R more compact, but its density may render it less readable for some users

Coding and running

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R vs SAS

- Repeated processing of the same analysis required for simulation:
  - R, "for (i in 1:n)";
    - alternative: **rv** [=**r**andom **v**ariable] objects: compact simulation-based representation of random variables, useful for simple statistics, e.g.

```
» > setnsims(2500)
» > sim.binom <- rvbinom(n=1, size=200, prob=0.20)an(sim.binom)
» > sim.binom
»      mean          sd 1% 2.5% 25% 50% 75% 97.5% 99% sims
» [1]   40          5.6 28   29   36   40   44   51    53   2500
» > sim.binom**2
»      mean          sd  1%   2.5%  25%  50%  75%   97.5%  99% sims
» [1] 1625          458 729  841 1296  1600  1936   2655   2916 2500
```

  - SAS, BY statement – built-in economies in re-use of matrices

Coding and running

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R vs SAS, elapsed time for simulations of drug development program, same machine used

- caveat #1: different programming styles and skill levels for each program language
- caveat #2: no particular attempt to improve time-efficiency of R code
- caveat #3: elapsed timings dependent on workload of machine being used

Coding and running

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R vs SAS, elapsed time for simulations of drug development program, same machine used

- 2500 simulations, no modelling involved
  - R: 10.65 minutes
  - SAS: 5 minutes

Coding and running

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R vs SAS, elapsed time for simulations of drug development program, same machine used

- 2500 simulations, no modelling involved
  - R: 10.65 minutes
  - SAS: 5 minutes
- simulation involving 4 logistic regressions
  - 2500 simulations, 7 scenarios, (run at night)
    - SAS: 18 minutes
    - R: 7+ hours
  - logistic regression alone, (run during daytime)
    - R: 77.93 minutes for 2500 simulations of **single scenario**
    - SAS: 8.77 minutes for 2500 simulations of **7 scenarios**!

Summary

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- Thorough QC of simulations is recommended when modelling a "chain" of clinical trials
  - requires careful specification
  - QC the generation of random variable data, which may not be matched across languages like SAS and R, separately from the processing of that data
- Problem: how to simulate selection of dose where this is not based on quantitative rule, as in some dose-escalation studies?
- tricky points in programming
  - "empty" simulations (where there was a safety issue or there was no efficacy detected, so development stopped for that simulation)
  - specify the structure of the simulation as well as the algorithms and analyses
    - » facilitate QC
    - » facilitate re-use of code for other the development of other treatments

/Summary

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- R vs. SAS
  - R compact, sometimes less readable
    - R's rv package nice for generating random variables, but of limited use for e.g. repeated simulations of ANCOVA or logistic regression
  - SAS somewhat faster than R for simulations where no generalised linear modelling involved
  - SAS considerably faster than R where generalised linear modelling is involved in simulations (by a factor of c.30)

Extra slides

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An example

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- Challenging drug development program
  - mechanism of action of treatment not well understood
  - data only from animals and healthy subjects
  - broad options:
    - high risk, explore few doses
    - cautious approach, more doses
  - outline of program:
    - small phase IIa to identify highest safe dose (as often in oncology)
    - phase IIb to identify dose for further development
    - phase III to provide enough evidence of safety and efficacy for regulatory approval
  - model based drug development to help decide design of the phase IIb study

Current practice in the pharma industry?

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- US, EU regulators
  - Robert O'Neill, FDA: "Clinical scenario assessments are **much, much** more important than anything else that statisticians in drug development are doing at the moment, including adaptive design…"
  - Robert Hemmings, EMEA: "I had a dream; 10 years from now there will be no drug development programs without clinical scenario simulations"

/Current practice in the pharma industry?

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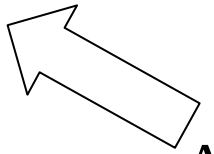
- Roche reported to work with Pharsight's "Trial simulator"

Simulates trials, "point and click", not based on a language

- (For most adaptive clinical trials, simulation or complex integration is required to estimate power of the trial.)



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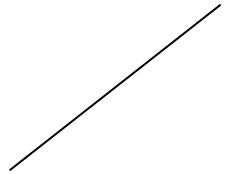

User can add modules in R

Results of our simulation of a development program

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- Difficult to perform simulation of small IIa study to find highest safe dose
  - in real development the decision about safety would be based on the totality of the clinical data: labs, adverse events, baseline scores, etc.
  - our simulation used only assumed proportion of SAEs/deaths

/Results of our simulation of a development program

QUINTILES

Recall broad options for the sponsor:

- high risk, explore few doses

- cautious approach, more doses

/Results of our simulation of a development program

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good success rate when no safety issues and all doses worked

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strength was in scenarios where some doses were unsafe or doses did not have efficacy