

Subject Randomization System

Infrastructure for Clinical Trials

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A Clinical Trial is launched

A researcher comes to me with a straightforward problem.

Two arm trial A and B . Need to randomize subjects to either arm (1:1).

Say 60 subjects overall.

Easy thing to do: Permuted Block randomization.

After all, paper is a versatile instrument. . .

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There ought to be a better way!

Efron's Biased Coin Design (Biometrika, 1971)

Two arms in a clinical trial: A and B .

Idea: Allocation probability to treatment A changes to keep balance in each group nearly equal

The total number of subjects so far: $n = n_A + n_B$, where n_A is number assigned to A and n_B is number assigned to B .

Initially, $n = n_A = n_B = 0$. Let $p = P(\text{Subject gets treatment } A)$.

- Let “running difference” $D = n_A - n_B$
- Set

$$p = \begin{cases} \frac{1}{2}, & \text{if } D = 0; \\ \frac{2}{3}, & \text{if } D < 0; \\ \frac{1}{3}, & \text{if } D > 0. \end{cases}$$

Implementation for a Multicenter Trial

- Note that n_A and n_B (and consequently D) change with each new subject recruited into the trial
- Some persistence (or a mechanism) is necessary to implement the scheme in real time.

Hook into Clinical Informatics!.

Other Methods

- Urn designs (Wei and Lachin, Controlled Clinical Trials, 1988); generalizations of Efron's design.
- Make treatment groups balanced with respect to prognostic or risk factors (co-variates). By far the most common.
Divide risk factor into strata and randomize within each stratum.
Example: Sex (M or F) and Risk (H or L) yielding $2 \times 2 = 4$ strata.

Minimization: A method to balance treatment assignment simultaneously over many strata. Multiple risk factors need to be incorporated into a score for degree of imbalance (*need to keep a running total of allocation by strata*). Described by Taves (1974) and Pocock and Simon (1975).

Minimization Example

Three stratification factors: Sex (2 levels), age (3 levels), and disease stage (3 levels)

Suppose there are 50 patients enrolled and the 51st patient is male, age 63, and stage III.

		Trt A	Trt B
Sex	Male	16	14
	Female	10	10
Age	< 41	13	12
	41 – 60	9	6
	≥ 60	4	6
Stage	I	6	4
	II	13	16
	III	7	4
Total		26	24

Minimization Example (contd.)

Look only at the marginal distribution. The person we want to assign to a treatment is male, age 63, and stage III.

		Trt A	Trt B	Sign of diff.
Sex	Male	16	14	+
Age	≥ 60	4	6	-
Stage	III	7	4	+
Total		26	24	2+ and 1-

Possible approaches:

- Count sign of diff. *A* is “ahead” in two categories out of three, so assign to *B*.
- Add the total overall categories (27 *As* vs 24 *Bs*). Since *A* is ahead, assign *B*.
- Or flip a biased coin in favor of redressing imbalance.

Package SRS

Provides two S4 classes: `ClinicalExperiment` and `PocockSimonRandomizer` implementing minimization

Typical use:

- Construct the `ClinicalExperiment`
- Construct the `PocockSimonRandomizer` class with the above as argument
- Call the randomization method with a subject ID and a list of factors for the subject.

SRS Usage

```
1  library(SRS)
2  expt ← ClinicalExperiment(number.of.factors = 3,
3      factor.names = c("Sex", "Age", "Stage"),
4      number.of.factor.levels = c(2, 3, 3),
5      factor.level.names =
6          list(c("Female", "Male"),
7              c("<41", "41-60", ">=60"),
8              c("I", "II", "III")),
9      number.of.treatments = 2,
10     treatment.names ← c("A", "B"))
11 randomizer ← new("PocockSimonRandomizer",
12     expt=expt,
13     seed=as.integer(12345))
```

SRS Usage (contd.)

```
1   randomizer ←
2     randomize(randomizer ,
3               subject.id="S051" ,
4               factor.values=c("Male" , ">=60" , "III"))
5   > lastRandomization(randomizer)
6       Sex Age Stage Treatment
7   S051 Male >=60   III         A
```

So this package can be used for treatment assignment. (In multi-center trials, site is often used as one of the factors.)

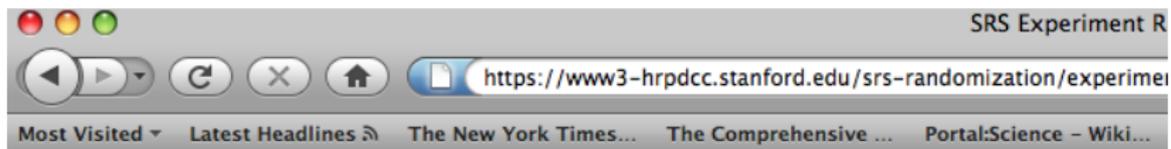
Options

- More than two arms can be specified
- The ratio of treatment counts can be specified
- Control over functions used for computing imbalance for each treatment
- Control over function used for computing overall imbalance
- The allocation probability can be customized

Web Interface

- Slap on a web front-end utilizing Apache Tomcat with Simon Urbanek's Rserve.
- Database for persistence of R state and storing some experiment characteristics.
- Transaction is to load state from database, randomize subject, save state back in database. (Concurrency).

Web App



New Experiment Setup

Please indicate the basic nature regarding the setup of your Experiment/Trial...

Experiment Name

Number of Arms

Number of Factors

Experiment Setup

Experiment Name: AAAStop

Arms

Treatment Arm 1:

Treatment Arm 2:

Factor 1:

Levels:

Level 1:

Level 2:

Level 3:

Factor 2:

Levels:

Level 1:

Level 2:

Factor 3:

Levels:

Level 1:

Level 2:

Level 3:

Experiment Randomization Setup

Randomizing Subject for Trial: AAAStop

Please enter a valid Subject ID and select the appropriate factor level value patient to a treatment.

Subject ID:

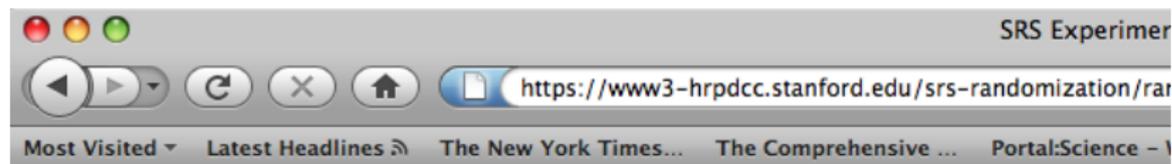
Factors **Level Options**

Factor: Age

Factor: Sex

Factor: Stage

Randomization



[Home](#) | [List/Search Experiments](#) | [Create New Experiment/Trial](#)

Experiment Name: AAAStop

Subject ID: 004

Supplied Factor Level Values:

Age: >=60
Sex: Male
Stage: III

Randomization Outcome: Exercise

Reality on the Ground

- Who is going to do the randomization?
- Train trial coordinator in some good practices, let him/her handle everything.
- Hope everything works, despite the fact that several other systems are in use in the conduct of a trial and you have just added another.

So the situation is still unsatisfactory!

Meanwhile. . .

Modern adaptive designs that move smoothly from one phase to the next (Lai & Bartroff, for example) or response-adaptive designs need even more detail on the trajectory of the trial so far, etc. in implementation.

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Modern adaptive designs that move smoothly from one phase to the next (Lai & Bartroff, for example) or response-adaptive designs need even more detail on the trajectory of the trial so far, etc. in implementation.

Into such a milieu as exists now, how do we accomplish the translation? In other words, not bench to bedside, but R code to clinical informatics?

Clinical Informatics

- Large and Complex
- Typical systems include those that manage, protocols, trial registration, CRFs, issue banking, Lab, Medication data, Outcome tracking
- Statistical tools not completely integrated (SAS may be close, but still does not allow you open programming)
- At least in Cancer, caBIG requirements apply. More and more centers are adopting caBIG technologies
- The Clinical Trials Management Suite (CTMS) suite of tools is open-source and is being recommended for use in Cancer Centers by NCI. Java/Web services based

Use of R in Clinical Trial Environments

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

August 17, 2008

The R Foundation for Statistical Computing
c/o Department of Statistics and Mathematics
Wirtschaftsuniversität Wien
Augasse 2-6

CTMS Tools

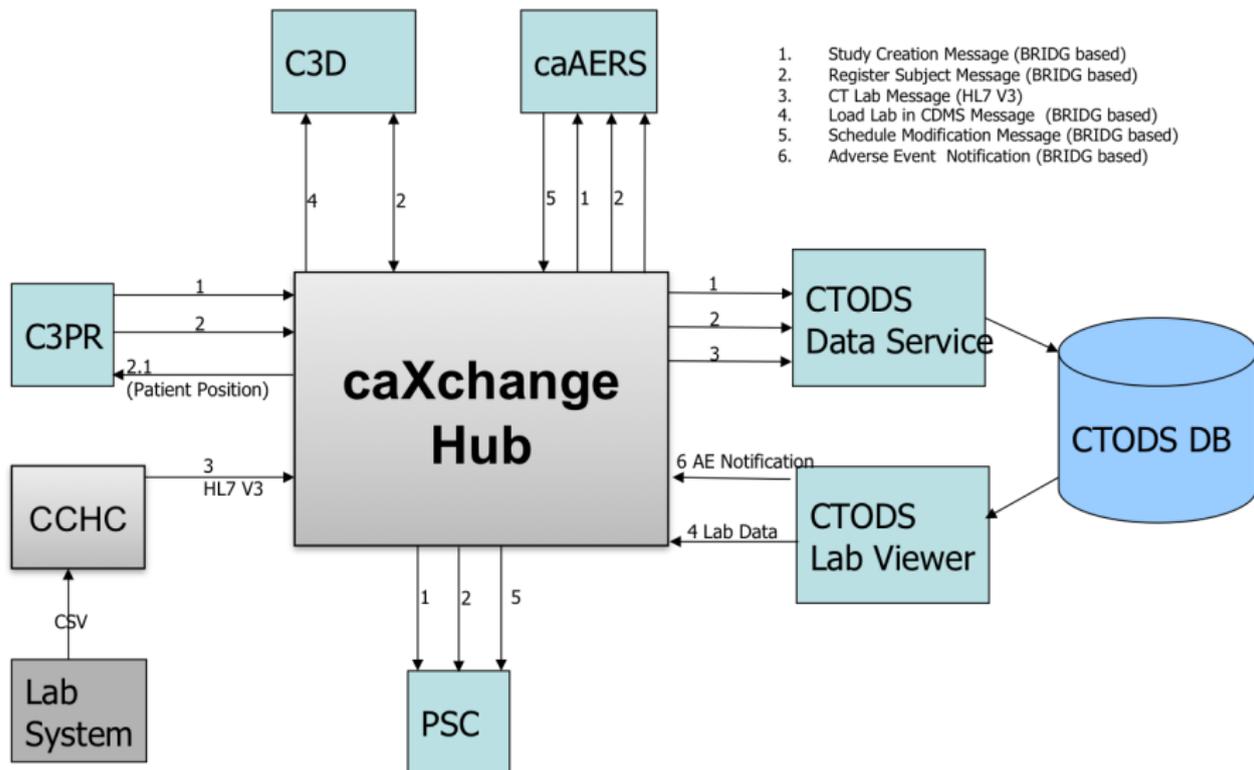
The [caBIG® Clinical Trials Suite](#) is a modular enterprise clinical trials management system designed to facilitate clinical workflows and data sharing in single and multi-site settings. Being designed primarily for use in trial sites, the suite is comprised of a collection of interoperable modules covering a broad range of key areas in clinical trials management. These include:

- Study participant registration (via [C3PR](#) )
- Patient scheduling (via [PSC](#) )
- Adverse event management and reporting (via [caAERS](#) )
- Exchange of clinical laboratory data and other clinical data (via [caXchange](#)  and [LabViewer](#) )
- Protocol, person, and organization management (via NCI Enterprise Services)
- Integration with clinical data management systems (via a series of [Connectors](#) )

[Click here to learn more about the Clinical Trials Suite](#)

Module	Acroynm	Function
Cancer Adverse Events Reporting System	caAERS	Webapp for documenting, managing, reporting, and analyzing AEs & SAEs
Cancer Center Participant Registry	C3PR	Webapp for end-to-end registration of patients (consent, eligibility, stratification, randomization, screening) with multi-site capabilities
Patient Study Calendar	PSC	Tool for managing study calendar templates, tracking patient activities during a study
LabViewer		Webapp for lab activities with <i>messaging</i>
caXchange		Central hub for exchanging info in a grid system

Architecture



Future work

- Work is proceeding on revising the SRS package with Rob Gentleman
- Make the classes safe from tampering. (better naming convention, controlled access to slots, better pass by reference semantics etc.)
- Integrate randomization into C3PR

A further distance away, once the R connection is established and working, integrate some new Phase I/II/III adaptive designs into CTMS