

# A GUI System for the Generation of Clinical Trial Randomization Plans for Collaborative Multi-institutional Clinical Trials

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## ABSTRACT

An important responsibility for a biostatistician supporting large collaborative multi-institutional clinical trials is to develop and maintain randomization according to protocol. The Central Unit of the Collaborative Antiviral Study Group (CASG), located at UAB, oversees many long-term antiviral pediatric and adult clinical trials most of which are long-term trials lasting 5 or more years. Accordingly, the Biostatistics Unit of the CASG provides the statistical services using several biostatisticians, as well as, data base managers and SAS programmers. A uniform approach in a user-friendly environment is mandatory in such situations, particularly since during the length of an on-going trial, staff turnover is highly probable. In this paper, we describe part of a GUI system built in a SAS/AF framework that incorporates PROC PLAN to generate the initial randomization table, provide project management capabilities and maintains a patient accrual database. An abbreviated list of randomization procedures available in RanPlanner contains completely randomized, site stratification, and block randomization designs. At initiation of a new protocol the user inputs the sample size, number of treatments, number of blocks and block combinations, expected accrual rates and other protocol specific parameters. It keeps track of key contact personnel for each site and, if necessary, generates blinding codes, as well as, assisting the un-blinding procedures.

## BACKGROUND

The Collaborative Antiviral Study Group was established by the National Institute of Allergy and Infectious Diseases, National Institutes of Health in 1972. Since its inception the University of Alabama-Birmingham has served as the Central Unit for the conduct of multicenter, controlled clinical trials of antiviral therapies for non-HIV diseases. The associated therapeutic studies are designed to result in licensure of compounds for improved health of people suffering from diseases such as herpes simplex encephalitis, neonatal HSV infection, and VZV infections, as well as, hepatitis B and C, human papillomavirus, influenza, hantavirus pulmonary syndrom, and enteroviral diseases of the newborn.

The RanPlanner application described herein was created in direct support of future and ongoing studies funded by CASG. It was designed for longevity, flexibility and expandability. The authors are two of several biostatisticians who are directly responsible for statistical protocol design, data collection and data entry, database management, generation and maintenance of sampling plans, interim and final statistical reports generation. The main purpose in developing this application was to provide a user-friendly GUI application so that people of varying backgrounds could produce, use and maintain sampling plans for protocols under their direct responsibility, rather than providing a full suite of design of experiments such as those available in SAS/ADX or other commercially available software package. For good introduction to using PROC PLAN in sampling plan generation see Deng and Graz (2002).

## THE RANPLANNER

This application was named the RanPlanner to reflect its dual role of generating randomization schemes and assistance in planning of the scheme. Figure 1 is a screen shot of the opening screen for RanPlanner. As indicated, multiple projects can be managed/planned concurrently by multiple users. Projects, their

associated randomization schemes and assignment/accrual databases are password protected to prevent breach of patient's confidentiality and blinding and avoid accidental corruption of the database.

RanPlanner is continually being updated and expanded. The suite of tools available in RanPlanner will continue to increase as the needs arise. Ultimately, this application will be combined into a full SAS based database management that is currently under development.

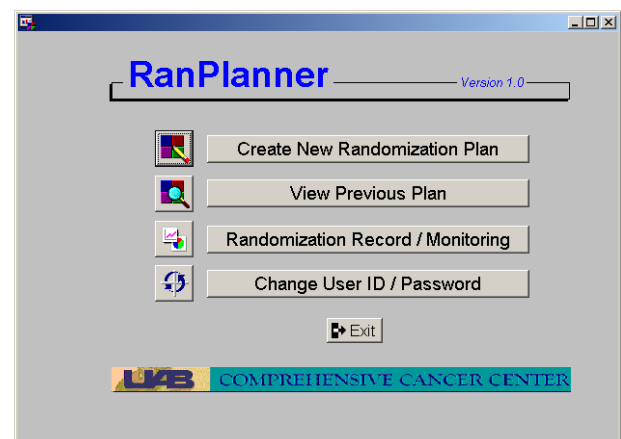


Figure 1: RanPlanner main entry screen. Note that each plan is password protected.

## RANDOMIZATION SCHEMES

It is important that the RanPlanner provide a variety of sampling designs, but RanPlanner was prioritized to include designs that were currently being used or had been frequently used in the past. Many additions are expected in the future. The application currently provides just a few basic designs, which include all currently maintained protocols. Since many of the protocols are Phase I/II multi-center trials, the stratified, completely randomized and block randomization sampling plans are fully operational. Figure 2 is a screen shot of the sampling plan selection screen.

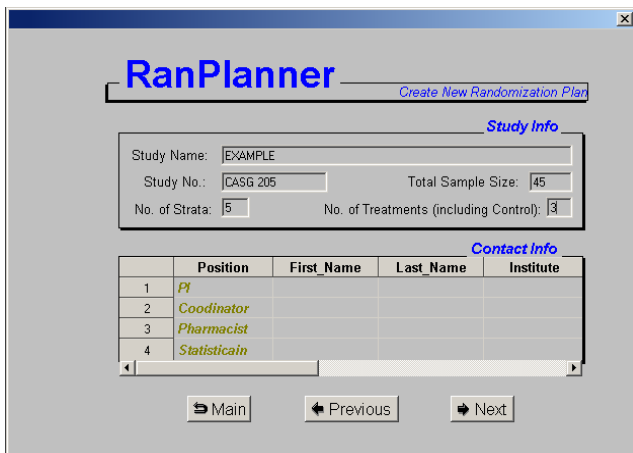


**Figure 2: Selection of the general types of sampling plans currently available.**

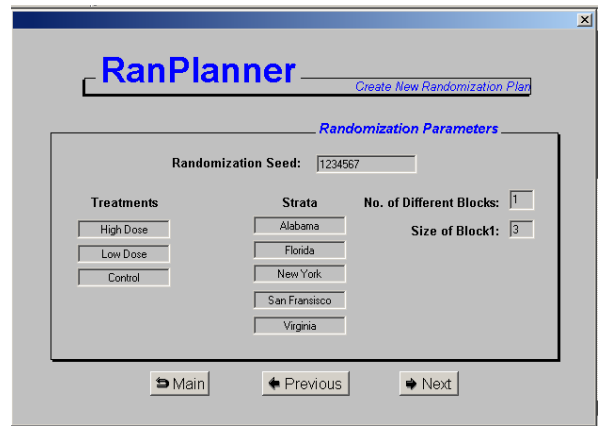
**NEW PROJECT INITIATION**

With multi-institutional trials organization is of paramount concern, particularly in trials where safety is a concern. Each site/institution typically has a local co-investigator for the study, a staff of nurses, and its own pharmacy each with designated personnel as key contacts who may be involved in more than one CASG protocols at a time. Depending on the nature of the protocol, many of these individuals will need to be notified when a patient is randomized into a study and be kept apprised of the patient's status.

Figures 3 A and B are screen shots of the study initiation screen. Here the title of the protocol is entered, the study is assigned a number within its series, important statistical design parameters are entered, and participating sites and institutions (UF, UCSF, UAB, etc) are named and key contact information is listed. The sampling design is usually dictated by the FDA/NIH approved protocol so the user would at this point enter in the total sample size, expected accrual rates, number of participating sites, the number of treatments (with titles) and any other pertinent information. If the randomization is blinded to investigators then reports generated should hide any patient specific treatment assignments and assist in the generation of any coded assignments that would be sent to the sites. For example, the sites may only know that patient 5 was assigned to treatment A, B, or C, where A might be low dose, B might be placebo and C might be high dose or standard of care. Of course, the pharmacists must be fully apprised of the patient's treatment.

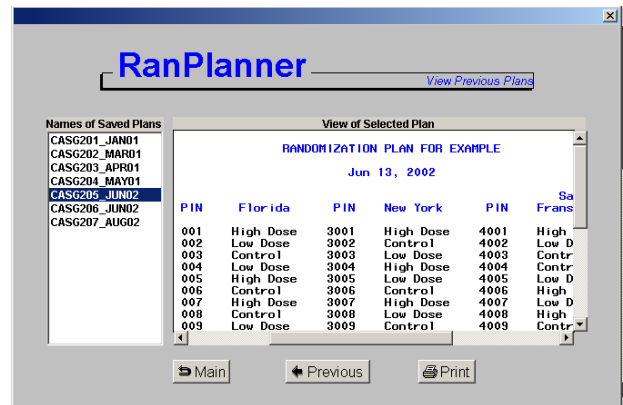


**Figure 3A: The user enters in the name and study number for the new trial and any other pertinent information.**

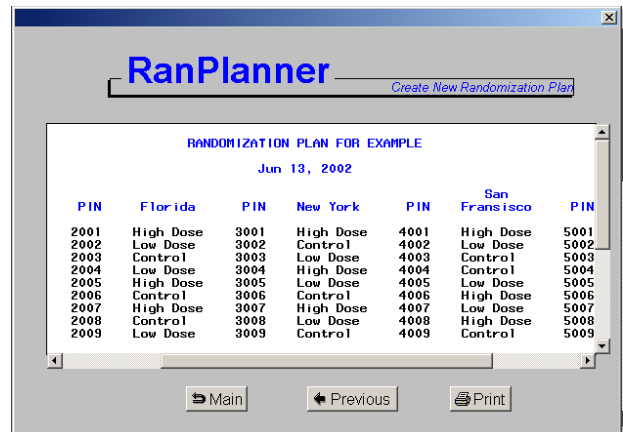


**Figure 3B: Example listing of the treatment groups, Sites for which to stratify, number and size of blocks for block randomization**

Figure 4, A and B, depicts the randomization plan browser where one can view the status of an ongoing trial or view the layout for from a recently initiated plan. Note that the user can only browse or edit those protocols under his/her responsibility.



**Figure 4A: Sampling/Randomization Viewer/Browser with patient assignments and numbers**



**Figure 4B: Sample of Single Randomization Report**

## WORKING WITH EXISTING PLANS

Figure 5 demonstrates a walk-through of gaining access, for editing or browsing, existing trials. The user must enter his/her user name, which has a trial specific and user specific connotation, and his/her personal password. The user is given the option of changing the password at any time.

## CONCLUSION

The RanPlanner has been very helpful in the day-to-day operations in managing clinical trials. New features and options are continually added and being discussed. Some of the planned features are

- Adverse Event – Safety Report Generation
- Patient accrual rate
- Patient screening databases
- Full database management including CRF-level data entry and data entry screens.
- Web-based applications.

## REFERENCES

Deng, C. and Graz, J. (2002), Generating Randomization Schedules Using SAS Programming, SUGI-27, Paper 267.

SAS/STAT® User's Guide, Version 6, Fourth Edition, Volume 2.

## ACKNOWLEDGMENTS

This project was conducted in collaboration with Richard J. Whitley, NIAID Collaborative Antiviral Study Group, University of Alabama at Birmingham, and funded in part by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (Contract NO1-AI-65306).

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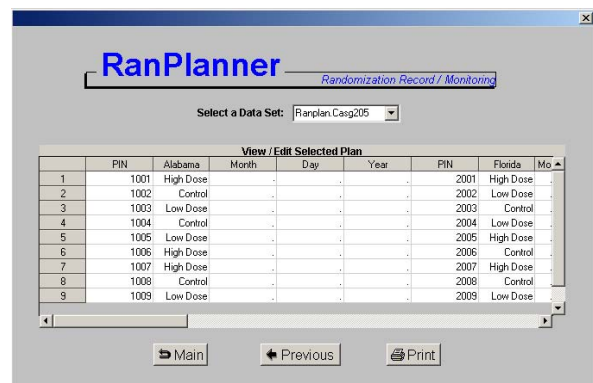
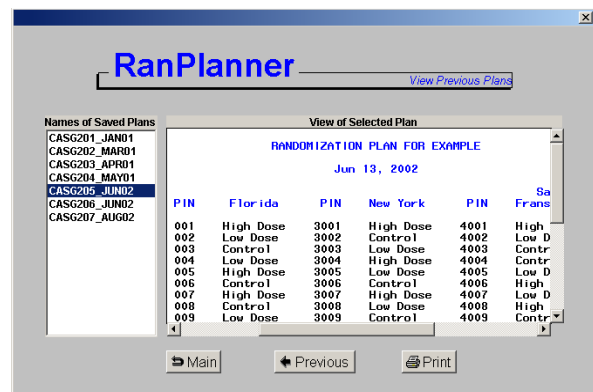
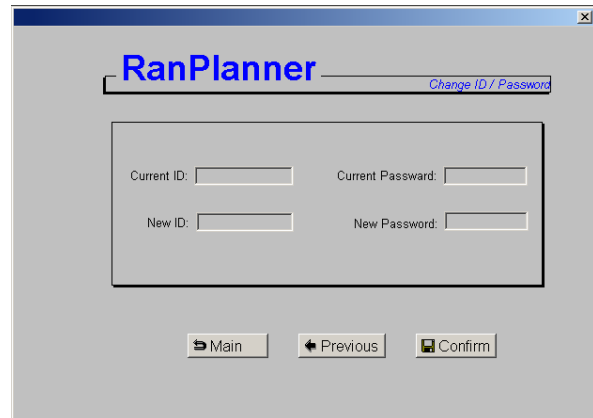


FIGURE 5: ACCESSING AND EDITING EXISTING PLANS