



Medidata Solutions and Cytel

Joint White Paper

A Blueprint for Flexible Randomization through an EDC System

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1 Introduction

Most clinical trials today use one tool for randomizing subjects into study arms and another for capturing the trial data. This means that clinical trial sites and sponsors must enter, retrieve and reconcile subject enrollment, randomization and treatment data in different systems, which is less productive than managing everything in a single, integrated system.

This whitepaper demonstrates the result of a collaboration between Medidata Solutions and Cytel to offer a joint EDC-Randomizer solution. The two companies have successfully integrated Cytel's FlexRandomizer® engine into Rave, Medidata's popular web-based EDC system. This allows clinical study sponsors to randomize trial subjects directly within the EDC system, both for conventional trial designs and for adaptive trial designs.

2 Flexible Trial Designs

In a conventional trial randomization, the treatment groups and subject populations are defined at the start of the trial, pre-specified treatments kits are dispensed as subjects are enrolled into the trial, and the treatment allocations are not adjusted until the trial is over. At this stage, the statisticians analyzing the data might determine that subjects could have been allocated to treatments in a more balanced manner and the trial could have provided more conclusive results if some change had been made dynamically while the trial was underway. Examples include the following:

- **Balancing treatment for small to medium-sized studies.** Consider a trial of 100 subjects (50:50 male-female), half of whom are allocated to control and half to an experimental treatment. Using a pure random method there is only an 11% chance that distribution by sex will be perfectly balanced (50:50) between treatment groups. If several subject characteristics are considered in addition to sex, the chance of imbalance increases dramatically. Clearly, a more balanced distribution would lessen the risks of the trial results being skewed. For small and medium-sized trials, particularly with several prognostic factors, dynamic randomization techniques like "minimization" nearly eliminate chances of any imbalance.
- **Dynamically adjusting sample size across sites.** The design of a trial requires estimating the number of subjects needed to show a statistically significant difference between the various treatment groups. If statistical significance has been reached before the maximum number of subjects has been enrolled, it might be possible to finish the trial early and save precious time. If statistical significance has not been reached, additional subjects could be enrolled, saving the torment of ambiguous trial results. Using centralized randomization integrated with EDC, subject accruals in each site can be monitored in real-time, allowing sample size adjustments and corrective measures for sites with slow recruitment.

- **Adjusting balance across dosing groups.** A phase II dose-ranging study is typically used to determine the minimum dose to achieve efficacy. Early results from such a study might indicate that a particular dose is too low or that another dose is too high, causing unwanted side effects. If these results could be determined while the trial is still underway, all new subjects could be enrolled into one of the other dosing groups and thus provide more useful results. An integrated EDC-Randomizer solution allows such data to be monitored in real-time. The results of the data captured can be used to dynamically change the treatment allocations, thereby providing dose-responsive randomization.

In all of these cases, the challenge is to design clinical trials with flexible randomization approaches that dynamically adjust to the changing outcomes from the trial, without compromising the integrity of subject-blinding. The best way to ensure dynamic treatment balance, minimize selection bias, and automatically act on real-time data from clinical trials, is by using centralized and dynamic randomization techniques directly through an EDC system.

2.1 Requirements

To implement flexible trials, the following components must be in place:

- **Centralized randomization.** A centrally-managed randomization system for all sites in a study allows for uniform eligibility criteria, monitoring of subject accruals in real-time and the ability to easily act on changes in expected treatment allocation, recruitment goals or drug inventory.
- **Sophisticated randomization algorithms.** This includes the ability to dynamically achieve treatment balance for small sample sizes within several strata or across several subject characteristics simultaneously. Flexible randomization requires the ability to use both static algorithms (like permuted block and biased coin) and dynamic algorithms (like minimization and response-adaptive), to suit the unique needs of different trial protocols.
- **Real-time data access.** This requires that the randomization system be directly integrated with an EDC system, allowing both monitoring and dynamic adaptation to subject accrual and data from trial outcomes.
- **Robust security and auditing.** The software must ensure that subject data is blinded and that only a select group of authorized personnel have access to treatment codes and actual subject data. In addition, all user actions and randomization requests should be captured in an audit trail.

2.2 The Blueprint

Recognizing the benefits of an integrated EDC-Randomizer solution that provides users with a single, web-based interface to implement flexible trial designs, Medidata Solutions and Cytel have collaborated to combine Medidata's Rave EDC system with Cytel's FlexRandomizer system.

A "proof of concept" protocol has been implemented on this joint solution, to demonstrate how both software products have been integrated seamlessly. Note that this protocol was implemented using currently available off-the-shelf production capabilities of both Rave and FlexRandomizer; hence the joint solution can be readily deployed today, for use in all clinical trials.

2.3 The Protocol

The chosen protocol is a single randomization based on the response to a screening question: "Does the subject have a genetic pre-disposition to breast cancer?". Based on the response, the subject is randomized into one of two strata and assigned an appropriate treatment. The treatments are balanced within a block size of 10, with the block mapping to the subject's study site. This is illustrated in the following diagram:

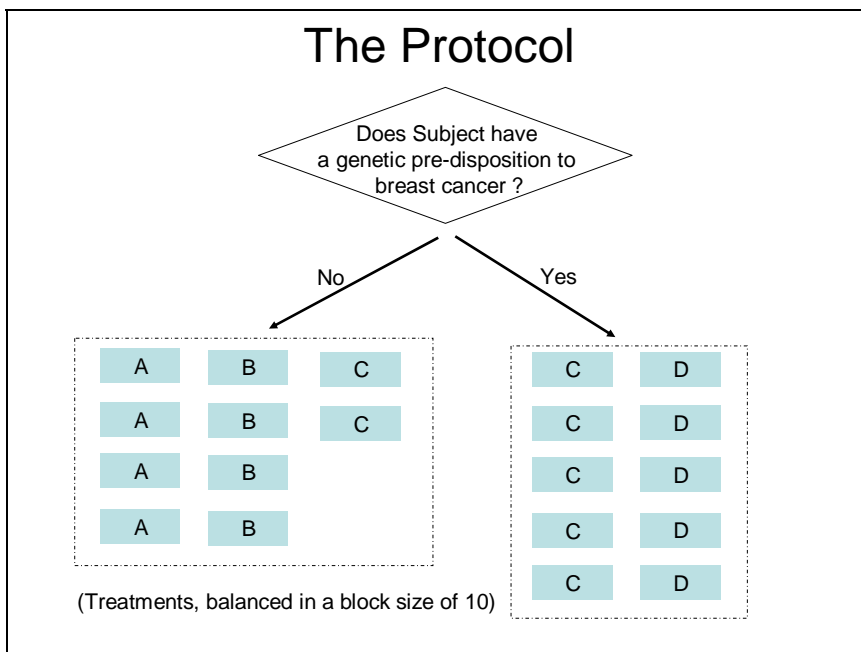


Figure 2-1: Sample Protocol

The protocol was implemented using a permuted block randomization method in the CytelRAND software engine, part of the FlexRandomizer product solution. The clinical trial protocol and all randomization requests are stored in the CytelRAND database

2.4 Mapping Treatments to Kit Numbers

The next step is to create kit numbers and map each kit to one of the treatment codes in the distribution shown above. Today, this mapping is either generated from the Clinical Drug Supply System (CDSS), or is generated using a separate randomization program, with the results transmitted to the CDSS. In this protocol, the latter approach was chosen, using a simple kit generation program that was executed for each site in the study. This is illustrated in the following diagram:

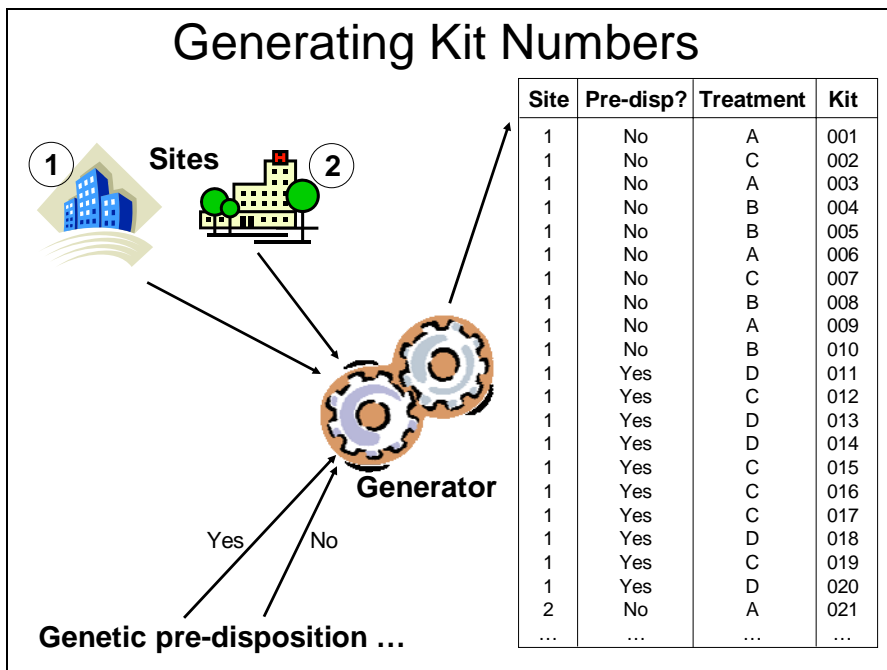


Figure 2-2: Kit Numbers Generation

This kit number information is stored in a table in the Medidata Rave database.

2.5 Modeling the Randomization eCRF

The electronic Case Report Form (eCRF) to collect the randomization information is modeled in Medidata Rave and is shown to the user in Medidata Rave’s web-based interface as follows:

Does subject meet all enrollment criteria?	Yes/No
Does subject have a genetic pre-disposition to breast cancer?	Yes/No
Kit number (derived)	
Treatment group (derived and hidden from most roles)	

An edit check on the second question makes a Web service call to CytelRAND to obtain the treatment code. Medidata Rave uses this treatment code to find the next available kit number in the local mapping table. The following diagram illustrates this:

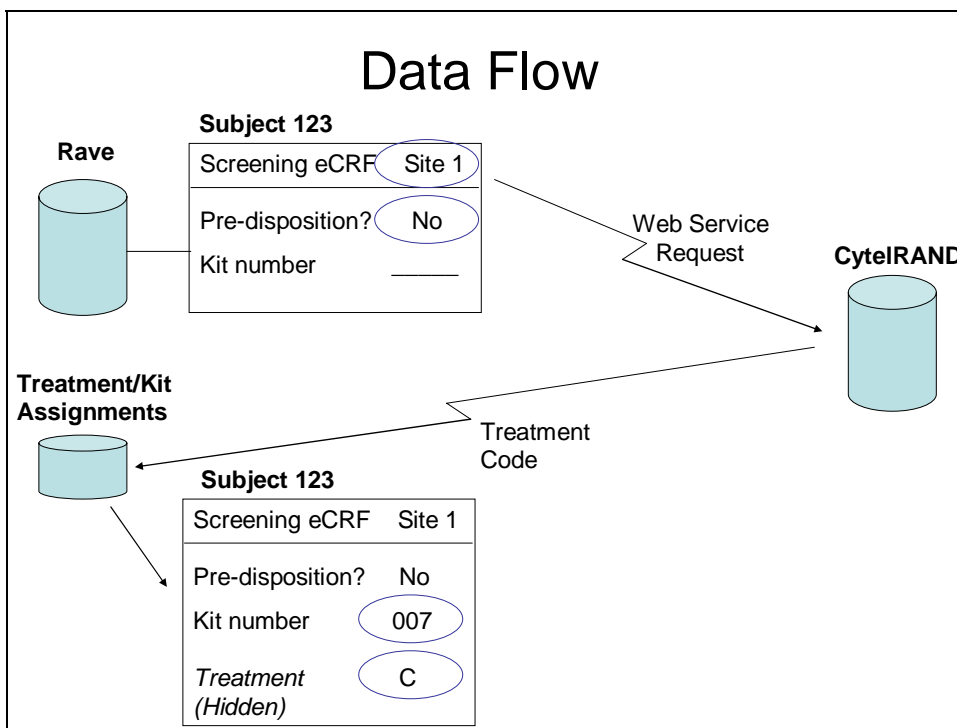


Figure 2-3: Randomization Data Flow between Rave and CytelRAND

The data entry user simply answers the first two questions and presses Save, at which point the corresponding kit number is displayed. This approach is highly convenient for site personnel, and removes the need for a separate system to provide the kit information. An example screenshot is shown below:

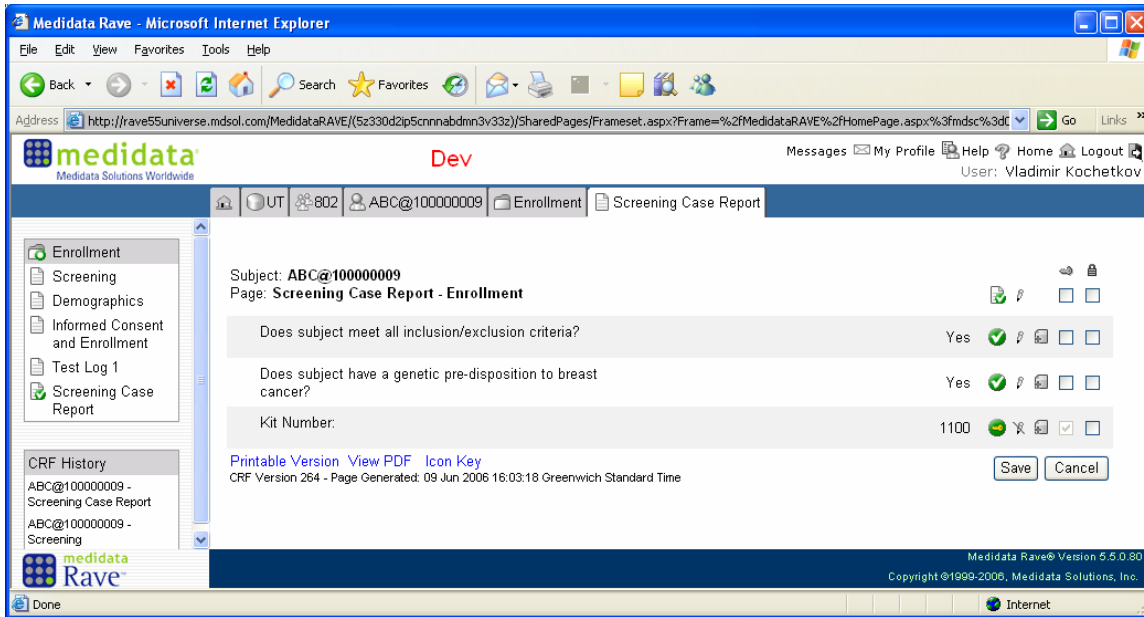


Figure 2-4: Rave Screening Form - as viewed by site personnel

2.6 Security

The treatment information is stored in the Medidata Rave database, and only made available to authorized users. The following screenshot shows the equivalent eCRF as viewed by a user with this special access role:

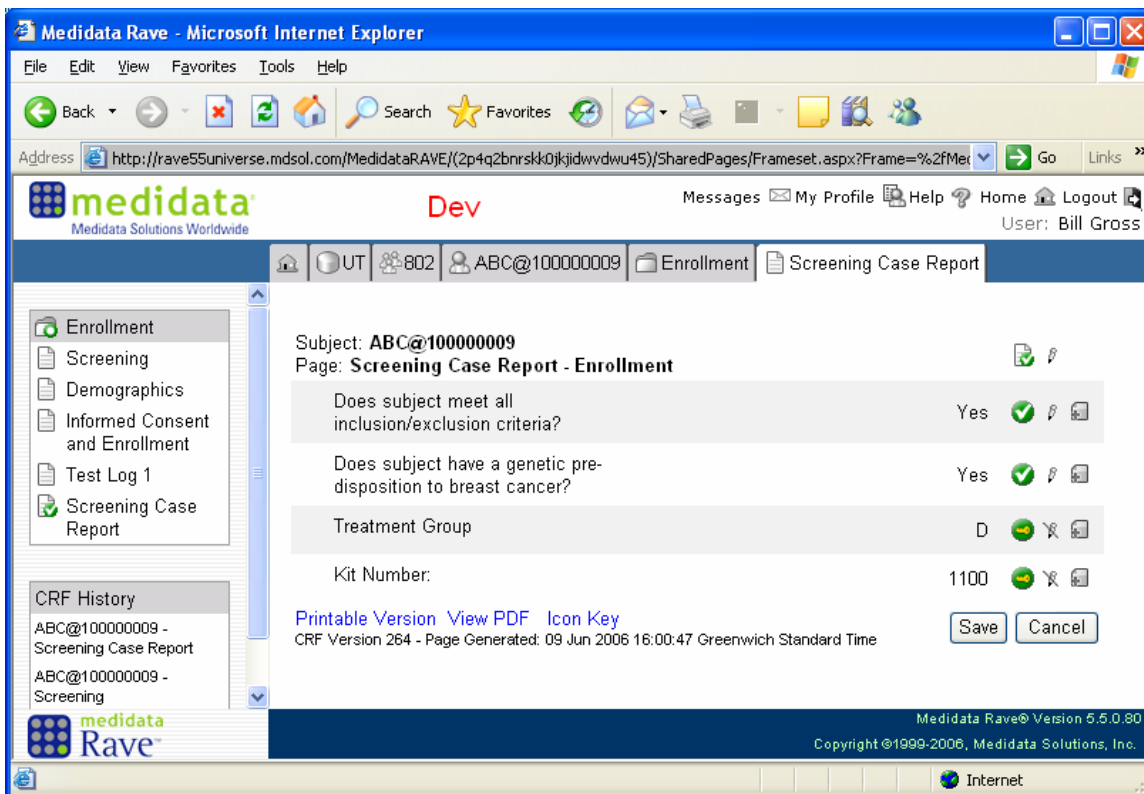


Figure 2-5: Rave Screening Form – as viewed by an authorized user

The information may also be accessed in reporting programs, ad hoc query tools or SAS extracts of the data, using the clinical views that are automatically generated by Medidata Rave. These clinical views inherit the same security mechanisms as are defined for the eCRF screens, so the sensitive treatment information remains protected. This is illustrated in the following diagram:

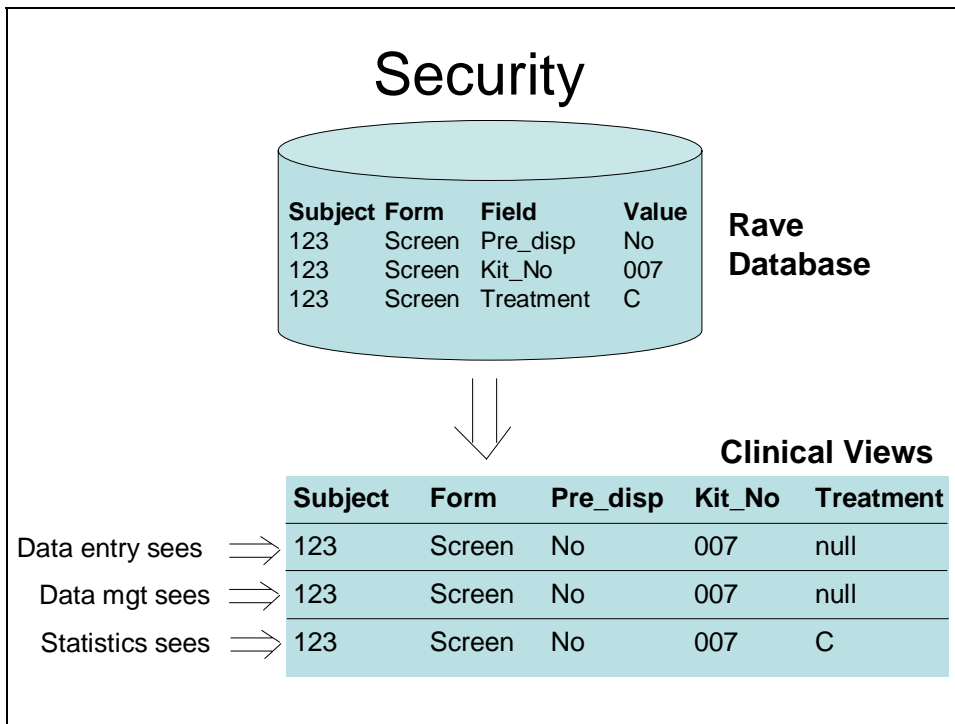


Figure 2-6: Clinical Views preserve security

With this information, an authorized statistician can easily compare efficacy and safety information for each of the treatment groups and make appropriate decisions for the clinical trial, while preserving the subject blinding for site and data management personnel.

3 Summary

This whitepaper demonstrates how Medidata Solutions and Cytel provide a secure, centralized and integrated web-based platform for data capture and randomization. This joint solution combining leading-edge EDC and randomization technologies provides the blueprint for flexible -- conventional and adaptive -- trial designs.

Companies wishing to learn more should contact:

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