

The background features a light blue and white color scheme. On the left, there is a large, semi-transparent fingerprint graphic. The upper right quadrant contains several 3D paper cutouts of arrows pointing in various directions, along with some paper documents. In the lower right, a pipette is shown dispensing a drop of liquid into a small glass vial. The overall aesthetic is clean and professional, suggesting a focus on precision and data.

CLINICAL RESEARCH SUBJECT VERIFICATION PROGRAM





A Web-Centric Model Gauges Attempted Dual Enrollment by Study Volunteers

by Ann Neuer

There is a growing awareness that dual enrollment, which is a research subject enrolling in overlapping clinical trials without meeting the required waiting time between them, is a serious issue affecting clinical research within the United States. The key concerns are the effect that dual enrollment may have on the integrity of study populations as defined by the protocol, and how data generated from dual enrollers may result in an inaccurate portrayal of the safety and effectiveness of an investigational drug or biologic.

The existence of dual enrollment should come as no surprise to principal investigators who experience this problematic behavior firsthand. Similarly, pharmaceutical executives are likely to be painfully aware of the hazards of dual enrollment, which, for the last few years, has served as fodder for several articles in the lay press spotlighting the issue, particularly as it relates to Phase I clinical research.^{i,ii}

^{iii,iv} As described in a recent article in *The New Yorker*, some subjects have self-described their continual enrollment in clinical trials as “guinea pigging”, and may actually view this endeavor as a job that is somewhat lucrative.^v

Unfortunately, little progress has made to deter dual enrollment, and this may be due to the fact that no single group or regulatory agency has the

capacity to compel change that would eliminate this behavior. While industry stakeholders can attest to dual enrollment as a problem, no group within the industry has stepped forward to assume responsibility, possibly due to a lack of resources and authority needed to enact and enforce meaningful change.

The purpose of this White Paper is to present a model that offers a possible solution—a central clearinghouse of study volunteers that can be used to identify potential dual enrollers. The model, known as the Clinical Research Subject Verification Program, or clinicalRSVP, is a Web-based central clearinghouse that uses fingerprint biometric identification technology. Its features are presented along with details of its use in a pilot study with five participating investigative sites in South Florida. In two short months, the five sites identified 38 instances of individuals attempting to enroll in another clinical trial within 30 days of receiving a dose in an alternate study, and 92 instances of individuals looking to enroll within 60 days of dosing in an alternate study.

Efforts by stakeholders to deter dual enrollment together with the capabilities of this model hold promise for improvement to a serious, if not intractable problem, in the clinical trials industry.



Start With a Central Clearinghouse

A Web-based central clearinghouse that investigators and other site personnel can easily access is the basis for a system designed to deter dual enrollment across the United States. Using this approach, potential subjects can be checked against a central database prior to enrollment to determine if they are participating in another study, have been dosed within the past thirty days, or have recently completed a study. This technology allows investigators to make well-informed enrollment decisions without having to rely on a subject's full disclosure.

The clearinghouse built for the model presented in this White Paper highlights the three essential elements needed for an effective clearinghouse: Centrality, Subject Identification, and Compliance.

Centrality is a multi-faceted concept that has to do with optimizing the impact of a central clearinghouse. First, it must operate on a single platform with easy access by all investigative sites within the US. This approach allows investigators at all venues—dedicated investigative sites, part-time sites, and academic medical centers—to access a central Web-based portal. Second, there needs to be standardized rules as to what data should be collected, reported, managed and validated. These rules should include guidelines regarding timeliness of data entry to allow other sites to benefit from information, such as enrollment and completion of clinical trials, and relevant dosing history, before a potential subject attempts to screen elsewhere.

Accurate **Subject Identification** is essential to an effective central clearinghouse. In a perfect world, identifiers already used by contract research organizations (CROs) and sites, such as initials and date of birth, would be sufficient. But, for a central database to work, the identifiers would have to be consistent, more expansive, less able to be forged, and obtainable in a cost-effective manner.

Finally, there must be **Compliance** with the guidelines put forth by the Health Insurance Portability and Accountability Act (HIPAA)—the

“Privacy Rule”; and 21 Code of Federal Regulations (CFR) Part 11—the Electronic Record; Electronic Signatures rule put forth by the Food and Drug Administration (FDA).^{vi} HIPAA provides federal protections for personal health information held by covered entities and gives patients an array of rights with respect to that information. While clinical research sites are generally not HIPAA covered entities, a subject clearinghouse may still be subject to HIPAA compliance if it houses elements of

Potential subjects can be checked against a central database prior to enrollment to determine if they are participating in another study.

personal health information and is accessible by research centers with adjoining medical facilities that are HIPAA covered entities, such as hospitals and universities. Meanwhile, 21 CFR Part 11 applies to records in electronic form that address the research, production, and control of FDA-regulated articles. A clearinghouse would not be required to submit electronically formatted documentation to a regulatory body, but it would want to exhibit many of the controls related to transparency, documentation, and audit trails of electronic data, as set forth in the regulations to assure effective data management.

Whose Responsibility?

Addressing Centrality, Subject Identification, and Compliance is a tall order, so it is not surprising that there has been limited development of a central subject registry, despite the continuing challenge of dual enrollment. The question becomes who should create, pay for, and maintain a centralized clearinghouse? Should it be a regulatory body? A sponsor? Participant safety and research integrity are public concerns, and fall under the Office for Human Research Protections (OHRP) within the Department of Health & Human Services (HHS), and the Bioresearch Monitoring Program (BIMO) within FDA. Although these mechanisms are in place, there



is no evidence that FDA has the resources or interest in assuming responsibility for the building of a centralized, compliant patient registry.

Building, deploying and maintaining the registry would require significant upfront and ongoing investment. Costs would include code development, user training, technical support, monitoring of timely reporting, implementing a biometric technology used to identify subjects, and continual upgrading as technology advances. Because of the required investment in time and dollars, it might be more reasonable for an industry provider to step forward to create and maintain the infrastructure. But to make the model sufficiently effective for the industry, each clinical trial stakeholder needs to assume responsibility. First,

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institutions conducting clinical trials must be committed to quality research and participant safety. Principal investigators must take a proactive stance against lax enrollment procedures that allow dual enrollment, and consider the value proposition presented by a central registry in terms of subject safety, public safety, and study integrity. Next, sponsors must be willing to either reimburse sites for the cost of accessing the registry by building dual enrollment protection fees into their study budgets, or be willing to pay an outsourced provider for this function and make it available to sites. Finally, institutional review boards (IRBs) must ask sites tough questions about how they go about deterring dual enrollment.

In an ideal world, if all parties cooperated, this scenario would greatly facilitate national acceptance and implementation of a central patient registry, but in reality, these massive sea changes start with finding champions for the cause, and identifying want to finish the design tonight and tomorrow to arrange the text benefits and costs.

Benefits and Costs

Because clinical trial data can be compromised when subjects dual enroll, stakeholders stand to benefit from a system that discourages this behavior. Specifically, sites and CROs that erect barriers to dual enrollment will be better able to protect subjects from receiving dangerous combinations of investigational medications, and they will be positioned to generate higher quality data. And since quality data is the site's most important deliverable—some may argue its only deliverable—improving data is tantamount to offering a better product. This may render early adopting sites more attractive to sponsors, conferring a competitive advantage. Over time, as more and more institutions join the registry, this competitive advantage may gradually decline but effectiveness or inclusiveness of the registry will increase.

Ultimately, sponsors stand to reap several benefits from a centralized subject clearinghouse. First, they will be the recipients of more accurate, protocol compliant data from the sites performing their studies. Sponsors may also be better able to adhere to clinical development timelines as less time and money will be wasted on enrolled subjects who are dual enrollers, meaning that fewer resources will be expended in replacing those subjects.

A central clearinghouse may facilitate the lowering of costs associated with reducing dual enrollment. According to some recent data, the mean cost per patient in global Phase I clinical trials, where dual enrollment is most widely acknowledged, is estimated at \$19,282.^{viii} Therefore, if a dual enroller were identified by the site and then removed from a Phase I study, it could cost the sponsor an additional \$19,282 to enroll a replacement subject, plus the cost of recruiting that additional subject, and the cost of impacting the clinical trial timelines. These costs would disappear if a potential dual enroller were prevented from entering a study. Additional figures appear in Chart 1.

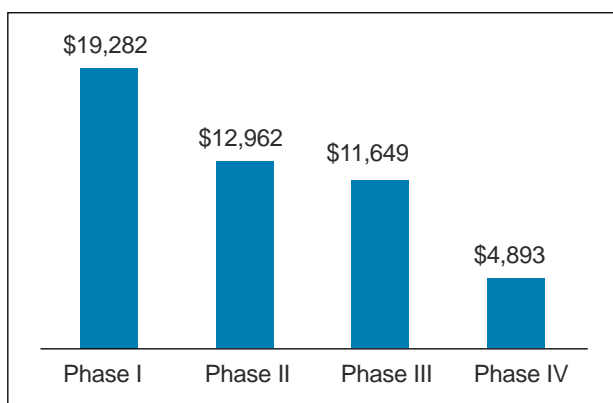
While cases of dual enrollment that are detected too late can be costly, they can be even more



damaging if the dual enrollment goes undetected. It could lead to false serious adverse events such as illness or death within subject populations. Without the appropriate controls to block dual enrollment,

Chart 1

Mean Cost per Patient in Clinical Trials by Clinical Phase, Worldwide 2006 – 2008



Source: TTC, Inc

sponsors risk millions of dollars on clinical trials with significant exposure to adverse events due to non-compliance with washout periods. A serious adverse event that is a result of an undisclosed combination is likely to create problems for any drug intended to reach market, and may prevent a viable drug from getting there altogether. Finally, the cost of poor quality research negatively impacts society as a whole. Drugs that reach market as a result of unsound research are destined to cost consumers. These costs eventually reach sponsors in the form of potential litigation and negative public image.

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From Theory to Practice

Independent Data Integrator (IDI), a company specializing in clinical database management has developed a model called clinicalRSVP; a web-based technology used to create a central subject registry. ClinicalRSVP is based on the three essential principles of a successful registry—Centrality, Identification Technology, and Compliance—and is designed to collect and house the fewest data points

Chart 2

Data Fields Collected by clinical RSVP

Subject Identifier Fields

- Initials
- Date of Birth
- Sex
- Last 4 digits of Social Security or Tax ID

Relevant Date Fields:

- Most Recent Dose Taken Date
- Scheduled Final Dose Date (if any)
- Scheduled Final Visit Date (if any)

Source: Independent Data Integrator

possible that can provide positive identification of potential clinical trial subjects. As shown in Chart 2, clinicalRSVP houses seven data fields, such as initials, date of birth, and others.

In addition to these demographic identifiers, the registry requires users of clinicalRSVP to enter critical date information within eighteen hours of subject dosing. These data are entered at time of initial dose and at time of final dose. This simple requirement ensures that the dosing history of subjects is reported in a consistent fashion, and facilitates timely access to this information by other clinicalRSVP sites, including whether a potential subject was dosed within the past thirty days.

The central platform is an open service capable of Web services that integrate an institution's existing software infrastructure in a way that does not inappropriately access proprietary or confidential information. There is a secure login to authenticate identity of users of the system, a secure connection, and use of encrypted passwords, password strength, and auto-expiry.



Identification Technology

ClinicalRSVP utilizes fingerprint biometric technology to safeguard against the risk of fake identification. In the clinicalRSVP platform, subjects are searched first by demographics, then verified by fingerprint biometric technology, which determines identity matches based on a probability score. The subject's fingerprint is scanned from which a code is generated and stored in the database. Any future verification will compare the code that is created with the code that is stored. The subject's actual fingerprint image is not entered or stored in the database.

How good are today's biometric identification technologies? Performance in biometrics can be evaluated using two metrics: False Acceptance Rate (FAR), and False Rejection Rate (FRR).^{ix} FAR is the frequency with which a biometric technology incorrectly matches two different identities as the same. FRR is the frequency with which a biometric technology incorrectly fails to identify a match when a match exists. Within the context of this model, neither type of error is desirable, so low rates of FAR and FRR are essential for a technology to be successful.

According to Griaule Biometrics, a provider of fingerprint recognition software, the rates listed below (Table 1) represent a very low FRR and a low FAR, independent of demographics.^x The actual realized rate of FAR and FRR is likely to improve measurably with the use of demographics. While a host of biometric solutions exist in the marketplace, such as iris, retinal, and facial recognition, fingerprint biometric technology is the one that most effectively balances performance and cost for clinical research purposes. A good quality fingerprint recognition device typically sells for a few hundred dollars, as compared to an iris recognition camera, which can exceed \$2,000.^{xi} Similarly, a biometric system that assigns a bar code to each prospective subject based on his or her DNA was at one time being considered, but its price tag of \$300 per subject all but rendered it too costly for purposes

of clinical research.² With its advantages, fingerprint technology has emerged as a strong biometric leader in recent years.

Table 1
Error Rates of FAR and FRR

Performance Error	Error Rate	Percentage
FaR	1 false acceptance in 300,000	0.0003%
FRR	1 false rejection in 1,000	0.1%

Source: Griaule Biometrics

Compliance

To comply with privacy guidelines, clinicalRSVP provides a Personal Health Information Authorization Form that allows subjects to grant release of their information for the purposes of deterring dual enrollment. The form complies with legal and ethical standards regarding the use and disclosure of personal information about individuals who seek to participate in research studies.

ClinicalRSVP ensures ongoing quality control and quality assurance by automatically documenting the integrity of data alteration, and providing the necessary controls to meet standards for electronic records. For accountability and auditing purposes, the system has two features: transparent tracking, which allows authorized database administrators to reconstitute and track any addition, modification, or deletion of data; and database-level audit triggers, which are implemented for auditing all changes to clinical data.

ClinicalRSVP provides a Personal Health Information Authorization Form that allows subjects to grant release of their information for the purposes of deterring dual enrollment.



Case Study

To document the value of a central patient registry in discouraging dual enrollment, a pilot study took place at five investigative sites in South Florida from October through December 2009. Organized by IDI, the pilot study involved training the sites to use clinicalRSVP, after which they used it in sixteen clinical trials, and were able to demonstrate successful identification of many instances of individuals attempting to dual enroll, and prevent those individuals from entering another clinical trial. The pilot study included a database of 1,400 subjects. The average time spent checking prospective subjects against the clinicalRSVP database was 20 seconds per subject, and the average time spent per study to report dosing activity of subjects was a total of 22 minutes.

Method

Five research institutions registered to participate in this study. Of the five registered sites, four are located in Dade County, Florida, and one in Lee County. Each registered research institution completed a site assessment form, which was used to allow training and implementation to be tailored appropriately for each site. The form also identified which employees were to be responsible for the various tasks of the application including screening subjects into the database. In addition, each site agreed to perform the following activities.

At Screening:

- Submit four demographic identifiers for all subjects that screen:
 - a. Initials
 - b. Date of Birth
 - c. Sex
 - d. Last 4 digits of social security or tax ID
- Submit the fingerprint biometric for all subjects that screen.
- Search the database to determine if the subject is already in its database and when that individual was last dosed in a clinical trial at a registered site.

At Enrollment:

- Submit the Initial Dose Taken Date of those subjects enrolled into a research study.
- Submit the Scheduled Final Dose Date of those subjects enrolled into a research study.

At Termination (Final Dose Taken):

- Submit the Final Dose Taken Date of those subjects enrolled into a research study.

Results showed that subjects frequently screen at multiple sites, and that several of these screenings occur within days of receiving a dose in another clinical trial (Table 2).

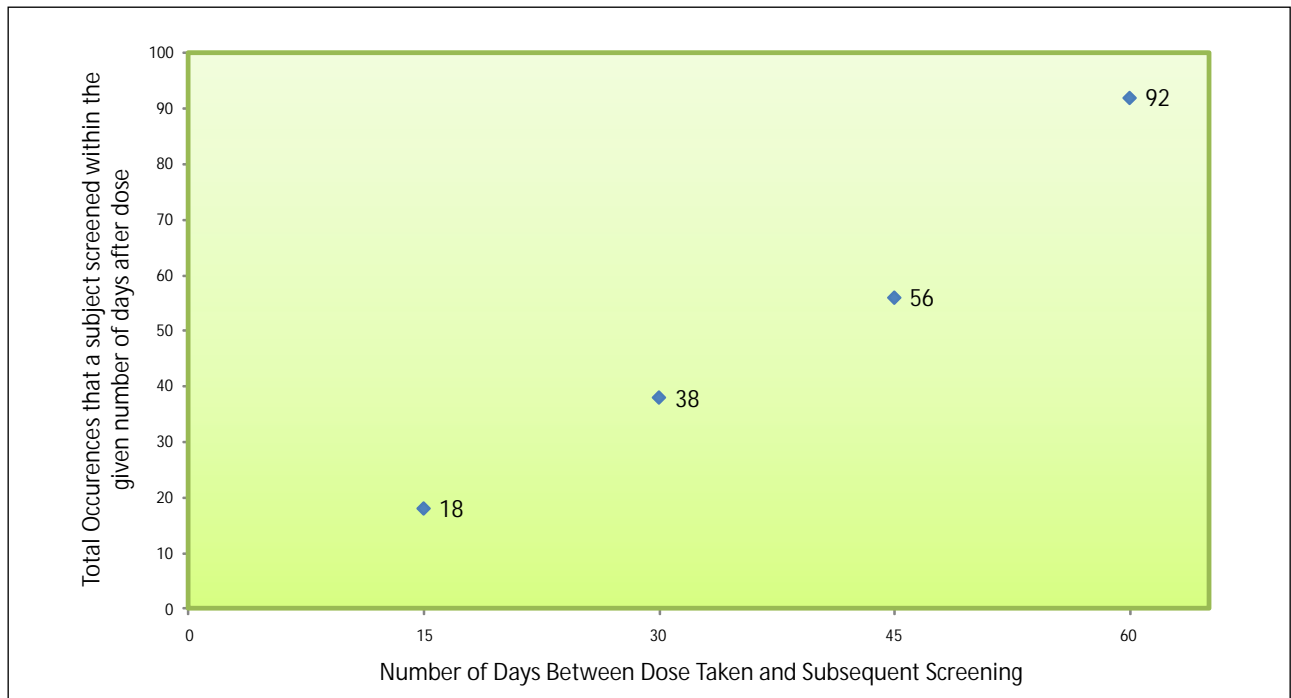
Registry's Potential

Due to the promising results of the case study, the five investigative sites continue to use clinicalRSVP. But the registry is only as good as the contributed data, so as the database expands, there will be an increasing likelihood that potential dual enrollers will be detected and prevented from entering clinical trials inappropriately. Consider there are at least three major research institutions conducting multiple early phase clinical trials within 200 miles of Dade County that did not participate in the study, and had they done so, it is possible that the number of dual enrollers spotted would have been greater. Research indicates that dual enrollers are willing and able to travel within a region and across state lines to participate in what some perceive as a good-paying job.⁵ The problem is particularly acute in Phase I clinical trials because of the higher level of compensation as compared to other phases of development, but the later phases are impacted as well. The concept of a registry is not a new one, but technology allows it to become a Web-based reality that is easily accessible by users, as only a Web-browser and password-protected login are required. With technology, the principles of Centrality,



Table 2

Frequency of Potential Dual Enrollment



Source: Independent Data Integrator

Subject Identification, and Compliance can be addressed by structuring a database composed of only a handful of demographic identifiers and a fingerprint biometric. With this technology, sites can make better-informed enrollment decisions.

The next horizon is for the clinical trials industry to acknowledge the continuing problem of dual enrollment and how it impacts clinical development timelines, the cost of replacing a subject who is pegged as a dual enroller, and how the data from non-detected dual enrollers may erroneously influence final trial results and the drug's performance if it comes to market. This issue may be most effectively handled by a group of industry stakeholders coming together to address this problem, or by sponsors requiring and paying for their investigative sites to enter data in a central registry that will grow overtime.

ClinicalRSVP is an important first step on the

way to becoming a single national registry capable of deterring subjects across all fifty states. Plans are already underway to introduce additional networks in the Midwest and Northeast.

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