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01/2014 WHITE PAPER

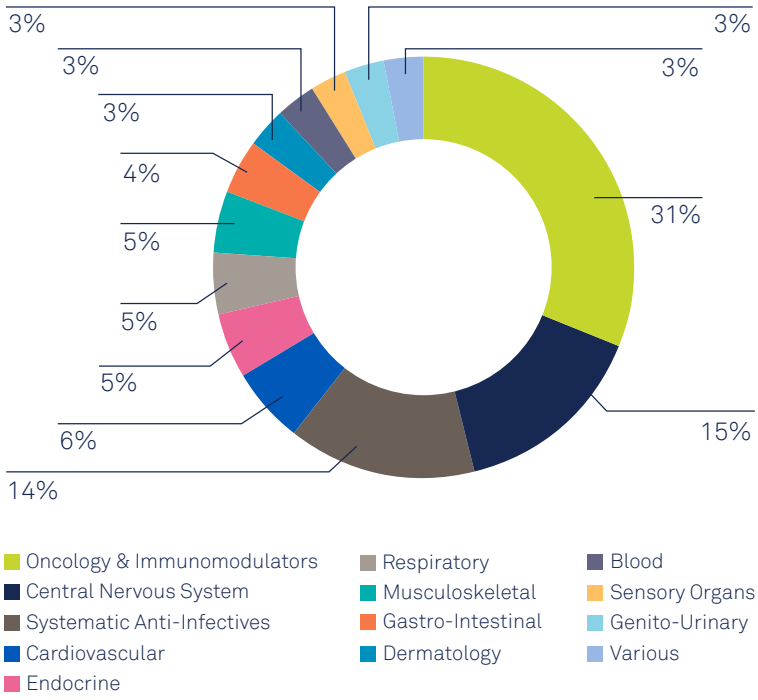
Using Technology to Deliver Complex Oncology Trials

Introduction

Cancer remains one of the leading causes of death worldwide, with 12.7 million new cases and over 7.5 million deaths worldwide in 2008[1]. While cancer incidence continues to rise, mortality has declined in recent years in many countries due to commercial and government investment in new treatments, early detection, prevention programs and outreach[2].

The enormous investment in oncology research reflects cancer's major societal impacts, the commercial benefits of successful treatments and the still-elusive goal of broad eradication. With almost $50 billion in cancer drug sales in 2008[3], the payoff for successful treatments is huge. Over 17,500 trials focusing on cancer are currently underway[4] according to the US clinical trial registry.

Figure 1: R&D project count by therapy area



Source: EvaluatePharma®, 30 April 2010

The need for cancer drugs is substantial, as is the effort being expended in the commercial and non-profit arenas. The rewards for success are socially, politically and financially vast, yet these are matched by challenges in scale and difficulty. Oncology clinical trials are widely recognized as being amongst the most complex trials to design, set up, execute and deliver. It is the intention of this white paper to highlight and discuss some of the specific challenges faced in bringing these important studies to conclusion, and how technology offers new solutions.

The white paper will illustrate how advanced technology, built on modern computer technology and standards-based architectures, can address these issues. We will use case studies to illustrate how this new technology can help resolve the implementation and structural problems inherent in this critical research area.

The Data Management Dilemma

Trial designs and development program design are growing in complexity; as measured by the Tufts Drug Development Center, executive burden has increased by more than 50 percent on average in trials from 2000–2003 to 2004–2007[5]. (Some argue that clinical trials have always been complex; other therapeutic areas are just catching up.)

Design of development programs to maximize data use, develop appropriate and supportable end points, and maximize time and other resources within patient safety concerns raise the demands on oncology research programs to high levels. The need for multiple early phase trials—limited first-in-man studies, cohort-driven accelerating dose escalation designed to identify the maximum tolerable dose (MTD), with small numbers of subjects with various treatment histories and metabolic markers—can burden development programs prior to reaching large-scale efficacy studies. Phase III studies carry their own set of challenges, including operational and data management issues, coordination and communication among widespread sites and sponsors, and patient recruitment and retention.

It is therefore no surprise that oncology studies are drawing interest in innovative trial designs and techniques, such as adaptive clinical trials, concurrent phase trials and dynamic randomization techniques. We are fighting a disease that remains elusive in the science books and laboratories around the world, so is it any great surprise that the ”Learn and Confirm” concepts which run hand in hand with adaptive trial design methodology make so much sense to the oncologists?

We believe that the ability to make maximum use of data collected from any one subject, within one trial and/or as part of another phase or comparative trial, can alleviate some of the complexities surrounding this research. We also believe that investigative site users must be able to participate in their roles in the data collection and management system with minimum requirements on their time and workloads. The rest of this white paper discusses the ways that an optimized, easy-to-access and easy-to-use data collection and management system can advance development programs.

The Need for Complete and Concurrent Data

Many of the structural complications of oncology trials can be remediated by the ability to review all patient data collected to date, at any time, and be assured of its availability at any time going forward. This leads to a need for "complete and concurrent data"—i.e., all study data in a single data repository in real time and of high and consistent quality (cleansed of entry errors). Consequently, in order to fully support oncology trials a data management solution must be able to facilitate, manage and streamline:

- Complex data collection, validation and reporting from multiple sources, including:
  - electronic case report forms (eCRFs)
  - Local laboratories
  - Central laboratories
  - Biomarker
  - Pharmacokinetics (PK)
  - Pharmacodynamic ("wet" and "dry")
  - Imaging data
- Multiple eCRF designs for multiple treatment arms
  - Simple, rapid and efficient deployment with no interruption to system access, in real time
- Deployment of eCRF pages on a patient-specific basis, including protocol amendments
- Handling protocol amendments (or adaptive design changes) without time or data loss
- Data collection and flagging for safety reporting, including serious adverse events (SAEs)
- Reduction of trial delays via:
  - Rapid database freeze/lock
  - Dose escalation timelines
  - Ability for immediate safety review (e.g., based on dose-limiting toxicity)
  - Interim analysis (IA)
- On demand data reporting, such as for:
  - Data safety monitoring board (DSMB)
  - Data monitoring committee (DMC)
- Monitoring
  - Safety signal detection
  - Targeted source data verification (TSDV)
- Clinical/Medical review

Addressing the Problems with Technology

In order for technology to not only encourage, but also facilitate fundamental changes in the way we perform clinical trials, it must meet our goal of collecting and managing complete, accessible data. To support the delivery of complete and concurrent data at all times, we must examine the personnel and functions that need to interact with the clinical data (inbound and outbound). There is the investigator at a clinical site, who needs to enter patient data into the trial records, have the right forms available and accessible when he is ready to enter the information, and have the data cleaned for miskeys and other errors as soon as possible to avoid the necessity of answering data questions at a later date. There are numerous other streams of data that are converging to create the trial record, many electronically captured: information from safety labs, PK, biomarkers response, patient diaries, etc. And then there is the data manager, clinical research associate (CRA) and medical team responsible for pulling all the data together in a coherent manner, no matter where it came from.

Technology should enable us to run the trial that has been designed to deliver maximum efficiency and minimize unnecessary risk. Solutions have been available for some time that automate parts of the process, but if they are separate and incompatible streams, they will result in study data still in different places, and require time-consuming and error-prone processes to merge and reconcile. Technology should not be adding to the difficulties of running trials and reaching conclusions; technology should not restrict our ability to deliver real solutions to today's clinical needs.

An Advanced EDC/CDM Platform: How Medidata Rave Meets the Oncology Trial Challenge

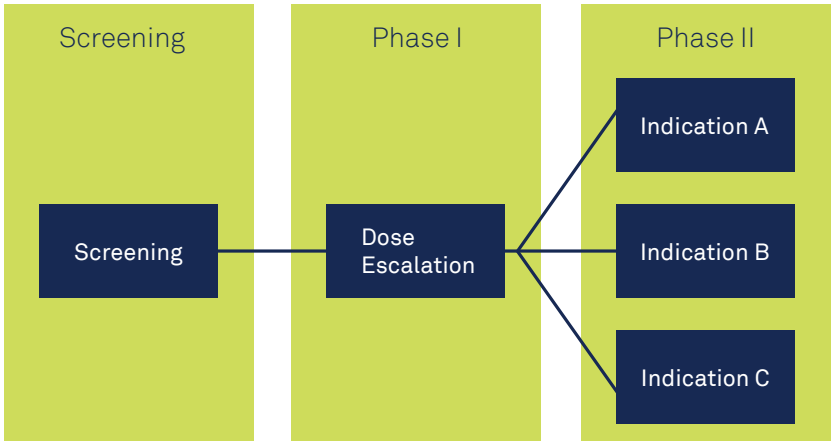
It is the intent of this white paper to explore how these requirements can be met through a software platform that is built on industry standards, interoperability and innovation. We will present two case studies that reflect the types of complex inputs and processes in oncology research and how technology overcame the operational and data management challenges.

Case Study 1: A Phase I/II, Multicenter Dose Escalation Study in Patients with Solid Tumors

This study covered two phases:

- Phase I: Dose Finding/Escalation
- Phase II: Initial Efficacy in Diagnosis-Specific Cohort

Figure 2: Case study trial design



Source: Medidata Solutions, 2010

The key challenges of this study surrounded the transition from a heterogeneous solid tumor population to individual indication-specific populations based on an intraspective analysis of the results generated in Phase I. This type of population/patient finding study is increasingly popular, as it allows sponsors to run a single trial across many indications versus multiple individual trials.

The main challenge in Phase I was delivering the data required for dose escalation rapidly, reducing the decision-making timelines (i.e., reducing white space), and ensuring that early signals could be accurately and confidently interpreted with respect to initiating Phase II. We discuss three of the core challenges in more detail:

I. Managing a Wide Variety of Laboratory Data, from Multiple Sources

A. Local Labs

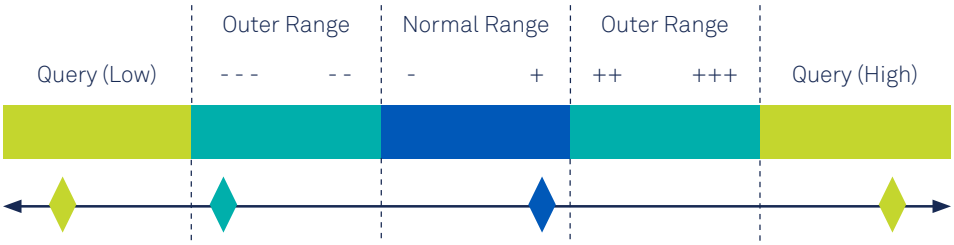
The need for real-time results to drive patient care at locations close to the clinical site at which the patient is being treated drove the need for the use of multiple local laboratories. Relying on central labs for specimen analysis may take too long, with costs for sample transportation outweighing other benefits. Using local laboratories, however, generates significant data handling pressures given the variance in normalized results. In order to validate the data collected, researchers need to collect and manage normal ranges for each laboratory used—often many per site. Once collected, these ranges must be periodically reviewed for the effective duration of the study, and the updates incorporated. Furthermore, in order to avoid unnecessary queries, many trials focus data cleaning not on all "out of range" values, for which there would be many, but on a set of outer ranges that are most critical to safety.

The supporting technology for data collection and cleaning in this case had to support the requirements of lab-specific input, provide for individual range setting and enable periodic updates, as well as allow automatic flagging of procedure results from trend data. The research sponsor used the clinical data collection, management and reporting platform Medidata Rave®.

Rave allowed trial management to simplify these tasks by facilitating a number of workflow processes through the Medidata Lab Administration module:

- Management entered local ranges for each site into Rave
- Data management entered outer ranges for the study into Rave
- Data sites entered local results directly into the eCRF
- Validation checks were tailored to target key expected safety signals and any values that fell outside of the outer ranges

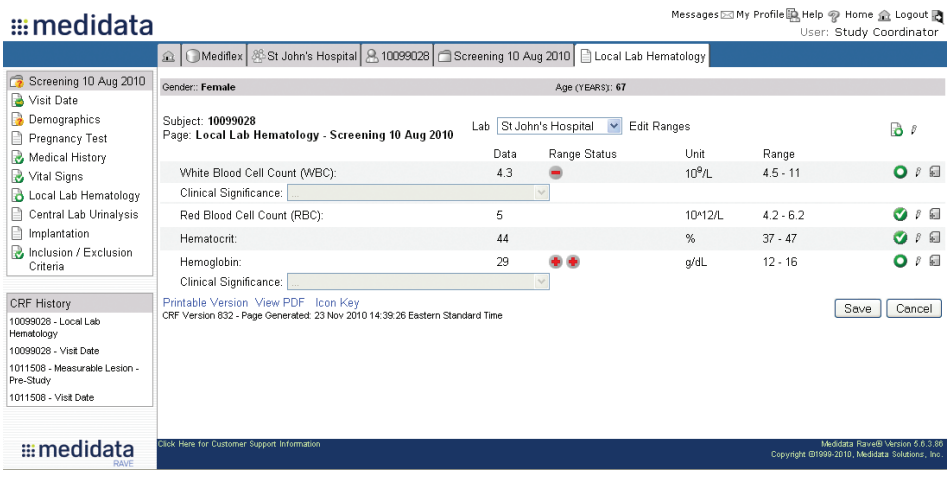
Figure 3: Query triggers



- Query raised for value that falls below outer range (low) and example in outer range (high)
- Query not required because investigator prompted to provide comment on clinical significance immediately upon entry
- Query not required because value within normal expected ranges

Source: Medidata Solutions, 2010

Figure 4: Medidata Rave screen shot of lab eCRF



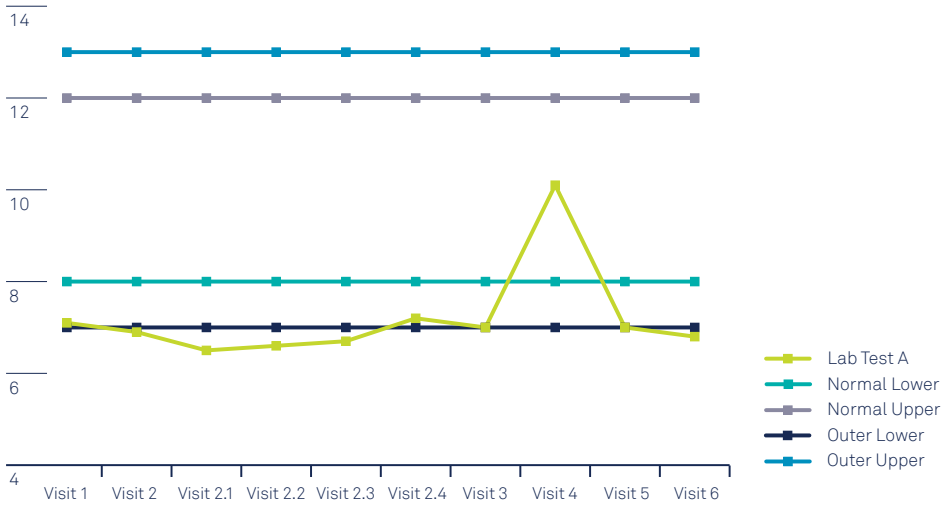
The story does not end here, because it is important to consider each and every data point within the context of the entire patient for safety implications. Rave facilitated this review with its ability to handle delta validation checks. Figure 5 shows that the patient is consistently out of normal range, except for visit 4; however, it is the visit 4 result that requires further investigation because the procedure result trends signalled an issue.

In oncology trials, normal ranges are a guide of what should be expected, but because of the range of morbidity of the subjects, additional monitoring on each patient is required to pick up potential safety issues. With an electronic data capture (EDC) system that could not flag this issue, the results would have been:

- Queries being issued against the out-of-range values (incorrectly)
- Acceptance of the "normal" result and failure to recognize and/or report the underlying adverse event

Because of its structure and flexibility, the Rave platform could review all patient data at once and issue alerts for unusual results—specific to the patient, not to a pre-defined range—adding a key layer of safety monitoring.

Figure 5: Lab results, by visit, for one patient



Source: Medidata Solutions, 2010

B. Pharmacokinetics Samples

The PK results were a key factor in determining treatment success in this trial and were required to fully assess the patient. Often treated like a central lab, the need to blind results, where appropriate, historically resulted in PK data being loaded only at the very end of a study. Rave allows differential blinding across users, hence allowing real-time data management and reporting without violating study requirements.

Moreover, a simple data transfer process was established whereby the centralized lab updated new results on a central drive location (FTP), and Rave automatically detected the availability of a revised data file and initiated the loading of this data without manual intervention.

C. Biomarkers

In this study, biomarker data were used to identify treatment candidate gene expression profiles, helping to further target successful patient candidates. Similar to PK data, in order for biomarker data to be entered into patient data files, the EDC system must ensure appropriate blinding. With the Rave platform's ability to set appropriate blinding and workflow levels, the biomarker data were able to be treated exactly the same as the PK data, ensuring appropriate trial rigor.

In summary, the complex requirements of this trial, with multiple laboratories submitting PK and biomarker data as well as procedure results, were met with the advanced technology of Rave, which provided the flexibility, configurability and granularity required for the trial. Rave's Lab Administration Module provides a full range management system for Central, Reference and Alert ranges. In addition, this module enables all lab tests to be associated with units of measure and conversion factors to support standard reporting of lab data in real time. Central lab data can be uploaded directly to Rave using the Batch Upload utility or Web Services, and out-of-range values are flagged for review automatically in EDC. Local labs are managed by associating ranges with sites. As data is manually entered, out-of-range values are flagged for review automatically in EDC.

II. Handling Multiple Treatment Arms Within a Single Trial

A. Phase I: Core Study

An initial core design was established with a 28-day treatment cycle. Up to six cycles of treatment were permitted during the initial phase of the study. After this time, patients were offered the opportunity to participate in a further Long Term Follow-Up (LTFU) phase or an Expanded Access Program (EAP) if they wished.

The challenge here was choosing when to allow a site access to the eCRFs associated with the optional subsequent cycles such that the site had access to the required eCRFs when needed but did not risk confusion or error through prematurely accessible or unneeded forms.

Because of its flexibility, Medidata Rave could allow each site user to access and populate eCRFs by cycle, with centralized forms available in a separate folder (e.g., adverse events, concomitant medications, end of study) when needed. In addition, Rave could allow site users to access and populate the appropriate forms for unscheduled visits or unscheduled assessments at any time, with no required intervention from data management.

This ability to add the appropriate eCRFs can also be configured to be manual or semi-automated in Rave, based on the need to control data collected or investigator input. Although not initially applicable to this study, a further extension of this feature can be used for dose escalation studies or multi-regimen treatments, where dosing schedules and therefore cycle durations may differ significantly. Rave's dynamic edit check capability ensures that only the relevant CRFs are presented for each subject, rather than expecting sites to navigate through a bulky subject schedule to select the relevant forms.

Differentially addressing subjects assigned to different treatment arms can also be managed by dynamic edit checks, enabling differing assessments and multiple visit schedules to be handled in a single trial. Allowing for the development of patient specific eCRFs is key to this type of research.

B. Phase II: Indication–Specific Extensions

The question here is simply, "Where are we going?" As patients complete the first phase of the study, the accumulating data can and should be used to identify the key target indications for the second phase. In this case, the first phase involved patients from a heterogeneous, solid tumor population and the second phase initiated research arms involving subjects with specific tumor types, such as sarcomas, carcinomas and lymphomas.

The challenge therefore was to avoid building multiple forms that would never be used for many of the patients. Creating new eCRFs for patients as they enter new stages of the research saves time up front and reduces the risk of unnecessary spend, as well as confusing site navigation; but unless they can be created and deployed in real time, they risk adding a layer of study build that increases time to study close and, moreover, may inconvenience patients. The balance between cost and time savings requires careful management and strategic oversight. Establishing an easily accessible library of potential forms and associated fields and edit checks can ease this concern and significantly decrease the time and resource required to create and modify trial designs. The Global Library feature of Medidata Rave fills this function elegantly.

Further, Rave allowed deployment of the new eCRFs to all or a selected group of patients, selectable by site, condition, previous treatment or other relevant field.

III. Real-Time Access to All Data to Support Interim Analysis, Adaptive Trial Design or DSMB/DMC

The culmination of the previous highlighted features is the delivery of complete and concurrent data. The ability to view, clean and report the entire study database from a single location is key to any study, but especially so for oncology studies. Rave additionally provides the user with a number of methods for reporting or extracting this data—all fully integrated and enabled—including:

- Standard Reports
- J-Review (including Patient Profiles)
- Business Objects
- SAS-On-Demand
- Web Services

Any user, with the appropriate access rights, could view and report the entire clinical database—subject, of course, to the blinding rules set by study management at the start of the trial. Different users can use any of the solutions listed above, and since each is looking at the same data, they will each return the same raw data.

Rave provides for a full-featured data extract module that allows authorised users to request data sets (in SAS or other formats including ODM, XML, CSV, etc.) through an on-demand basis, eliminating the need for any vendor/contract research organization (CRO) intermediary to request and receive your datasets on a 24x7x365 basis. ODM extractions use Rave Web Services (RWS) enabling both snapshot and transactional data extraction to be streamed in real time.

Case Study 2: A Phase III Blinded, Multicenter Study

This pivotal clinical trial faced a number of key challenges, such as an exceptionally large number of sites and patients, large volume of data collected and ultimately the complexity of that data.

Study Schedule

Study Details

- 1,000 subjects
- Global site locations (US, South America, EU, Asia, Australia)

The primary challenges faced by this study were:

- Complex Data (including RECIST)
- Dynamic CRF Design/Development Requirements
- External Data
- SAE Management
- Interim Analyses
- Data Safety Committee

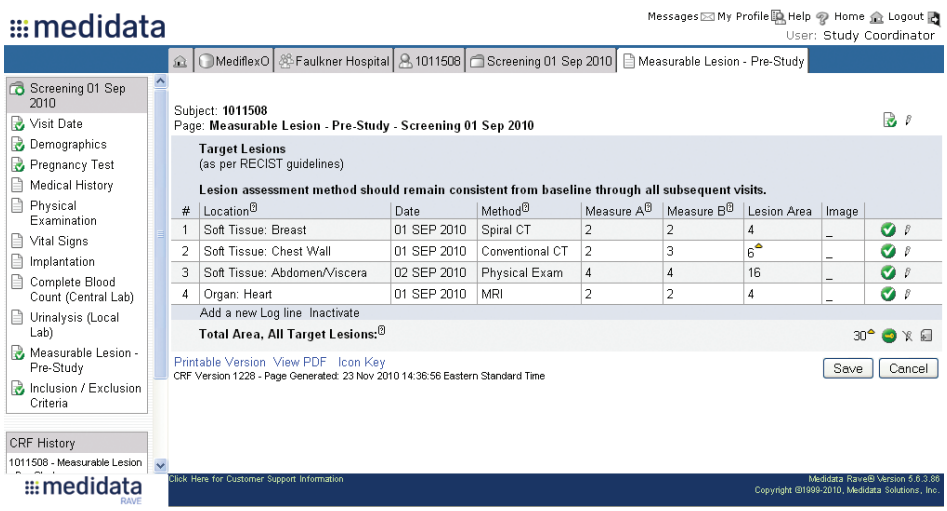
I. Handling Complex Data Such as Tumor Measurements over Time and Supporting Workflow

RECIST tumor measurements were complicated to collect and review and generated more queries than any other data set in the study. This type of data was of pivotal importance, and is frequently an ubiquitous component of oncology research, either as a primary or secondary endpoint. It was imperative that the technology solution enabled the site to collect this data in a timely and accurate manner.

The challenge in this study, as in many oncology studies, was that the same tumor measured at baseline was the same tumor measured tracked over time points, in the face of multiple and, in some cases, evolving lesions.

Medidata Rave uses a combination of derivations to "carry over" previous visit readings into the next visit in a read-only manner. This feature was designed to facilitate the accurate collection of RECIST data while reducing the burden of collection effort and the potential number of queries.

Figure 6A: Medidata Rave screen shot of management of tumor/lesion measurements



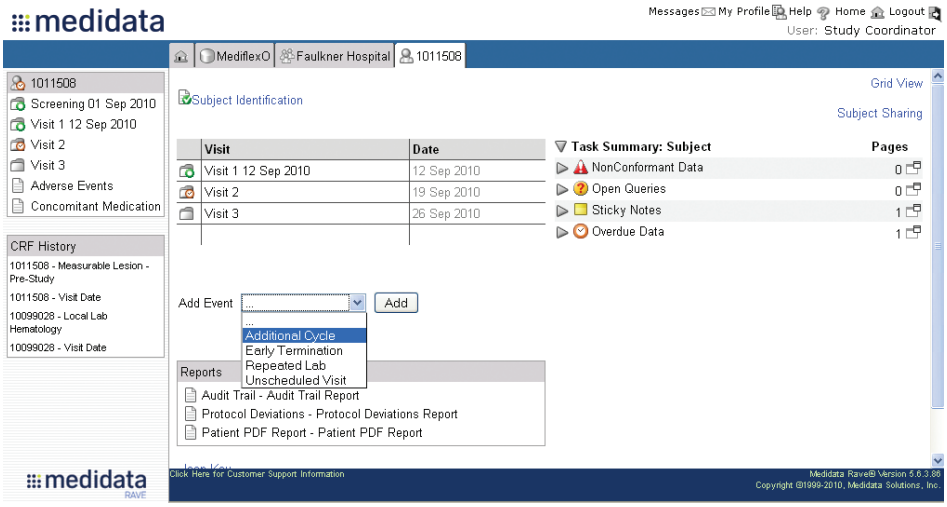
II. The Ability to Add Additional Cycles of Treatment Dynamically to Relevant Subjects

The clinical endpoint for many studies is survival, and patients will therefore be enrolled for an unknown duration. The ability to seamlessly add additional cycles visits without any external interaction is vital.

Sites do not want to wait for external intervention (e.g., data management) to "make pages available"—they need to utilize them on demand, especially in studies where unscheduled events are commonplace and patients can readily exceed the expected study duration.

Medidata Rave manages multiple and repeating patient schedules seamlessly and within the same database. This feature is essential for not only multiple cohort studies, but also adaptive protocols, and for studies where country-specific languages/protocol requirements might be necessary (see Figure 6B).

Figure 6B: Medidata Rave screen shot of creation of additional/unscheduled events



III. Handling Other External Data Sources Such As Central Laboratories, CT Scan Images and Associated Data

Rave supports the ability to upload different types of images so that they can be viewed and compared on a visit-by-visit basis alongside things such as tumor measurement data. Rave supports the centralized collection, management and cleaning of all data types, and can facilitate the transfer of data in various formats, including;

- CDISC LAB Model
- CDISC ODM
- CDISC SDTM
- SAS
- Flat File/ASCII
- Excel Spreadsheet

Types of data commonly loaded include:

- Central Lab Data
- PK Data
- PD Data
- Biomarker Data
- Central ECG Data
- Randomization Data
- Patient Diary/ePRO Data

Medidata has developed a suite of tools that support integration of data from third-party vendors such as interactive voice-response systems (IVRS), electronic patient-reported outcomes (ePRO), central electrocardiogram (ECG), etc., in real time. RWS utilize the CDISC Operational Data Model to interchange data between systems. Any integration developed between Rave and a third party using RWS can be reused for future studies by simple configuration in a published application programming interface (API).
Data can also be loaded directly into Rave in a flat file using the Batch Upload utility. All tools are certified against the CDISC ODM standard. This ensures that Rave is a single source of all data, and there is no additional need to merge or reconcile data at the end of the study, potentially saving weeks of time from last patient last visit (LPLV) to Database Lock.

IV. Dealing with Subject Safety in a Timely Manner by Eliminating Redundant Paper Processes

Oncology trials may result in a higher than average number of SAEs than other studies. Collection of safety-related data outside of an EDC system may lead to a requirement to reconcile two databases, making this one of the most resource-intensive and painstaking steps in the data cleaning process.

An additional module in Rave, Rave Safety Gateway is an add-on module that automates the flow of required data between critical systems, obviating redundancy and expediting the reporting process. It leverages the clinical data captured in Rave and allows it to be passed over to any E2B compatible safety reporting system in E2B (XML file) format. Once sites enter SAE data into Rave, Rave Safety Gateway will, based on business rules and configuration mappings, automatically create an E2B XML with the SAE information that can be electronically and automatically forwarded to a safety system—with or without manual intervention. Both initial and follow-up reports are generated. Rave Safety Gateway eliminates redundant paper SAE collection and minimizes any reconciliation processes.

V. DSMB/DMC

Phase II/III studies often have an internal/external review board (DMC/DSMB). Data reporting for this level requires more information than is often available by the periodic generation of simple data listings. The data is under review for safety-related reasons; as such, not only is it vital that the reviews occur as soon as necessary but that they rely on reviewed and clean data from all available sources.

Rave can facilitate these reviews through real-time 24/7 reporting, combined with read-only access which allows the reviewer to further investigate specific issues.

VI. Interim Analyses

In the days of paper CRFs, an Interim Analysis (IA) would result in data management preparing the IA data and then "downing tools" for six weeks, until biostatistics were satisfied. There was then a dramatic "catch up" phase, with data management desperately trying to reduce the backlog in collected data and regain concurrency with data processing.

Today, Rave allows for the ongoing freezing and/or locking of not only patients, but also visits, pages or even individual data points. This obviates the need for any delay in data processing.

In addition, each data point is subject to a full audit trail, detailing any changes since the last data extract was delivered.

Medidata Rave Technology

The Medidata Clinical Cloud™ is designed to streamline clinical research through advanced technology. Built on highly scalable architecture and based on industry standards, the platform is built to be scalable and cost-effective, whether handling a single clinical trial or large-scale global implementation. For over 10 years Medidata has consistently brought next-generation innovation to the life science industry to lower the total cost of clinical development through informed trial planning and management, optimized clinical processes and platform interoperability.

Medidata Rave is an industry-leading clinical data capture, management and reporting platform, which meets the requirements of rigorous oncology trials through features including:

- Single platform supporting both EDC and clinical data management (CDM) functionality;
- Computer, browser and platform independence, accessible from any Internet-ready computer;
- Configurable workflows;
- Study build tools that can incorporate individual trial requirements; and
- Multiple language capabilities, enabling different users to work and see reports in different languages from the same data.

Medidata delivers an interoperable clinical services platform through an industry standards-based architecture, supported through:

- CDISC, including CDASH forms, for clinical data;
- Technical standards including web services and Service-Oriented Architectures (SOA);
- Flexibility to interface with legacy systems with limited integration options, e.g., via ASCII file import and export;
- A plug-in architecture that facilitates the addition of new interfaces and functionality; and
- Open, documented API.

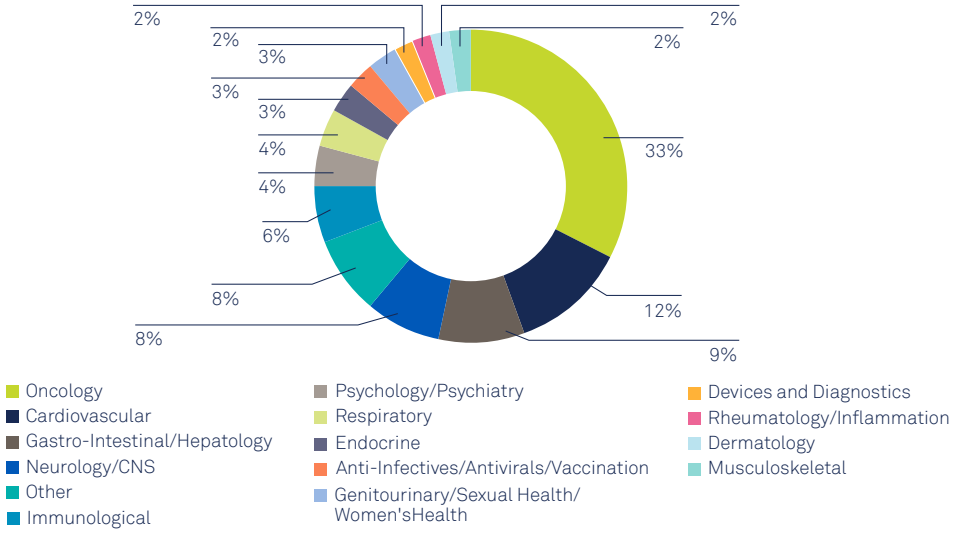
Medidata offers other advanced solutions that address key functions throughout the clinical development process including:

- Study design and protocol development (Medidata Designer®);
- Trial planning and management (Medidata Grants Manager®, Medidata CRO Contractor®);
- User and learning management (iMedidata®);
- Randomization and trial supply management (Medidata Balance®);
- Monitoring (Medidata CTMS™, Medidata SQM and Medidata Rave Targeted SDV); and
- SAE capture (Medidata Rave Safety Gateway).

Medidata Rave's Use in Oncology Studies

Oncology studies, with their demands for data access and general usability, present unique and challenging requirements for clinical trial technology. The flexibility and functionality of Medidata Rave has resulted in its use for hundreds of oncology trials to date, and oncology continues to be the major therapeutic area for which Rave is used. Fully one third of all trials implemented by Medidata services in Rave have been in the oncology therapeutic area, illustrating the strong support for the complex technology challenges of this important field.

Figure 8: Medidata Rave trials, by therapeutic category



Source: Medidata Solutions, as of 2Q 2010

About Medidata

Medidata Solutions is the leading global provider of cloud-based solutions for clinical research in life sciences, transforming clinical development through its advanced applications and intelligent data analytics. The Medidata Clinical Cloud™ brings new levels of productivity and quality to the clinical testing of promising medical treatments, from study design and planning through execution, management and reporting. We are committed to advancing the competitive and scientific goals of global customers, which include over 90% of the top 25 global pharmaceutical companies; innovative biotech, diagnostic and device firms; leading academic medical centers; and contract research organizations.

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Endnotes

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