The Almac Clinical Technologies Team on Clinical Trial Design and Execution with their Clients

An interview with Cheryl Kole, Jennifer Ross, Richard Wzorek and Matt Lowrie

Introduction

As with all healthcare procedures and practices, precision medicine methods need to be tested and proven in clinical trial settings. Precision medicine methods and associated diagnostics, medicines, and computer algorithms, must be tested in parts or in total for the trial to address the trial design. As precision medicine has progressed, regulatory agencies and healthcare professionals have developed a framework for the growing complexities of questions asked in precision medicine, including adaptive, multi-branch trials that allow decisions to be made at critical junctures, even allowing some subjects to participate in another trial arm should the arm they are in fail to

reach a designated endpoint. Such complications require not just flexible technology but also educated, dedicated teams that are able to react accordingly.

We approached an Almac Clinical Technologies team with questions about their approach to clinical trial design and Interactive Response Technology (IRT) implementation as well as relations with clients/partners. Their main claim is that their team facilitates more than simplifying patient and trial material management – they engineer quality into the clinical trial process. Their technology provides sponsors and CROs with the visibility and control needed to make data-driven decisions by leveraging advanced randomization and supply management functionality coupled with the real-time site and patient data in a closed-loop environment.
Below are the team's replies to our questions.

Part 1. Study Build: Design plans and criteria of clinical trials

Q. Protocols are written to describe the details of the objectives, design, and procedures of a clinical trial to ensure patient safety and data integrity. Sponsors come to Almac with protocols for clinical trial execution using the IXRS technology. Is the implementation approach clear from the details in the protocol or does Almac have to ask further questions in order to best understand the study's needs? How does Almac assess IRT implementation of the protocol and determine which IXRS® platform is most appropriate?

A. We approach each study individually and first perform a thorough evaluation of the protocol. We recognize that every clinical trial is different depending on the specific study's design and objectives. Regardless of the protocol's level of clarity or complexity, since we consider ourselves as world class consultants, we always ask questions, as well as provide guidance, to ensure that we deliver an IRT that meets the study's needs and expectations.

We work with the sponsor to address any unique challenges of the protocol or supply chain. Almac Clinical Technologies will provide consultancy for the study's optimal IXRS® design and implementation of, which tends to concentrate on enrollment, randomization, and supply management.

Of course, some trials are more straightforward than others with the objectives and procedures clearly defined in the protocol. Others that are more complex, such as Master Protocols, require a higher level of consultancy for determining the most effective approach for eClinical systems operations regarding flexibility and stakeholder coordination. Such studies would typically fall under our IXRS® UNLIMITED package, however, we would usually check the study's compatibility with Simplify™ configurations as well.

In a case study Accelerating Outcomes with a Pancreatic Cancer Adaptive Platform,[1] we provide an example of how IXRS® was able to accommodate an adaptive trial for Pancreatic Cancer Action Network® (PanCan®).

Where there are different implementation options, we would formulate materials to illustrate each possible option (including associated benefits and considerations). We then hold a series of meetings with the sponsor/study team to go through these materials and collaborate. Together, we are able to establish the most favorable approach that both meets the needs of the study and aligns with IRT implementation best practice.

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Q. What is the process at Almac of taking a protocol with an Adaptive clinical trial design and translating that into an IRT?

A. We consider ourselves industry leaders of the IRT implementation for complex innovative designs (interactive/adaptive clinical trials). We have the Adaptive Trial Design Center of Excellence (ATD COE) team in place to advise and oversee adaptive trial designs across all phases and functional areas of the study. This cross-functional team of experts comprises of representatives from Biostatistics, Software Development, Testing, Project Management, IXRS® Design, Data Integrations, Quality Assurance, Contracts / Proposals, and Medication Management.

Based on experience (with implementing hundreds of Adaptative Designs), the ATD COE has worked together to comprise several standard approaches and best practices. Upon protocol evaluation, we will determine which approaches will fit the study best and will outline the different options for the sponsor/study team, along with any variations within each option. We present these options to the client with illustrative examples that are easy to understand, so that they are able to make an informed decision.

Ultimately, during the IRT requirements specification phase, Almac collaborates with the sponsor/study team/stakeholders in determining the optimal implementation of the trial design approach by engaging them with important considerations.

Q. Almac offers different IRT configuration approaches for its IXRS® platform. Can you describe the general functions and differences between these three offerings? How does the sponsor decide?

A. Our three IXRS startup modes are tailored to different protocol requirements and study needs. See the fact sheet for details at https://www.almacgroup.com/clinical-technologies/wp-content/uploads/sites/8/2022/06/IXRS-BROCHURE-DIGITAL-FINAL.pdf

- **Simplify™**, Almac's rapid IRT start-up mode, is designed to provide easy and fast platform configuration. With all core functions of IXRS already included and pre-built, Simplify™ delivers a proven, industry-leading solution without the hassle of defining a fully customized IRT project.
  - Rapid deployment from just two weeks
  - Affordable and transparent pricing
  - Low-touch start-up
  - Flexibility to customize post go-live
- For our customers, being able to build their IRT within Simplify configuration translates into the most transparent and straightforward process, and, often most importantly, speed to go-live: as seen on **Figure 1**, starting at just 2 weeks. In fact, our fastest Simplify build was only 1.2 weeks!
- Our "How to add a new randomized part to an ongoing study in three weeks"[2] case study is a great example of how it can be quicker and more efficient to build a new IRT system under Simplify configuration from scratch than changing an already existing one.
- **Simplify™PLUS.** Since the launch of our novel platform configuration system, our engineers and developers never stopped finding new ways to expand its capabilities to include the most popular custom features and add-ons without switching to a fully custom build. With all core IXRS®3 functions already included, Simplify™PLUS allows you to add select upgrades and still keep the short timeline and lower cost.

A customer would choose SimplifyPlus when their protocol fits Simplify but certain add-ons or adjustments are required. As seen in **Figure 1**, these additional features increase the build stage length to about 5 weeks, which is still quite low for the market.

- **UNLIMITED**. With the most comprehensive and customizable delivery model available, we are able to tailor the IXRS® platform configuration and workflow to sponsor-specific requirements, as well as integrate with any third-party system.

IXRS®3 UNLIMITED is the result of over two decades of Almac's IRT experience. From complex to adaptive, there isn't a protocol this start-up mode can't accommodate, including Master Protocols – Platform, Basket, and Umbrella.

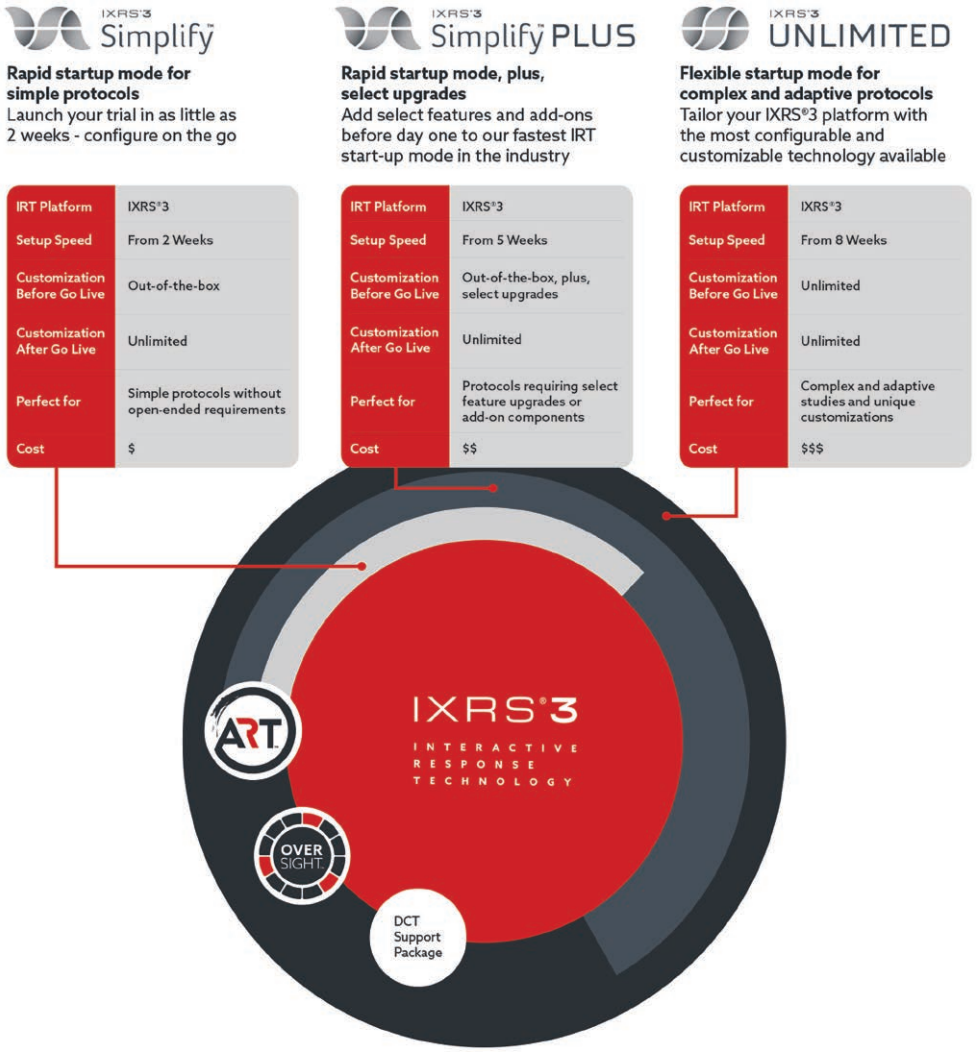

Figure 1: About Almac Clinical Technologies IRT Suite of Solutions

The suite includes:

- IXRS®3 IRT Platform – the most innovative, flexible, and the most popular IRT platform in the industry.
- Three IRT startup modes: Simplify™, Simplify™PLUS, and IXRS UNLIMITED.
- These startup modes provide 3 ways to configure the IXRS platform varying in levels of customizations, speed to go live, and costs.
- Integrations: EDC, CTMS, Clinical Supplies, Optimization, Central Labs, Clinical Assessment
- Biostatistical services

IXRS® Unlimited is a preferred choice for sponsors whose clinical trial requires a unique or highly tailored approach. As stated in **Figure 1**, it's a preferred solution for studies with complex/adaptive components since such studies could be perpetual and nature which calls for a very high level of flexibility and adaptability built into their IRT system from the start.

Q. Unforeseen events occur in the course of running a clinical trial – how does Almac work with the sponsor to design the trial to be robust enough to ensure data integrity and biostatistical rigor?

A. IXRS®3 offers a comprehensive set of features providing flexibility and control in regard to changes that commonly occur during the course of a trial. Through effective evaluation and collaboration with the sponsor/study team, we strive to build the IXRS® with the right level of flexibility that can accommodate a variety of adaptations, especially in terms of complex innovative designs (e.g., adaptive trial designs, Master Protocols, etc.)

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Of course, it is unrealistic and impossible to account for an infinite number of adaptations within the initial IRT design, and unforeseen elements can always arise during the course of the study. When these unforeseen elements are presented that may require an IRT amendment, we would do a full cross-functional evaluation of the revised protocol against the current system design. Based on this evaluation, we would come up with effective implementation options. Similar to how we approach the initial design, we would work in a collaborative manner with the client to ensure that the optimal approach is chosen to meet the needs of the new element. Regardless of whether it is the initial IRT design or an amendment, with our robust processes and solutions, we approach the implementation by ensuring the highest level of data integrity and biostatistical rigor.

In considering the lifetime of the study, with the initial build and with incorporating any amendments / changes, ensuring data integrity must be built-in and hardened through both process and product. Throughout the duration of a clinical trial, it is imperative that the eClinical systems have the capabilities in place to protect and account for changes to the data. Additionally, it is equally important that the system providers have a known commitment to Data Integrity (i.e., based on their history, experience, and how well-established that provider is in their space).

A provider who is willing to tell you "*No*" is not a negative, nor should it be considered as such, as long as it comes with advisement and alternative solutions. Much like an architect building a house, your eClinical providers should have the experience and confidence to explain the design and how the system will operate with that design. Your provider should also be able to support the design decisions throughout the life of the trial and explain the risks and impacts to changes and how they will ensure the data maintains its overall integrity.

Q. Sponsors need to specify inclusion and exclusion criteria for the sake of recruiting a test population. How are these criteria used in ensuring enough participants are included in multi-arm trials?

A. Ultimately the Sponsor is responsible for sites' recruitment numbers and making sure they include the investigators at the right sites with enough to meet the study's recruitment goals. The IXRS® may include inclusion/exclusion criteria collection to ensure that subjects who enter the study meet the specific inclusion criteria and assess when subjects do not meet the criteria. Almac's IXRS® includes critical functionality that programmatically assigns each patient the appropriate treatment arm in accordance with the protocol design.

Protocol designs and the supporting IXRS® functionality vary in determining patient eligibility and how treatment arms will be assigned. The IXRS platform also allows enforcement of various entry/enrollment caps to assist sponsors in tracking, alerting, and ultimately preventing over-enrollment of patient populations (e.g., stratification level, region-based, site-based, biomarker type, etc.). The caps can ensure that the right numbers are met – for example, at the study, cohort, country, or site level (or combination of levels) – to ensure that enrollment is stopped when the particular caps have been met. IXRS® can also alert study managers or other interested parties when enrollment caps or targets are approaching. IXRS® has the flexibility to allow the designated user(s) to open, close, and edit these targets or caps as needed during the course of the study.

Q. Once these plans are in place, what role does Almac play in recruiting the clinical and clinical site leads?

A. As above, it is ultimately the Sponsor's role to recruit clinical sites. Our services do not extend to site recruitment.

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Part 2. Physical and digital clinical supply chain management: Audit, analysis, and data report

A. Data collection is primarily gathered through online resources. How does Almac set up site interfaces for gathering data – software installation? Online portals? What measures are taken to ensure security and privacy of remotely collected data?

A. Almac's IXRS®3 platform is a web-based system that is configured per the protocol's unique design needs. It is easily accessed via desktop/laptop or mobile device with a URL and a user's unique login credentials (email address and secure password). Each user account is associated with a study role which defines their responsibility within the trial and what tasks they are authorized to perform within IXRS and what data they are approved to view, which is key in protecting study blinding. For example, an Investigator or Study Coordinator at an investigative site may only be able to view blinded data about subject participants at their location. They will be able to perform transactions like subject screening, randomization, and medication assignment.

IXRS®3 treats all data within the system as protected data. All data is encrypted both in transit and at rest using best-practice encryption algorithms and key lengths. The IXRS®3 requirements gathering process helps ensure that only the required data for the IRT to complete the tasks for which it has responsibility is entered and saved. All transactions performed in IXRS®3 are audited and attributable to an individual user or integrated system. Privacy-based requirements are configurable by country to allow compliance with local privacy laws when the scope of the trial is across many jurisdictions, Including the US, EU, Japan, UK.

Q. Given the prevalence of digital devices (cell phones, laptops, etc), can you briefly outline the mobile capabilities that Almac supports?

A. IXRS®3 is designed as web application to render on desktops, laptops, tablets or mobile devices across various screen sizes and operating systems. Given the global nature of studies and the multitude of users, this allows maximum flexibility.

Q. In follow-up, does Almac offer any type of telehealth connections for clinical trials – e.g., for recruiting subjects or reporting data? If so, can you provide a brief description?

A. Almac currently does not offer telehealth connections.

Q. Almac notes in its literature that the IXRS®3 acts as an electronic clinical report form (eCRF). How does this work in practice?

A. Interactive Response Technology systems, such as IXRS®3, collect and report on protocol-required clinical data and in some instances are the first point of entry for key data points within the study. Data such as randomization stratification factors or subject data being used to determine doses like height and/or weight. This data is often then fed into the main eCRF and/or clinical databases.

Q. How does the Simplify IRT on the IXRS® platform allow for recording and reporting trial documentation to audit protocol consistency (or deviations) and data integrity? What corrective actions can be taken to rectify these issues? Is it possible to design a trial to be robust to these issues by redundancy or re-randomization?

A. Managing large global trials that can involve tens of thousands of patients is only possible with the help of automated systems such as Almac's IXRS®. Yet, even with the use of software to randomize patients and manage medication assignments, anomalies can crop up in the way that sites deal with patients and kits.

From time to time, studies require manual intervention in the system records – a process that can jeopardize data quality if it is not handled and recorded properly. The audit trail is an integral part of any e-clinical system and should be utilized as a tool to drive data reviews. The OVERSIGHT solution within IXRS®3 provides a series of reports and dashboards that give at-a-glance information for Clinical, Quality, Site, and Supply

personnel. This allows for each of these critical roles to be empowered and informed. The Clinical team, or designee, can look at site participation, PI/Site initiated data changes, or potential site non-compliance issues.

Audit trail reviews conducted by data managers, statisticians, safety staff, and other roles can help identify data inconsistencies, outliers, and protocol deviations; plus, any errors in data collection and reporting at a site or across sites; and other data integrity issues. It is critical to be able to quickly see trends and issues, then drill down into the details to accurately analyze what the trends show and take necessary action.

Q. A point of interest is Almac's strategy to "re-route" patients in arms with clearly ineffective responses to arms that might promise better efficacy. Can you discuss the process by which this is managed with the sites and the regulatory agencies?

A. It all depends on how a protocol was designed and if it includes the option for patients to be reassigned/rerandomized to more effective treatments. Of course, the design also has to be fully approved by the regulatory agencies. This is a common element in Platform studies with Bayesian Response Adaptive Randomization (BRAR) Designs – where effectiveness is consistently assessed by the BRAR algorithm and new treatments can be introduced. The 1st case study mentioned above (Accelerating Outcomes with a Pancreatic Cancer Adaptive Platform) includes a BRAR Platform protocol.

In BRAR Platform designs, patient response is routinely assessed, probabilities are adjusted, ineffective treatments can be dropped. Some of these designs include rerandomizing subjects who were originally assigned to ineffective (dropped) to more effective treatments. For these designs, the logic and protocol's criteria for rerandomization is programmed into the IRT to re-randomize subjects when needed. If rerandomization is required to be kept blinded to site users, the IRT can ensure that this is executed in a blinded way.

Q. Does Almac conduct a post-trial review with the sponsor? For example, reconciling discrepancies or discussing lessons learned?

A. Almac is always willing to conduct reviews and learn lessons. Our Mission at Almac is to advance human health and that is directly embedded into our Quality Culture. We are always happy to look back upon the conclusion of a trial or, more preferably, at intervals during the trial to look at what is going well, what we can focus on, and how the current systems can be improved. This level of Oversight is great for all participants to maintain their due diligence and ensure the health, rights, and safety of clinical trial patients.

Novel trial designs, including complex innovative / adaptive designs / master protocols (e.g., umbrella, basket, platform), are steadily increasing in number. These complex innovative / adaptive trials when well-designed result in lower drug development costs, reduced timings, faster decisions, and improved patient safety. For success, these designs require flexible, high quality technology solutions to execute their designs, as well as trusted partners with proven expertise. JoPM

About the Almac Group

The Almac Group is a contract development and manufacturing organization that provides a wide range of integrated services across the drug development lifecycle to the pharmaceutical and biotech sectors globally. Its innovative services range from biomarker discovery, development, and commercialization to API manufacture, formulation development, clinical trial supply, and IRT (IVRS/IWRS) through to commercial-scale manufacture. Almac, an international company, is a privately owned organization that has grown organically over the past five decades now employing over 6,000 highly skilled personnel across 18 facilities including Europe, the US, and Asia.

About Almac Clinical Technologies

Almac Clinical Technologies is a global provider of Interactive Response Technology (IRT) and expert consultancy for the biopharmaceutical industry, empowering trial sponsors to proactively manage sites, patients, and clinical supplies through our industry-leading technology solutions.

Our solutions facilitate more than simplifying patient and trial material management – they engineer quality into the clinical trial process. We provide sponsors and CROs with the visibility and control needed to make data-driven decisions by leveraging advanced supply management functionality, coupled with real-time site and patient data in a closed-loop environment.

For more information, visit: almacgroup.com/clinical-technologies.

Cheryl Kole

Head of Solution Strategy and Commercialization, Almac Clinical Technologies

Cheryl has over 20 years of experience in the pharmaceutical technology field, joining Almac in 2000. Cheryl is responsible for the solution strategy and commercialization for Clinical Technologies products and services as well as overseeing the product management and marketing teams.

Jennifer Ross

Director of Biostatistics, Almac Clinical Technologies

Jennifer leads the Biostatistics Group responsible for providing statistical consultancy on randomization methodology and IXRS® (IRT) implementation. Jennifer has over 13 years of IRT experience and over 18 years of experience in Biostatistics. She holds a Bachelor of Arts in Psychology from LaSalle University, a Master of Science in Statistics and a Master of Philosophy in Education in Psychometrics from the University of Pennsylvania.

Richard Wzorek

Director, New Products & Service, Almac Clinical Technologies

Since joining the Almac Group in 2011, Rich has been instrumental in the creation and implementation IXRS®3. Rich also currently manages the development teams who enhance and maintain this intuitive platform. Before taking on his role at Almac, Rich spent fifteen years strategizing, planning, and developing software in numerous roles of increasing responsibility in the property and casualty insurance industry.

Matt Lowrie

Quality Assurance Manager, Almac Clinical Technologies

Matt has 18 years of experience within the Pharmaceutical world with an extensive focus on regulatory inspections, auditing, software, and risk management.

References

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