Less is More: Designing IRT for Oncology Trials

From early-stage studies to global, late-stage trials, oncology research is expanding at a rapid rate, and this advancing innovation has resulted in increasingly complex clinical trial protocols.

Managing patient enrolment, randomisation, dosing and clinical supplies, not to mention tackling low patient recruitment levels, inefficient trial design and economic constraints, are just some of the challenges facing researchers.

More and more sponsors are finding the answers lie in utilising interactive response technology (IRT), but designing systems to match study requirements is not without its challenges. Here, Brian Dunton, Senior Director, Regional Operations CRF Bracket, explains how simplicity is the key to creating IRTs that enable efficient clinical trials.

IRT is Not a Commodity

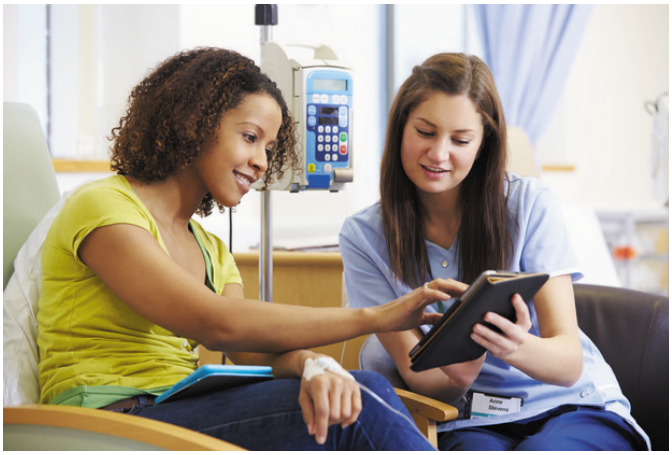
IRT solutions have two main functions. They randomise participant allocation in real time, ensuring the study is balanced, and they manage clinical supply logistics, making sure the right drugs are available at the right centre at the right time.

But this technology is not a commodity; it needs to adapt to the task in front of it. When setting out to design an IRT, then, it's important to think strategically about what is needed for each project.

Always consider back-end adaptability, the need for mobile app technology and whether it needs to work with other clinical supply chain systems.

Three Key Considerations

As we all know, protocols change, and most studies will see one or two potentially costly and time-consuming protocol amendments. When designing the IRT, anticipate this and structure a flexible system. That doesn't mean building with potential future functionality in mind, but rather ensuring that changes are easier to tackle if they arise.



Secondly, keep it simple. Study protocols are getting ever more complicated, but that doesn't mean the systems to support them have to be.

While there are many other things an IRT system can do, it should primarily be used to randomise patients to dose them properly.

There is a tendency to overload powerful IRT systems simply because it is possible. However, much of the clinical assessment data teams included are better suited to design other applications, such as the EDC.

Simplicity results in flexibility and ease of use. Complexity makes systems difficult for users to navigate and makes it easy for mistakes to be made, which get in the way of sites spending time with patients.

Finally, it is crucial to note that the IRT should not lead the user; rather, it is a tool that enables better decision-making.

Keeping the system simple and flexible allows the experts, not the technology, to own the calculations and decisions.

Cohort Set-up

While there are thousands of ways to group patients into cohorts in an IRT system, these are the most common cases found in oncology studies:

In *sequential cohorts*, users can have just one cohort open for enrolment to randomisation at a time. This is used when the protocol states that there is no going back once one cohort is closed and the next opened. There is no need to enforce this rule in the IRT, as sponsors should be allowed to control cohorts in any order.

When looking at *parallel cohorts*, multiple cohorts may be open for enrolment at the same time. Users can also reopen closed cohorts. In this situation, it's important to keep the decision-making process simple so that when data is entered, each patient is placed on the correct path.

Both set-ups share common parameters such as dose, treatment arm, combo therapy options, randomisation ratio, and open label versus double blind. However, any of these could be amended at any point, so it's important to structure a system that can adapt to change.

Tips for designing a flexible, expert-led IRT:

- Identify the key cohort parameters, such as tumour type or intended dose, as set out in the study protocol. Then design the system so that study team users can select any combination of these parameters when opening a cohort
- Structure the system so that protocol rules are enforced by an individual rather than the IRT technology
- Give sites as much control as possible. If subjects need to be approved by sponsors before being enrolled, ensure all teams

have the resources they need to do the job and that realistic expectations are set
- Before going live, define an error handling process for situations such as a patient being enrolled into the wrong cohort or an incorrect dose being selected. This will avoid unnecessary delays and stress

Challenges and Recommendations
Change is not uncommon mid-trial, but rigid IRT systems will render even the simplest amendment a time-consuming headache to address. Try to anticipate common changes and build these into the design of your IRT from the start.

3+3 Dose-finding Design
Common in early-phase studies, 3+3 dose-finding trials have two phases. The dose escalation phase establishes the maximum tolerated dose (MTD). The study then moves onto the dose expansion phase, during which additional patients are enrolled.

When designing the IRT, remember that an additional dose level will be needed and allow for it in the system's framework. With no new coding needed, the technology vendor will be able to carry out a simple data insert: a much cleaner operation.

Randomised Cohorts
Randomisation is also subject to change in earlier-phase studies. Building a framework into the IRT that allows for a new process to be implemented without changing the basic system architecture will save time and money.

Protocol Rules
Try to give researchers, rather than the IRT, as much control over the protocol rules as possible. Setting rules such as a minimum or maximum cycle time between visits in the absence of safety prohibitions, for example, could result in patients being sent home without a drug. Consider including the option of an out-of-window visit if necessary. This will help to reduce the trial burden on the patients.

Variable Dosing
Dispensation logic in oncology trials can be extremely complex, with dosing and titration calculations being based on a variety of factors and responses. This can make it difficult for the IRT system to predict how much medication is needed and to manage restocking. Where possible, allow an end user to select the desired dose, rather than having the system calculate it.

Standard of Care (SOC) Management
A trial may have a standard of care (SOC) therapy to be dispensed in combination with the study drug. SOC can be dispensed outside of the system in some countries but not in others, so try to keep things flexible.

It's also worth noting that packaging may be consistent globally at the start of the study, but things can change. Including an option for centres to source materials either via or outside of the IRT will allow researchers to easily adapt if necessary.

Multiple-phase Studies
Where studies have a Phase I MTD enrolment followed by a Phase II randomised controlled trial, consider treating each phase as a cohort. Within the IRT, define the parameters and the randomisation enrolment logic of each phase.

Also think about how you would want the data to be displayed within the system. Will you need web reports or subject counts, for

example? Work with your vendor to establish how the information can be organised in a way that makes the most sense for the project.

Adaptive Cohort Design

It is common for study teams to drop treatment arms, or change visit schedules, doses or the randomisation ratio part way through a trial.

To handle these amendments, systems should be designed to support such changes with minimal edits to the system architecture.

Summary

Clinical trial protocols, particularly in oncology, can be extremely complex. The systems we use to support studies should reduce, not increase, that complexity.

The IRT system should not make the decisions, rather it should be a tool that allows researchers to make better choices. Designing systems that focus on the fundamentals of enrolling and randomising patients will give the experts the time and space to concentrate on what they do best.

The key to success is employing the most flexible approach. Change is a constant, and protocol amendments can be expected, so anticipate and plan for predictable change to avoid upheaval later.

Minimising the rules, input requirements and calculations within the IRT will bring greater simplicity and flexibility in managing randomisation, dose levels and clinical supplies.

Because, as with most things in life, the simplest solution is usually the best.

Brian Dunton

Brian Dunton is a Senior Director of Regional Operations at CRF Bracket. He joined CRF Bracket back in 2006; he spent a full decade managing IRT projects for clients, then joined Roche/Genentech as an IXRS and ePRO Global Category Manager before returning to CRF Bracket in his current role.