

Qualitative and quantitative benefits of IVR and IWR in clinical trials

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The decision to use electronic trial management solutions will often be based on cost. However, the cost benefit calculation may be quite different, depending upon the budget holder

Interactive voice response (IVR) and interactive web response (IWR) systems are common and often necessary components in clinical studies today. Modern IVR systems enable users to interact with the computer system via two interfaces – the traditional telephone-based system (IVR) and now an internet-based system known as interactive web response (IWR). Nevertheless, the decision to use such electronic trial management solutions will often be based on cost. Commonly, electronic trial management solutions are perceived to have the greatest impact on clinical trial supplies, largely because such savings are tangible and easily defined. However, this article will argue that the prevention of over-recruitment of study subjects often yields a larger cost benefit for IVR and IWR, although it is considered less frequently. For example, we'll see how over-recruiting a 500-subject study by 10% can lead to costs exceeding \$300,000.

IVR and IWR can play a number of roles in clinical studies, including randomising subjects to treatment, 24-hour emergency codebreak services, management and re-supply of drug inventories at study sites and depots, tracking of patients through the study, patient diary data collection, and patient pre-qualification and triage during recruitment campaigns.

COST BENEFIT PERSPECTIVES

The decision as to whether to employ IVR or IWR in a study is often protocol-driven. For example, collection of information detailing packs shipped from a local depot to site may be better carried out via IWR since this type of information is easier to manipulate visually. On the other hand, IVR may be more appropriate for randomisa-

tion events, especially if information is required very quickly and away from the PC. Many studies will employ a mixture of both IVR and IWR to take advantage of each of their strengths, and to allow for different end-user preferences.

The budget for a clinical study is often held by the clinical team or by the trial supplies group. The cost benefit calculation may be quite different depending on the budget holder. A clinical budget holder may be less influenced by a saving in medication overage if they are not responsible for the drug supplies budget, unless medication shortage means a delay to the study timelines. Clinical, however, may be more persuaded by using IVR in preventing over-recruitment, meaning that the study can stop promptly, so limiting expenditure due to the unnecessary inclusion of additional patients. In considering the utility of IVR it is important to consider the whole picture in terms of benefits – this includes cost savings across more than a single study team department and budget holder, and qualitative benefits that are less easy to quantify numerically in terms of cost savings. Qualitative benefits may include, for example, simplification of the logistics of managing the medication supply chain in a large multinational clinical trial.

In considering the whole picture, pharmaceutical companies categorise studies to facilitate decision making. A simple way is to define categories of increasing complexity, with those above a certain point advocating a need for IVR. Such categories in the simplest case might include:

- **Type A.** A small number of subjects, short study duration, patient tracking only, no complex dose or randomisation algorithms, small number of countries and sites

involved, no medication management issues

- **Type B.** An increased level of complexity with regards to functionality and/or larger in size than type A.

- **Type C.** As above, but with a combination of all or some of the following: very large trials; centralised distribution of supplies; medication shortages; drug expiry issues; packaging contracted out; subject resupply; and complicated drug dispensing (for example, titration up and down, treatment crossovers and so on).

A more complicated alternative might include a utility score derived from the consolidated responses from an extensive yes/no checklist. Scores are calculated from the number of yes responses obtained, but may also be weighted by the importance of individual checklist items. An example is detailed in Table 1, overleaf.

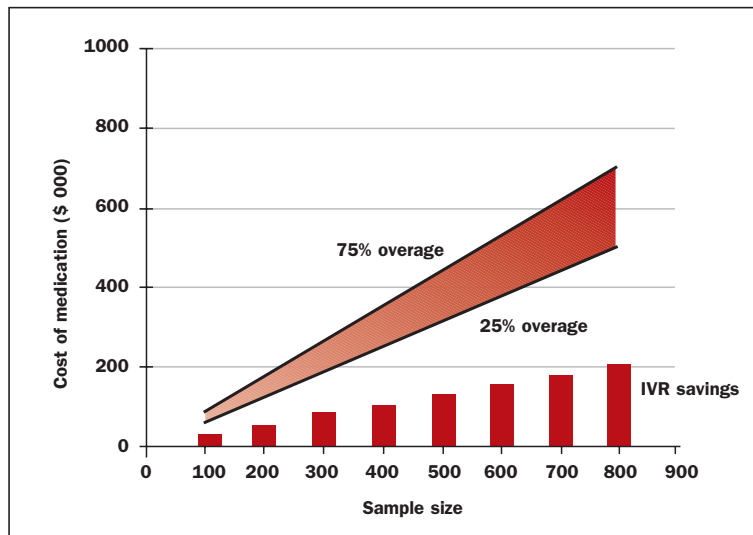
BENEFITS TO DRUG SUPPLIES TEAM

In the estimation of the savings in drug supply, the cost of supplying drug to subjects needs to be estimated. This can be surprisingly difficult to calculate although consensus from the industry suggests clinical trial supplies for a single subject cost US\$500 on average. The range of values, however, appears to be vast with per-subject drug costs varying greatly depending on the therapy area, comparator treatment and duration of the trial. Using IVR has been shown to reduce the need for supplies from the often-packed 75% overage to 25% overage (assuming the use of IVR has actually been built into the design of the study rather than simply bolted on). In fact, in reality many studies (particularly those involving repeat dispensations to patients) can run on even lower overages. Simply having fewer supplies in the

TABLE 1. TO APPLY IVR/IWR OR NOT? CATEGORISING CLINICAL TRIALS BY LEVEL OF COMPLEXITY

Item	Weight	Yes/no
Is a dynamic allocation randomisation method required?	50	
Is there a limited supply of drug available for the study?	10	✓
Is the investigational product expensive?	10	✓
Is the comparator difficult or expensive to source?	10	
Is it important to stop the trial when the desired number of subjects has been recruited, or an identified number of endpoints achieved?	15	
Are there a large number of countries/sites covering a number of different time zones? Etc...	8	✓
TOTAL SCORE	28	

Figure 1. Cost savings attributable to reductions in medication overage required



supply chain introduces tangible cost savings in the areas of purchase of raw material, manufacture, packaging and storage costs. Using the average value for clinical trial supplies quoted above, with a trial size of 500 subjects, a potential saving of \$125,000 may be achieved (Figure 1).

In addition to estimated cost savings are the benefits of automated computerised drug shipment. The logistics of manually managing inventories at study sites and local depots involved in large multinational studies can be substantial. An IVR system is configured to automatically generate consignment requests that include all shipping details so that the supplies distributor can respond quickly and efficiently to the study needs. This is a quality benefit that is more difficult to express in terms of cost savings.

BENEFITS TO THE CLINICAL TEAM

Prevention of over-recruitment. Over-recruitment of patients can be an expensive and time-consuming problem in some studies and reducing the over-enrolment of subjects is preferable from both ethical and financial standpoints. While each study is different, over-recruitment may commonly exceed 5–10% and may be as high as 20% in some studies. Using the same example as before, if this 500-subject study over-recruited by 10%, this would mean that 50 extra subjects were recruited. Using industry average values for laboratory fees (\$400 per subject), data management (\$12 per page for 100 pages) and investigator fees (\$4,500 per subject), preventing this over-recruitment would result in a cost saving of \$305,000 (Table 1, above, and Figure 2, overleaf).

IVR systems contain a real-time picture of study recruitment progress and can be configured to advise the sponsor and site teams when a study should close to avoid significant over-recruitment. Using an IVR system to capture both screening and randomisation events enables the IVR system to continuously track the screening failure rate and predict the date for closure of screening or the actual numbers of screened patients required to achieve the necessary number of randomised patients. Thus studies managed using IVR can close with very few patients randomised in addition to the target sample size.

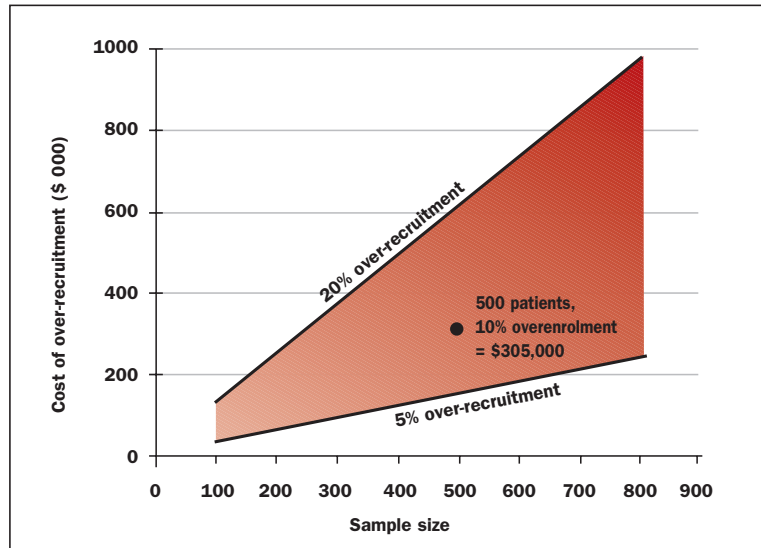
Patient recruitment. More recently, electronic trial management systems have been used in the recruitment of patients to clinical trials. IVR patient recruitment is implemented in combination with the services of an advertising firm. Patients responding to advertisements to participate in a clinical trial complete a study-specific IVR qualification instrument. Potentially eligible subjects record their name and telephone number during the IVR call. Study site staff can access new patient records by telephoning into the IVR system.

The use of IVR in combination with advertising represents an effective means of improving study recruitment performance. In addition, pre-qualification has the benefit of reducing the screening failure rate, leading to a greater throughput of eligible patients at site, and a reduced cost of screening failures. In comparison to the use of a call centre, this represents a highly cost-effective solution that is simple to administer across multinational and multilingual studies.

The costs of delayed patient recruitment are often argued in terms of lost time to market, which can be substantial. Making enrolment both more predictable and more efficient is a major quality benefit, as recruitment is one of the activities involved in the study least in the control of the sponsor.

Quality and study integrity. Other functional groups, for example statistics departments, choose to implement IVR or IWR for reasons other than cost, or at least not directly related to cost. Their decisions are often based on whether

Figure 2. Cost savings attributable to reductions in over-recruitment



or not IVR/IWR is crucial to the design and success of the study. For example, if the study design requires balance between treatment groups in a large number of prognostic factors this is difficult to achieve without employing an adaptive randomisation method using a computer. In this case, IVR may be considered essential to the study design. In addition, using IVR to administer the randomisation scheme in an open label study makes the process transparent and prevents potential criticism that investigators may introduce selection bias. ICH E9 guidelines recommend central computerised randomisation such as IVR in such studies.

Electronic patient diary data. Because of the drive to improve the quality and integrity of patient recorded data, IVR has been employed more and more for the collection of clinical data directly from patients, such as patient diary data¹. This has included data that are increasingly important to regulatory submissions, pricing and launch activities, such as health economic and quality-of-life data. Pre-recorded prompts list the various options available to the patient or request responses to particular questions. For example, a simple smoking cessation diary may ask the patient to rate his or her desire to smoke for that day on a 0 to 7 scale (where 0 represents no desire and 7 represents extreme desire), or to indicate the number of cigarettes smoked during that day.

The key benefits of IVR in direct data collection from patients centre around the fact that all data, and the diary application itself, are hosted centrally on a secure computer system. This means that following the patient call, no data are held locally but are immediately stored and made accessible within the central study database. Hence, diary data are viewable and reportable in real time and patients failing to make scheduled diary assessments may be identified immediately. The system may be configured to send an automatic fax alert to a study site, or to a call centre to allow the proactive follow-up of patients to encourage them to make their diary call. Camilleri *et al*² reported this feature to be a major benefit of using an IVR patient diary to successfully collect primary efficiency data in irritable bowel syndrome patients.

Ensuring the quality of patient-reported outcome data is increasingly important as these data represent primary endpoint data in some therapy areas and may influence labelling in many indications. Many recent publications have also indicated the serious limitations inherent in patient diary data collection using paper diaries. This has included surprise findings that paper diaries are not only completed retrospectively, but in some cases prospectively³. Preventing retrospective and prospective completion of diary data using IVR eliminates this integrity issue, and where diary data are important is of significant value.

PROJECT MANAGEMENT BENEFITS

As mentioned earlier in this article, IVR and IWR systems are commonly used for inventory management. Because IVR/IWR are used to administer randomisation and medication dispensing events, the IVR database represents a powerful real-time picture of the status and progress of each patient through the study. Building reporting functionality to display these data in the most useful way creates a powerful project management tool. Clinical project managers can identify the key performance indicators for each trial and accurately track them against data collected by IVR/IWR. Key metrics might include, for example:

- Rate of site initiation (percentage of sites that have initial supplies requested, sites/month initiated)
- Rate of site activation (percentage of sites that have recruited one subject, site activation/month)
- Rate of recruitment (over the study to date, over each previous month, by country and by study)
- Screening failure rate
- Tracking of end points being reached (for example, number of deaths, number of successful completers)

CONCLUSIONS

This article has aimed to show that there are many benefits to using either IVR or IWR in a clinical study. Some of these benefits are easily quantifiable in terms of the cost savings that can be made, such as savings in trial supplies and limiting over-recruitment. While the decision to implement an IVR/IWR system can be justified on cost savings from this element alone, there are many more potential benefits, which are not always taken into account. It is arguable that many of these qualitative benefits far outweigh the direct cost savings that IVR/IWR can realise. ●

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