

discrepancy between the SOC required by the protocol compared to that practiced at many of the hospital-based sites selected for the study. Despite their prior agreement to participate in the study, some 73% were identified as non-aligned on this critical issue. This non-alignment was often identified as the result of resistance by reluctant participants in the complex clinical environment – pharmacy heads, corporate boards, department chairs, residents, etc – who, having not been sufficiently educated as to the merits of the study, were not owning it and/or were not compensated. It was determined that the PIs faced nearly impossible odds in reaching required enrollment levels.

To rectify the situation, steps were taken to improve communications between the sponsor and existing sites. This included an enriched communications programme and promotional campaign to raise the profile of the study within academic medical centres by revisiting those with ongoing potential – a significantly lower-cost option than recruiting additional sites. As a result of the intervention, US enrollment was increased by 11%.

Gaining momentum

Malcolm Gladwell's best-seller *The Tipping Point, How Little Things Can Make a Big Difference* presents the notion that new trends are created when ideas take hold and spread like wildfire. According to Gladwell, ideas or fashions spread quickly for various reasons, but mostly because lots of little changes can lead to big effects.

Clinical trial patient recruitment methods are experiencing lots of small changes too, as momentum builds towards a 'tipping point'. The days of viewing patient recruitment as an afterthought are numbered as the trend advances towards collaboration, information sharing and a sophisticated, proactive planning process.^{8,9} Although change is successfully underway, turning this approach into an industry-wide standard practice will take some doing. It will mean implementing process changes so recruitment and enrollment issues are routinely handled upfront in an organised, systematic fashion, while still allowing the unique features of individual trials to be recognised.

IPM offers a best-practices approach to improving the many steps that comprise patient recruitment – protocol development, budgeting, site selection, media campaign,

education and training – that will ultimately tip the scale towards more predictable and effective recruitment and enrollment practices.

Frank S Kilpatrick is president and Jeanne Floyd vice-president/chief operating officer of Healthcare Communications Group. Susanne I Steinberg is director, sexual health, with Pfizer Development. The authors acknowledge the contribution of Ann Neuner of Medical deDescriptions, and of Cindy Gianelli and Mykel Lefkowitz from the Healthcare Communications Group.

References

1. 'Public awareness of clinical trials increases: new survey suggests those conducting trials are doing a better job of informing potential participants of opportunities', *Harris Interactive*, 4(10), June 11, 2004.
 2. 'Most physicians do not participate in

clinical trials because of lack of opportunity, time, personnel support and resources', *Harris Interactive*, 4(9), June 10, 2004.

3. CenterWatch, 2001.
 4. J Maloy et al. 'Technology', ACRP White Paper, *The Monitor*, 18-23, Summer 2003.
 5. P Bleicher. 'Clinical trial technology, at the inflection point', *Bionline*, 1(5): 163-168, Nov 2003.
 6. P Bleicher. 'Managing the information supply chain in clinical trials', *European Pharmaceutical Contractor*, 42-49, Summer 2003.
 7. M Gladwell. 'The tipping point, how little things can make a big difference', Back Bay Books, 2000.
 8. DL Anderson. 'A guide to patient recruitment and retention', *Thomson CenterWatch*, 6, 2004.
 9. J King. '10 ways to faster and easier patient recruitment', *R&D Directions*, 10(4):34-46, April 2004.

Questions faced by empowered patient-enrollment teams

- Can the clinical trial team become comfortable with the complex and dynamic nature of the subject enrollment challenge – including understanding its resource demands, need for interactivity based on daily-changing outcomes and the creative, non-linear nature of its solution?
- On what basis are the stated recruitment goals and timelines feasible?
- From the perspective of the sponsor's development pipeline and corporate strategies, is this trial truly pivotal, and if so, what investment in subject recruitment can be made to ensure its on-time completion?
- What historical documentation exists to confirm that the best enrolling sites have been selected?
- If enrollment outcomes are not as expected, is there an efficient exit strategy to terminate untenable site situations?
- By what recruitment performance standards will outsourced providers, ie CROs, patient recruitment companies, etc, be selected and evaluated?
- Does the recruitment process include a high degree of interaction with investigative sites by providing rigorous, real-time tracking of investments and continuous measurement of success and reallocation of resources as the project unfolds, versus waiting until project rescue?

Proactive planning at Pfizer

In 2003, Pfizer launched the Clinical Trial Recruitment Services (CTRS) group, a centralised, global patient recruitment resource for the company that operates from the premise that patient recruitment is about much more than recruiting patients for individual studies.

"We are working toward making patient recruitment a standardised business process with defined best practices and a consistent look and feel across the company", says Pfizer's Peter DiBiasi.

CTRS believes that successful patient recruitment requires early consideration at the programme level, where 30-40 studies may be in various stages of development. Because Pfizer is interested in building relationships with investigative sites, the company may move toward discussions with sites of interest to discuss the entire package of studies as a way to strategise about recruitment, promote training, and encourage long-term commitments.

In keeping with the company's proactive approach to patient recruitment, Pfizer has adopted a metric whereby the recruitment plan needs to be adopted and established ten weeks prior to the projected first subject's first visit.



Trial recruitment reassessed

Patient enrollment for clinical trials is coming of age, say Frank S Kilpatrick, Jeanne Floyd and Susanne I Steinberg. Recruiters are more and more likely to carry out detailed planning in the early stages of protocol development and select principal investigators according to their track records

There is a growing awareness among pharmaceutical companies that adopting a proactive patient recruitment process can significantly reduce delays in Phase II, III and IV clinical trials. But to be effective, recruitment planning and execution needs to be established as a core clinical development process, requiring a fundamental shift in both culture and procedure so that this expertise ranks alongside purposeful protocol design and objective data management as an essential element of 'good study practice'.

Study enrollment can be problematic for a variety of reasons – low subject and referral awareness,^{1,2} demanding protocol inclusion/

exclusion criteria, the plethora of competitive studies seeking the same patient population, and concern over experimental drug safety. In addition to these very real challenges, there are also deeper systemic issues in some organisations, often rooted in siloed structures that relegate the vital activity of subject enrollment to 'reactive' mode. As a result, enrollment can miss out on the upfront resources and senior level support that is needed if scheduled trial timelines are to be met.

With study sites traditionally expected to take responsibility for timely enrollment, juxtaposed against the dismal statistic that 80%

of research trials are not completed on time,³ a more effective approach is the interactive process model (IPM) which is increasingly being implemented by progressive drug developers such as Pfizer and Sanofi-Aventis to assure consistent and timely enrollment outcomes.

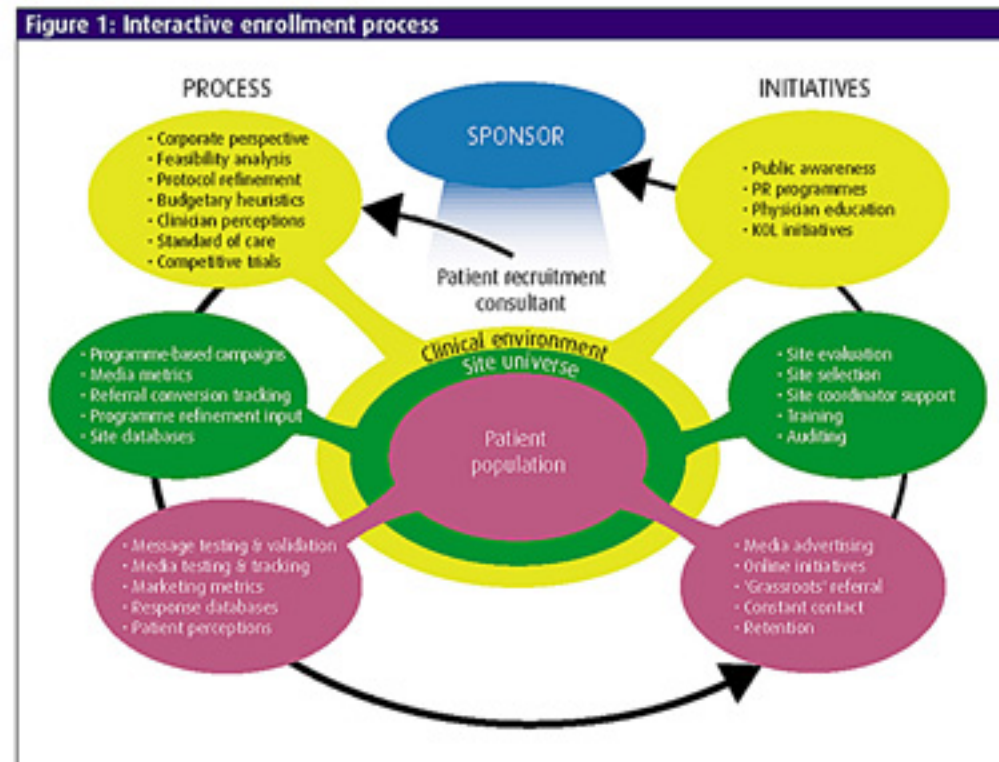
Model overview

IPM is not a magic bullet offering a single solution to study-specific patient recruitment problems. Instead, it recognises the need for a broad and externally-focused perspective on the complex dynamics of trial enrollment. At the same time, it integrates the roles and responsibilities of all clinical team members and partners, so that patient enrollment challenges are seen by the stakeholders as factors on which they can have some impact and for which they have accountability.

IPM employs 'processes' and 'initiatives' (See Figure 1), putting these into action using a three-stage process of 'diagnose, develop and deliver' to build a system of effective study enrollment that can be applied across multiple therapeutic areas (see Figure 2). These processes begin by seeking exhaustive understanding of the trial(s)' position within its larger environment, through:

- Evaluation of disease prevalence in the subject population, including geographical, demographical, psychographical indices and/or seasonal drivers.

- Assessment of the alternatives that prospective trial patients may



consider in deciding whether to participate.

- Review of qualitative and quantitative research on what institutional review board (IRB)/ethics board-acceptable messages will be best received by patient, clinicians, caregivers and referral sources.
- Ranking of competitive trials based on the principal investigator's (PI) perception of scientific value, grant amount, global vs domestic execution, scale, protocol difficulty, and research referral network contribution.
- Thorough assessment of sites to identify which have historically proven their ability to screen and randomise patients to similar protocols and to determine the needs of new sites in reaching top performance.

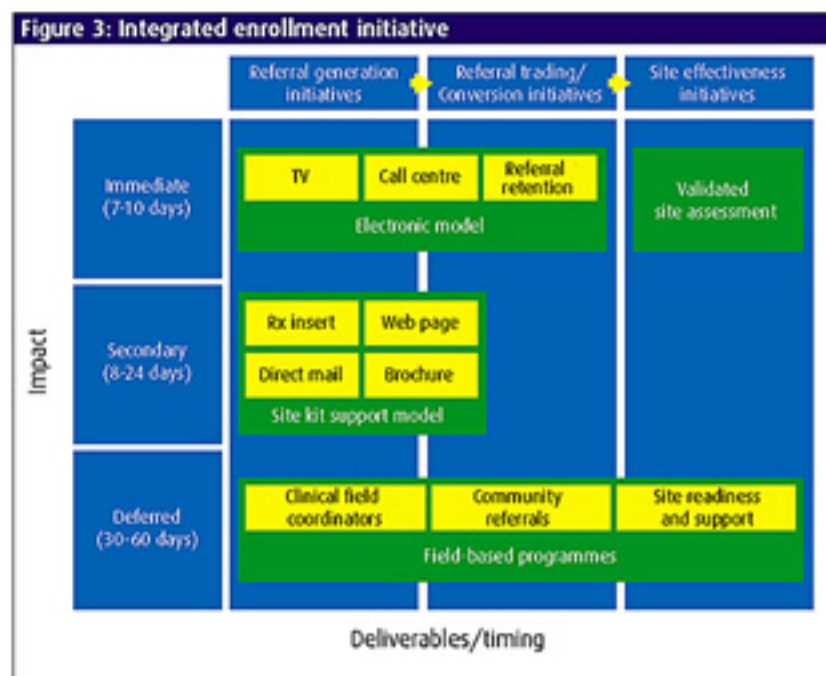
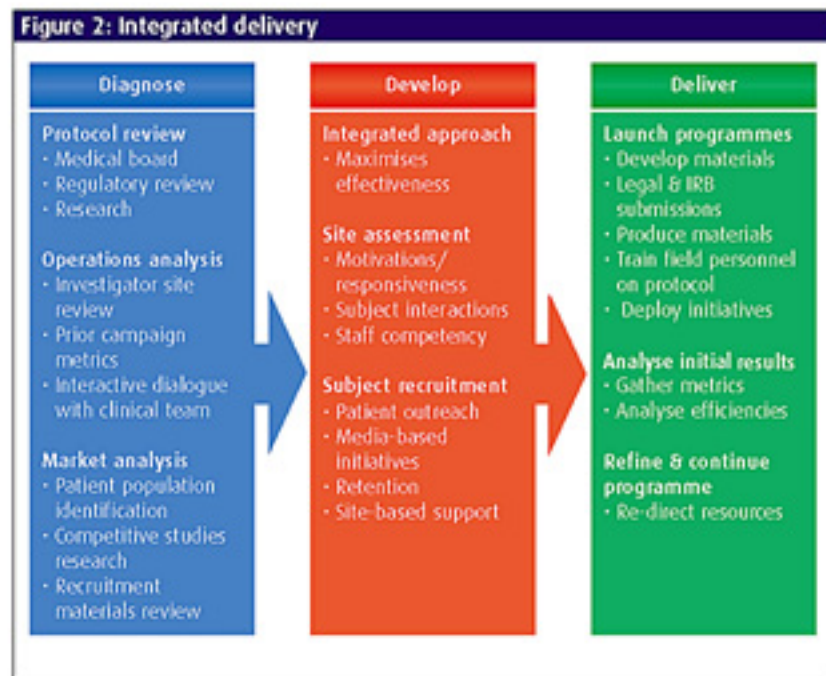
This careful analysis relies heavily on an interactive relationship between all trial managers, internal cross-functional teams and external consultants, including the contract research organisation (CRO). The process requires a high degree of data-sharing so that stakeholders can be ranked according to their past ability to evaluate protocol feasibility, identify the best-matched investigative sites for the study (from an enrollment perspective), seek out and resolve process problems, and analyse competition for the study.

The resulting recruitment strategy is developed to be most responsive in reaching potential subjects with the greatest interest in participation. The campaign's 'integrated components' may include patient or site education; a referral contact campaign to prospective subjects through caregivers, institutions or family members; and/or a media campaign tied to patient-direct motivation for participation (see Figure 3). From there, the model proposes real-time analysis of outcomes by continuously refining the approach and redirecting resources to deliver continuous improvements in trial enrollment.

Shared success

The interactive relationship between sponsor and support team(s) as empowered taskforces is essential, as they are jointly responsible for establishing and reaching consensus-based goals, ideally from the broader perspective of the subject drug's overall position within the sponsor's portfolio.

In order to reach consensus-based goals, teams need to ask tough questions about the study, including how realistic the timeline is for its completion, how the best enrolling sites will be selected, and what the exit strategy is



for non-performing sites (see Box on page 4). They must allocate and track financial resources for recruitment initiatives. And, according to Dr Frederick Bode, a clinical scientist at Roche, it is critical that teams remain in frequent contact with investigative sites during the trial. "It's much more of an interactive, consultative process. To believe that a study, once it starts, is on autopilot is a definite mistake," he says.

Adoption process

Because IPM impacts on every aspect of subject recruitment and seeks to establish

early and ongoing communication among all players – sponsor, recruitment consultant, CRO, clinical investigators, and, most importantly, study volunteers – it represents a radical departure from fragmented, but historically-accepted, patient recruitment processes. Radical process changes are challenging to implement in their entirety for all but the most adventurous early adopters,⁴ so incremental implementation may be the preferred choice for some.⁴

Applying this logic to IPM, sponsors might aim to improve recruitment processes through a sequence of improvements in key functions.

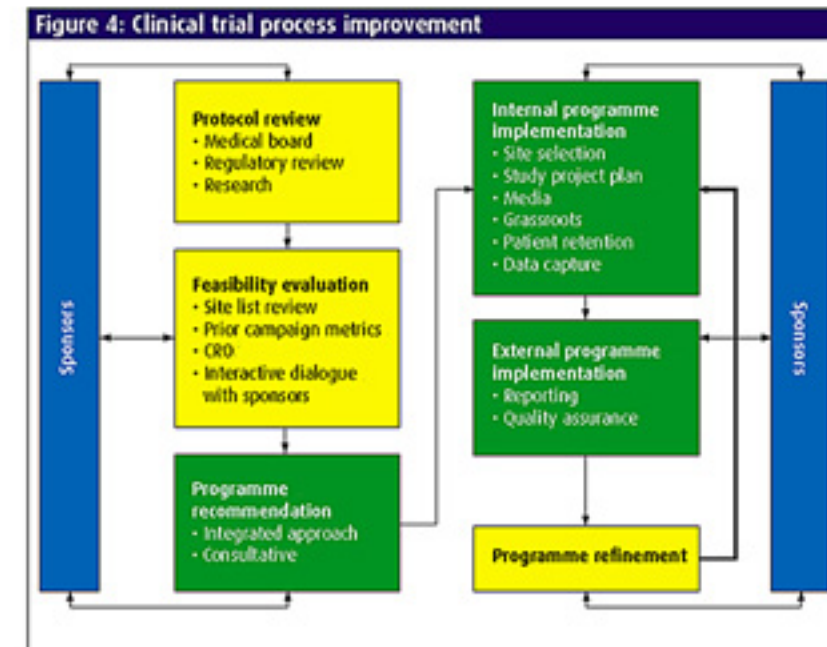
Figure 4 illustrates some of the processes involved, including enrollment-focused protocol development and site selection.

New protocols

To deliver real-world enrollment success in accordance with scientific objectives, IPM recommends that study protocols be written with an eye towards efficient subject

Past performance

Another key focus is on improving the site selection process so that PIs are selected based on their track record of enrolling subjects for similar trials, as well as their ability to deliver clean clinical data. But it cannot stop there. Predictions for enrolling the desired number of subjects from investigators' internal databases often drop



recruitability and acceptance by ethics committees. To facilitate this process, it is wise for the protocol to be reviewed by experienced consultants who can comment on the feasibility of enrollment as well as the likelihood of acceptance by ethics committees.

Detailed planning in the early stages of protocol development is key. Peter DiBiao, of Pfizer's Clinical Trial Recruitment Services (CTRS) says, "The biggest shift in recent years is that there is a better appreciation of early planning at the protocol level for the required elements of recruitment planning."

Javier Szwarcberg, medical product leader at Sanofi-Aventis has similar views. "Very early in the development of the protocol, we think about the inclusion/exclusion criteria and how they will impact our ability to recruit. Once inclusion/exclusion criteria are drafted, we tend to examine them to assess if they will be easy for patients or if they will make the trial attractive to physicians," he says. "If we don't work hard to simplify the inclusion/exclusion criteria, it will be difficult to meet our timelines."

significantly as more study details become available. As a result, a more rigorous quantitative process often needs to be initiated if the enrollment deadline is to have a reasonable chance of being met. The IPM method reviews patient population segments from each site. They are measured, cross-tabulated with the requirements of the protocol and then coefficients for competitive studies and site administrative efficiency are applied to this output. The result is an index that indicates expected yield by site.

Compare the likely outcomes of these proactive steps to what is obtained with a hands-off process, in which the sponsor accepts the site's enrollment estimate without further analysis. Typically, this 'reactive' approach leads to recruitment falling behind schedule so that rescue interventions are needed. Today, this is giving way to an early needs assessment process whereby the sponsor and recruitment consultant confer in-depth with each PI during the selection process to verify the site's recruitment forecasts and to discuss the type of recruitment support it may require.

According to DiBiao, Pfizer has embraced the collaborative approach and views the patient recruitment function as a shared responsibility between sponsor and sites. It begins with the sponsor laying the groundwork upfront. "Sponsors need to do a better job of identifying the types of sites that they want to work with and then help the sites understand what the sponsor is looking for. Just trying to find out how many patients the site thinks it can enroll isn't good enough. Prior to site selection, we sit down with the site to understand its capacity to enroll and the goals of the study. This is part of our plan to do a much more robust job and a lot more due diligence at the front end. The greater the specificity of the questions we ask at the front end, the greater hopefully will be the pay-off at the back end," DiBiao says.

Realignment with protocol

Without upfront assessment of site motivation, confirmation of protocol understanding and acceptance by all stakeholders, enrollment may suffer dramatically and require intervention at the trial re-engineering level.

Consider the recent case of a major pharmaceutical sponsor conducting a pivotal international cardiovascular trial in which the US sites were underperforming in comparison to non-US counterparts. The sponsor selected a patient recruitment provider to achieve several objectives: to explore why US sites were behind in recruitment; to re-engage PIs who had previously been contracted for the trial but who subsequently withdrew their participation; and to rapidly add more US sites to increase the domestic percentage of the study's enrollment universe.

To address these challenges, the recruitment provider started by conducting a site assessment survey. Initially it included ten face-to-face interviews, but it was later extended to telephone canvassing the 45 additional sites that had originally expressed interest in the study but had later withdrawn their participation. Information was gathered on topics such as standard of care (SOC); subject, study staff and vendor challenges; the impact of competing studies; clinical motivation; and perception of the study's scientific promise – none of which, although critical to the success of the trial, had been studied previously in any detail.

The survey revealed a significant