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Accelerating Patient Recruitment in Clinical Trials



in-depth report from the SMi 2nd Annual Conference
held in London, 27–28 March 2006

by Dr Richard KH Wyse



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Accelerating Patient Recruitment in Clinical Trials

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Accelerating Patient Recruitment in Clinical Trials:

*in-depth report from the SMI
2nd Annual Conference*

Dr Richard KH Wyse

Executive summary

All pharmaceutical companies want to find cost savings. The industry conducts large numbers of clinical trials each year. Regulatory requirements, as well as other scientific and marketing needs, mean that many of these studies continue to need ever-larger numbers of patients. The cost of running trials is now approaching 30% of pharmaceutical companies' entire drug development budgets. However, 75% of patient studies fail to make their timelines, often causing expensive delays in regulatory approval and market launch. Slow patient recruitment represents a major reason for this, as does poor retention of patients within ongoing clinical trials. Close scrutiny of, and adherence to, a variety of factors that promote timely patient recruitment, however, mean that pharmaceutical companies have tangible mechanisms that can substantially enhance their profitability. The 2nd Annual Conference on Accelerating Patient Recruitment in Clinical Trials, held in London 27–28 March 2006, organised by SMI, discussed a diverse range of approaches now used by some companies and their Contract Research Organisations to adhere to timelines, to shorten them, and to try to identify recently evolving best practices.

This *Conference Insights* review provides analysis of the pertinent issues raised in selected presentations made at this event, discussing proven strategies to maximise patient recruitment, tools to assist the process, investigator-site selection and public perceptions of clinical trials. It makes clear why the old method of opportunism in patient recruitment is not effective, and looks at why companies are starting to abandon expensive advertising campaigns in favour of evidence-based patient recruitment strategies.

From a business point of view, optimising patient recruitment and retention, with the aim of getting new products on the market as soon as possible, now represents an important, achievable goal for all pharmaceutical companies.

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2nd Annual Conference on Accelerating Patient Recruitment in Clinical Trials – Programme

Organised by SMI, London, 27–28 March 2006

Day one

Chairperson:

John Needham, *Chief Operating Officer, Patient Recruitment Strategy, LLC, USA*

KEYNOTE ADDRESS: ACCELERATING PATIENT RECRUITMENT

The Eisai standpoint

Karen Foley, *Senior Director, Clinical Operations, Eisai Global Clinical Development, Eisai*

PUBLIC PERCEPTIONS OF CLINICAL RESEARCH STUDIES: A global survey conducted in 2005

Rowena Dickerson, *Associate Director, Fast4wD Ogilvy*

MASLOW'S HIERARCHY OF NEEDS AND CLINICAL TRIAL PARTICIPATION: Assessing, understanding and addressing the needs of potential study participants and their families

John Needham, *Chief Operating Officer, Patient Recruitment Strategy, LLC*

ACCELERATING THE PATIENT RECRUITMENT PROCESS: The application of response technologies

Dr Simon Chapman, *Chairman, essentiapharm*

GETTING THE MESSAGE RIGHT: STRATEGIC AND TACTICAL APPLICATION OF MARKETING PRACTICES TO THE CLINICAL TRIAL ARENA:

Global case studies for accessing and retaining the right patients

Janet Jones, *Director, Patient Access & Retention, Kendle*
Kate Spencer, *Business Unit Director, Langland*

GLOBAL PATIENT RECRUITMENT: Practical considerations and case studies

Beth Harper, *Vice President, D. Anderson & Company*

OPERATIONAL AND LEGISLATIVE ASPECTS OF PAEDIATRIC RECRUITMENT FOR CLINICAL TRIALS: New regulations stimulating paediatric research

Dr Richard Tiner, *Medical Director, Association of the British Pharmaceutical Industry (ABPI)*

RETENTION OF PATIENTS IN CLINICAL TRIALS: How do you avoid patient drop-out?

Jim Kremidas, *Global Enrolment Optimisation, Eli Lilly*

Day two

Chairperson:

Beth Harper, *Vice President, D. Anderson & Company, USA*

SITE SELECTION: Research site selection and evaluation

Dr Sue Tempest, *Site Implementation & Training Manager, Merck Research Laboratories*

INVESTIGATOR SITE NETWORKS IN CONTINENTAL EUROPE: Implementing a recruitment campaign focusing on Germany

Dr Hans-Detlev Stahl, *Chief Executive Officer, Clinpharm*

IMPLEMENTING AND DRIVING SUCCESS OF INTERNATIONAL PATIENT RECRUITMENT AND RETENTION STRATEGIES THROUGH THE CONVENTIONAL CLINICAL RESEARCH PROCESS AT THE INVESTIGATIVE SITE: The CRO perspective

Tom Ruane, *Director, Patient Recruitment, Quintiles*

COUNTRY STUDY MANAGERS: The Cornerstone for Successful Multinational Recruitment 2006 Survey – results and analysis

Jaime Cohen, *Enrolment Manager, BBK Worldwide*

THE ROLE OF THE REGULATOR: What did directives ever do for us?

Dr Malcolm Barratt-Johnson, *Medical Assessor, Clinical Trials Unit, Medicines & Healthcare products Regulatory Agency (MHRA)*

METHODS AND METRICS FOR PATIENT RECRUITMENT AGAINST PROTOCOL DESIGN: Recruitment success by design

Dr Alan Wade, *Director, Community Pharmaceutical Services (CPS) Research*

CANDIDATE QUALIFICATION AND MEASUREMENT OF CAMPAIGN PERFORMANCE METRICS: A technological approach

Dr Bill Byrom, *Product Strategy Director, ClinPhone Group Ltd*

RECRUITING ADULTS WITH NORMAL LIPID BUT ELEVATED CRP LEVELS: Budgetary implications on recruiting adults without disease and unknown CRP levels

Dr Ian Smith, *Medical Director, Synexus*

PATIENT RECRUITMENT BEST PRACTICES AMONG TOP PHARMACOS: The Wise Investments initiative

Donald Greene, *Vice President, Veritas Medicine*

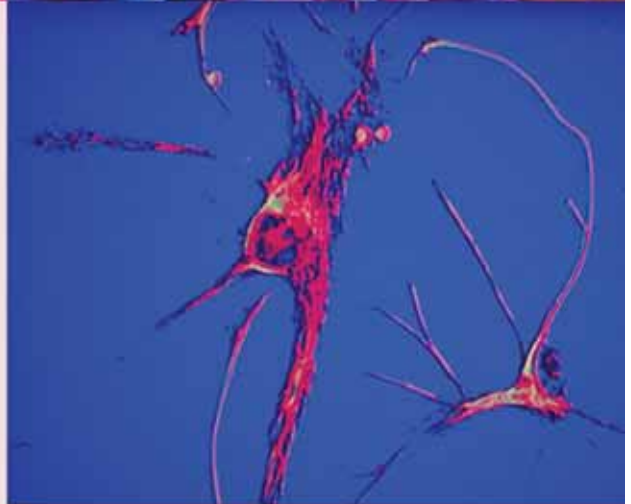
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SMi Group Ltd, Unit 122, Great Guildford Business Square, 30 Great Guildford Street, London, SE1 0HS
Tel: +44 (0) 20 7827 6000 Fax: +44 (0) 20 7827 6001 www.smi-online.co.uk

Introduction



The 2nd Annual Conference on Accelerating Patient Recruitment in Clinical Trials, held in London 27–28 March 2006 and organised by SMi, brought together speakers and delegates from a wide range of pharmaceutical and medical device companies and Contract Research Organisations (CROs). Many of the speakers enjoy direct responsibilities for ensuring patient studies are optimised within their companies, and that they run to budget and to agreed timelines. Over the course of the conference it emerged that, although speakers often shared similar patient recruitment problems, the approaches they take to address these issues now vary considerably between companies, as do their relative success rates. Some companies have replaced inefficient large advertising campaigns (that seldom produced sufficient patients anyway) with streamlined evidence-based patient recruitment methodologies that are adaptively agile to the particular requirements of each individual trial. Further, it became clear that, to assist both patient recruitment and investigator support and morale, 'best-practice' companies have been able to identify optimum managerial structures for handling their multinational clinical trials across large numbers of investigator sites across many countries. They have also been able to identify the factors that predispose to higher levels of patient recruitment and retention in different countries, and the most cost-effective solutions. Several companies shared how they benefit by the use of a range of support tools (patient databases, metrics and benchmarking, and cost-effectiveness analyses) to make better choices about their patient recruitment strategies (and their selection of investigator site where this impinges on rates of recruitment). Subsequently, some have now found out what works well and what doesn't. The audience seemed fascinated to learn by these experiences.

The issue of public and patient perceptions of clinical trials was at the forefront of many of the presentations, since a very high-profile incident during a drug trial, news of which immediately reached television and newspaper audiences globally, had occurred only days before in a nearby hospital. Everyone was aware that this crucially important new public image onslaught poignantly affects the livelihoods of almost all the speakers and delegates in the auditorium. This is because, as industry patient recruitment specialists, and as individuals, their future success depends on their own abilities to try to regain supportive perceptions of clinical trials within the general public. They are also aware that they now need to come up with the most effective reasoning for their patients to ensure they remain enrolled in existing trials, and to find the best ways to persuade patients to enrol in adequate numbers in all of their new prospective studies.

Dr Richard Wyse
July 2006

About the author

Formerly senior lecturer in paediatric cardiology at Great Ormond Street Hospital in London, Dr Richard Wyse now has joint commercial and academic careers. He is the author of over 100 medical and scientific papers, and pharmaceutical industry articles in journals. He has also written four industry books, and several independent evidence-based medicine reports in various therapeutic areas. Commercially, he has worked for a CRO as Director of European Health Economics, and as Medical Director for a US pharmaceutical IT company, and a medical device company. He has been involved in a wide variety of industry clinical trials and several other areas of drug development for many years. Academically, he is currently a visiting professor in Saudi Arabia and President-Elect of the Division of Genetics at the Royal Society of Medicine. He is on the editorial board of several journals.

Richard has spoken at many academic and international pharmaceutical and medical device conferences, and has chaired 25 of them. Notably, he was global chairman of a major cardiac patient database initiative that involved 2700 hospitals worldwide, speaking at national conferences in a large number of first- and third-world countries. In this capacity he reported a landmark paper on risk prediction and outcomes in more than 600,000 US patients.

Richard can be contacted at rkhwyse@yahoo.co.uk

Accelerating Patient Recruitment in Clinical Trials:

in-depth report from the SMI 2nd Annual Conference

Background

All pharmaceutical companies are eager to identify substantial cost savings. The industry conducts large numbers of clinical trials each year. Regulatory requirements, as well as other scientific and marketing needs, mean that many of these clinical trial studies continue to need ever-larger numbers of patients. The cost of running these studies is now approaching 30% of entire drug development budgets. However, 75% of patient studies fail to make their timelines, very often causing expensive delays in regulatory approval and market introduction of the product. Slow patient recruitment represents a major reason for this, as does poor retention of patients within ongoing clinical trials. The 2nd Annual Accelerating Patient Recruitment in Clinical Trials Conference discussed a diverse range of strategies and support tools currently used with increasing effectiveness by pharmaceutical companies and their CROs to increase their success at maximising patient recruitment levels, as well as adherence to budget and timelines.

Optimising both patient recruitment and retention, and thus getting new products on the market as soon as possible, represent twin goals for all pharmaceutical companies

Whilst this conference was positioned to be about accelerating patient recruitment in clinical trials, it also addressed the retention of patients once they have been recruited. Optimising both patient recruitment and retention, and thus getting new products on the market as soon as possible, represent important twin goals for all pharmaceutical companies as they seek to maximise return on their research and development (R&D) investment.

Many of the speakers at the conference enjoy direct responsibilities within their companies for organising and

optimising patient recruitment and retention. It became clear that achieving significant improvements requires a diversity of approaches. Speakers described their own experiences and identified those factors they considered were important for success. With common, shared goals there was inevitably some overlap among speakers, but critical success factors emerged when evaluating across the entire conference. The main themes that were addressed from many perspectives by several of the speakers were:

- the importance of influencing public and patient perceptions of clinical trials on global and local levels
- strategies for accelerating patient recruitment
- tools to achieve this (the use of patient databases, and use of metrics to track patient recruitment demographics, as well as financial and cost-effectiveness tools)
- site selection, site support and investigator-site networks
- strategies for increasing patient retention.

The importance of influencing public and patient perceptions of clinical trials on global and local levels

Proceedings began with the Chair, John Needham (LLC), introducing the notion of Maslow's theory of motivation – his 'hierarchy of needs'. Needham adapted this concept to show how these needs can be directly applied to issues of successful patient recruitment and retention. He emphasised why it is important to understand and actively respond to the fact that both patients and investigators are motivated by a series of needs. So as to maximise participation, retention and compliance, these needs must be addressed in a particular order (a hierarchy) until each need is satisfied. Using any higher-level motivator out of order would be ineffective and, once a need is satisfied, continuing to emphasise it is no longer useful as a motivator. These needs, applied to

Needs	For study patients	For investigator-site staff
Physiological	"I'm testing a new therapy"	"Is this within my capabilities?"
Safety	Better treatment; ethics approved	Earlier results known; better trained
Social	Special Group member; friendly site	Form part of a problem-solving team
Esteem	"I'm important"; gives recognition	Can publish results; gives recognition
Self-actualisation	For humanity's well being	Good that public's health is improved



Table 1. Maslow's 'hierarchy of needs' applied to issues of successful patient recruitment and retention in increasing order of importance.

issues of successful patient recruitment and retention in increasing order of importance, are outlined in Table 1.

According to Needham, dealing with individual needs in the correct consecutive order translates directly into a successful progressive mechanism for maximising the number of patients and investigators likely to agree to be recruited into a clinical trial. What's more, the approach helps ensure that patients remain within the trial for its full duration. These needs drive the views, motivations and concerns of prospective patients (Tables 2 and 3).

This theme was then taken up by Rowena Dickerson (Fast4wD Ogilvy) who presented the results of a 2005 survey on perceptions of clinical trials in France, Germany, Spain, Italy, the UK, Poland and India. The survey was conducted by Harris Interactive in collaboration with Fast4wD Ogilvy, Eli Lilly and Company and CISCRP among 2935 adults over the age of 18 years. The survey revealed substantially different findings across the geographical areas. Whereas there was generally a low level of participation in clinical research studies (USA 10%, Europe 6%, India 8%), there were large differences in patients' opportunities to participate (USA 15%, Europe 8%, India 14%), being lowest (5%) in Spain and Italy. It is particularly worth pointing out that those patients who had already participated in clinical trials in the USA (84%) and Europe (80%) said they would do so again.

Dickerson said that there was a general mistrust of pharmaceutical companies and that participants felt that they were guinea pigs being experimented upon in clinical trials. In particular, people in developing countries sense that they are being exploited.

Factor	Responders (%)
Possible side effects	58
Distance from investigation clinic	42
Required number of visits	30
Study duration	28
Free medication	24
Financial	15
All of the above	29
Other	9

Table 2. Factors most likely to affect an individual's participation in a clinical trial. Original data from a Thomson Centerwatch survey.

The message that drug response may differ in Asians, thus necessitating studies, is not getting across, and there is a public perception that more trials are being carried out for no substantial reason. This mistrust has potentially been exacerbated by the recent high-profile, Oscar winning film, 'The Constant Gardener' which portrayed shady deals involving tests on unsuspecting people with no ethics committee clearance. Dickerson said that this is clearly an inaccurate message, but the high profile of the film has meant that it has been heard by a global audience. She cited a previous Harris Interactive Healthcare News survey,¹ which showed that although 16% of US cancer patients were aware of clinical trial options, 75% of these patients had actually turned down the opportunity to participate. Reasons given included:

- Patients believed that the treatment they would receive would be inferior to standard care.
- Patients felt that they might get a placebo.
- Patients feared that they would be treated like 'guinea pigs'.
- Patients thought their insurance companies would not cover costs.

These points simply reinforce a negative perception of the pharmaceutical industry.

Such negativity was, argued Dickerson, in stark contrast to the quotation of Dr Larry Norton of the Memorial Sloan Kettering Cancer Center that "people who participate in clinical trials do better than those who don't", which represents a powerful counter-argument. Dickerson recommended that there is a need to improve the public perception of the pharmaceutical industry and to improve methods of communicating about clinical trials with the public. There is a need for clear communication about

Concern	Responders (%)
Flexible hours	54
Procedures not risky or invasive	43
Minimal risk of side effects	40
Volunteers not given a placebo	29
Easy to get to by public transport	27
Only requires a few visits	21

Table 3. Concerns most frequently expressed by study participants. Original data from a Thomson Centerwatch survey.

clinical trials in general as well as specific studies. There needs to be a public perception that pharmaceutical companies are being open and honest about results, both good and bad, and that the public can access registries listing studies and results – this is happening to some extent with Centerwatch, for example. There is also a benefit of linking corporate and clinical trial functions in pharmaceutical companies, for example, GSK’s advertising about bird flu research shows how research today is building for tomorrow’s needs.

In the search for improved therapies, Tom Ruane (Quintiles) suggested that patients could correctly be told they are stakeholders, and certainly not guinea pigs.

To add to the recent ‘Constant Gardener’ persona of industry-led clinical trials, just a few days before this conference a disaster occurred that will have global repercussions on patient recruitment for clinical trials. Undergoing a first-to-human study at Northwick Park Hospital (London), all six volunteers receiving a new drug immediately experienced an extremely severe, life-threatening immunological reaction and went into major organ failure. With 100% of the volunteers experiencing these adverse reactions, and given the severity of these effects, this is unique in the pharmaceutical industry in decades of performing such studies in tens of thousands of trial compounds. The incident understandably dominated the thoughts of many of the attendees, and also led to the amendment of several speaker presentations.

Conflicting reports among delegates and speakers (most of whose livelihoods depend on recruiting new patients) were that phase I trials might have to be abandoned altogether since no-one would subsequently be prepared to be the first ever human recipient. There was a converse acknowledgement that the huge publicity surrounding this disaster had made many millions realise how much money could be made as a clinical trial volunteer, leading to a surprising increase in interest by the general public in participating.

newspaper	Comment
<i>The Guardian</i>	‘Six men in intensive care after drug trial goes wrong’
<i>The Times</i>	‘Drug trial ignored guideline on safety’ “I walked in and nearly fainted, he was like elephant man, all puffed up and weird. The doctors say he needs a miracle”
<i>The Sun</i>	‘Horror of men fighting for life as drug trial ends in disaster’ “We saw human guinea pigs explode” “Human guinea pigs collapse writhing in agony after getting trial injections of new drug”
<i>Daily Star</i>	‘Drug test disaster: six fight for life in head swell terror’

Table 4. UK newspaper comments on the recent clinical trial tragedy.

This very recent trend is perhaps even more surprising given the press reports at the time. That the story broke on CNN on the same day that it broke in the UK press demonstrates the significance of the tragedy as a global message. The UK press reports at the time were interesting and varied: whereas *The Guardian* presented an unsensationalist account, other newspapers were less restrained, as highlighted by Dickerson (Table 4).

So what will be the long-term repercussions within the community of this tragedy? In particular, how will it impact on future patients considering enrolling in a clinical trial? We know it was a phase I study and therefore did not actually involve patients. We also know that, while it was tragic, it was incredibly unlucky. But the message that is going out to millions is that this might happen to you if you choose to enrol in a drug trial.

Happily, all the patients survived, and the Medicines and Healthcare products Regulatory Agency (MHRA) has now issued a detailed interim report on the incident.²

The importance of the backdrop of public perceptions of industry-led clinical trials in patient recruitment and retention cannot be over-emphasised. While the public in general, and prospective patients in particular, continue to receive negative messages about such trials from the variety of high-profile sources outlined above, some industry professionals who must fight this trend have, nevertheless, been immensely resourceful in accelerating their own patient recruitment. How they do this forms the remainder of this report.

Strategies for accelerating patient recruitment

The general consensus at the conference was that pharmaceutical companies and CROs have begun to develop tangible, evidence-based approaches that substantially enhance their profitability. Close scrutiny of, and adherence to, a variety of factors aimed at promoting timely patient recruitment demonstrates that adherence to timelines cannot only be improved, it can even be shortened. Using their wide range of relevant experience, several speakers shared their evolving best practices on how they are currently achieving high levels of recruitment.

Diligently run feasibility studies are a vital factor for success, but, even with these essential data in place, recruitment still underperforms about 50% of the time

A consistent view was that, across the many trials they all conduct, everyone finds that some are far better than expected in terms of patient recruitment, and some

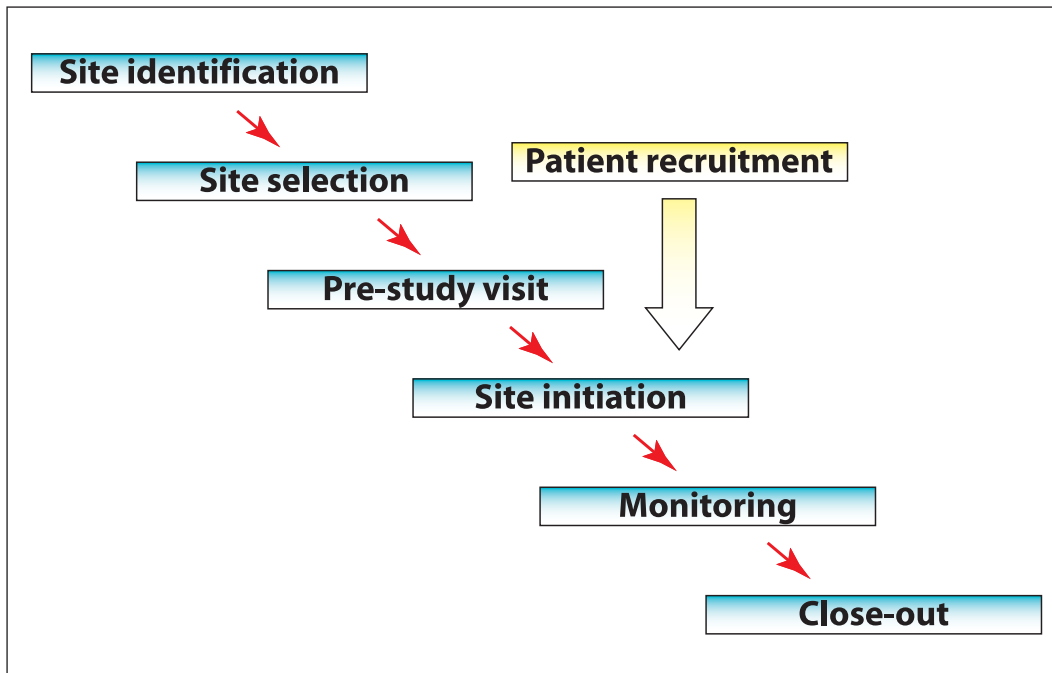


Fig. 1. The conventional approach to patient recruitment. Reproduced with permission from Ruane (Quintiles).

are worse; few proceed as predicted. One major new development this year was that nearly everyone appears to have learnt by experience that it is vital to plan early. Particular emphasis is being placed on carrying out an accurate feasibility study some 6–8 months before the first patient is screened, and also on designing substantial and robust contingency plans to improve recruitment if the trial underperforms. The consensus was that, even with the best prior feasibility studies, recruitment underperforms about 50% of the time. It was thought until recently that poor patient recruitment was therapeutic area-dependent. Now, with the emergence of more detail and experience, it has been found advantageous in all therapeutic areas for study teams to follow a set, rigorous process with regard to performing thorough feasibility studies, and thence to develop an appropriate recruitment strategy and robust contingency plans.

The basic, classic approach to patient recruitment was well described by Ruane (Fig. 1).

However, to achieve accelerated patient recruitment, the three presentations by Karen Foley (Eisai), Dr Simon Chapman (essentiapharm) and Beth Harper (D. Anderson & Company) showed the sequential importance of ensuring that a number of key components are given thorough commitment in terms of early, prior planning. Harper stressed the importance of maximising patient participation by providing solutions along the entire patient participation continuum:

- build awareness for the study
- identify and maximise all sources of patients
- enhance understanding of the study
- efficiently screen patients
- facilitate scheduling and ease burden of participation due to logistical issues

- aid study implementation by site personnel
- enhance patient compliance and retention.

She said that, for recruitment in different countries, one size does not fit all, so detailed prior analysis is required as to where the patients are, and what will attract them to take part in a clinical trial. Countries also differ greatly in their requirements for physician-to-patient letters, physician-to-physician letters, study awareness flyers and educational brochures, chart review and screening worksheets, and patient compliance aids.

Foley expanded on this theme, citing that, in order to accelerate patient recruitment to maximum achievable levels, there are a number of main areas on which companies need to focus (Table 5).

- Overall recruitment planning
- Feasibility studies
- Recruitment plans
- Contingency plans
- Strategies for recruitment
- Site selection and multicentre studies
- Site support and communication
- Identifying eligible patients
- Advertising, networks and referrals
- Motivating patients to participate
- Matching patients to investigator sites
- Recruitment tracking
- Maintaining patient and investigator commitment to study
- Recruitment strategies – the pitfalls and successes
- Ensuring patient and investigator compliance
- Managing time and cost

Table 5. The main individual areas on which companies need to focus to accelerate patient recruitment to achieve maximum levels.

- Plan well, and conduct the feasibility study several months before the planning of final site selection
- Prepare a feasibility questionnaire for all sites
- Select more countries and sites than are needed, and conduct feasibility in all
- Be aware of differences in country start-up times; these can be influenced by regulatory and ethics committee approvals, as well as drug importation requirements
- Ensure there are clear criteria for the patient population
- Ensure that specific study procedures are clear

Table 6. Crucial factors in conducting a good feasibility study. Reproduced with permission from Foley (Eisai).

Eisai's experience was that good planning, particularly taking into account all the diversity of the particular study (therapeutic area, patient availability, countries to be used etc.), can eliminate study delays and wasted investment, and thus reduce time to market and return on R&D investment. The opportunism, previously used in patient recruitment, she said, simply does not work, nor is it cost-effective.

Feasibility studies

Presenters were particularly stringent on the need for good feasibility studies and ensuring that these are conducted early. A poor feasibility study will often lead to poor patient recruitment later. The crucial factors in conducting a good feasibility study are given in Table 6.

The importance of feasibility studies is underlined by the fact that most CROs and some sponsors now have a separate feasibility group. Speakers concluded that feasibility questionnaires should specifically address the number of patients seen per month with the disease at each putative site that would fulfil the inclusion criteria, and the anticipated number that would have perceived problems with these inclusion criteria. Where these patients would be coming from should also be closely scrutinised, as should their anticipated payment requirements. It was widely felt that a greater number of sites and countries should be included in the feasibility study than previously thought necessary to complete the final clinical trial.

A poor feasibility study will often lead to poor patient recruitment later

In terms of the investigators, it was commonly felt that feasibility questionnaires should seek to determine the catchment area of each site, which patient databases are available for review and whether sites have already conducted studies in similar patient populations. If a site is currently conducting a study in a similar population, what are its recruitment statistics? Feasibility questionnaires should also cover issues such as whether there are any study-specific procedures that may affect

patient recruitment, and whether a particular site has adequate staff to perform these procedures. They will also seek to determine how long ethical committee submission and approval take in each geography under consideration and whether there are any specific requirements of that country that may pertain to the proposed trial.

Finally, it was agreed that feasibility studies should seek to determine how long each site agreement is anticipated to take (sometimes it can take a long time, especially in Spain), and whether there are any specific requirements or issues that must be taken into account in the months leading up to study commencement. Ideally, a feasibility study should include sensitivity studies on all its major aspects including predicted patient and investigator recruitment levels and costs.

Study-specific recruitment plans

Commonly, the results from detailed feasibility studies are then used to develop study-specific recruitment plans, which are used to form the core strategic structure of the final clinical trial. Plans differ depending on disease area, type of site and protocol requirements. The general consensus was that, while site selection is crucial, it is also important when selecting the countries in which studies are to be performed to consider back-up countries. Countries should be selected in which start-up times are appropriate for the study timelines. The choice of study population should be reviewed at this stage to ensure the population of patients exists and can be assessed, and that the correct investigators have been targeted. Normally, investigators would have been sent a statement of interest months earlier during the feasibility stage in an effort to get them to reserve resources for the upcoming study, but their situation may have changed.

Study-specific recruitment plans differ depending on many factors, including disease area, type of site and protocol requirements

Once these issues have been established, the procedures within the protocol should be reviewed and revised as appropriate. According to a range of speakers, the following questions should be asked:

- Is the protocol well designed?
- Is the design consistent with standards of care?
- Are the protocol procedures too demanding to get patients to take part and then comply?

Additionally, some clinical sites may find screening large numbers very difficult. External experts are typically recruited to advise on all these issues.

Overall recruitment plans

Once this is done then the overall recruitment plan is constructed. Once again, presenters covered common ground, citing factors such as the overall number of patients per country, together with the anticipated recruitment dynamics of each, based on their own approval process, as key aspects. At this point, the projected first patient in-date for each of these countries can be estimated. From this, the rapidity with which the other sites in each country will come on board can be anticipated, along with how quickly it is expected they can then recruit their patients.

The overall recruitment plan will include many factors including the overall number of patients per country and the anticipated recruitment dynamics of each country

If the first patient in-date is crucial for the company then known sites in known countries are chosen so that this key timeline is met while running set-up procedures in all other chosen sites in parallel. Also, most importantly, presenters spoke of the need to develop site-specific recruitment plans. This includes the number of sites per country, the number of patients per site, the first patient 'in' for each site, and the recruitment dynamics. According to Foley, it is very important to put these together for each site so the investigators know precisely what is expected of them. This key information is then used to track the progress of the study throughout its duration. Eisai's experience is to reduce their own expectations of the numbers of patients that all investigators say they anticipate recruiting by at least 50% to get their target for that site, even when dealing with experienced investigators. What helps greatly is individually telling each investigator the research question as it helps them recruit appropriately. Industry has hitherto been typically poor in explaining exactly what it is trying to achieve on a wider level.

Contingency plans

According to Eisai's model, strong, clearly defined, workable contingency plans should be developed at the same time as the feasibility study, and placed on standby to be introduced, rapidly, if patient recruitment falls below the expectations that have been drawn from the earlier feasibility studies. As has already been mentioned, less than 50% of studies closely follow the predictions given by the feasibility study (however diligently it was prepared); therefore, Eisai's experience is that contingency plans have to be implemented at some stage during the majority of their clinical trials.

Opening sites in additional countries may provide one way of increasing recruitment, but this possibility needs to be thought through at the outset within the feasibility/contingency framework. Some Eastern European countries are very fast at putting new site agreements in place, and therefore at starting studies; these may therefore be excellent for use as contingency back-up.

Strong, clearly defined, workable contingency plans should be developed and placed on standby to be introduced, rapidly, if patient recruitment falls below expectations

Opening additional sites in countries that are already part of the study may be another answer. Some sites can be specified from the outset as back-up. This is one area in which the feasibility studies feed directly into the contingency plan. The sites are told up-front that they are contingency back-up sites, and are paid for their ethics committee submissions. Many sites are prepared to do this, especially if they are paid, knowing there is a reasonable chance they will eventually be used, and knowing it increases their likelihood of becoming full sites in the future. There may also be sites that were identified during the earlier feasibility studies who are just finishing studies and who may now be available to come in as contingency to pick up shortfalls in patient recruitment.

Investigator-site selection and training

A number of speakers highlighted that the goal of good investigator-site selection is to deliver the requisite number of evaluable patients within the defined timeframe, and with maximum efficiency with regard to quality, resources and cost.

Important factors to take into consideration when selecting an investigator site include: prior experience of the site, literature it has produced, word of mouth recommendations, the key opinion leaders available and the level of interdepartmental liaison. Using an evidence-based approach, it is important to measure the performance of the site against internal and external benchmarking. As part of this process of implementing best industry practice, site training should cover protocol structure, good clinical practice, informed consent, adverse event reporting, data capture, site records and financial disclosure.

During the study the focus should be on clinical supplies, study procedure and drug accountability, followed by a review of adverse events laboratory data. Source data verification, data capture/data discrepancies and ethics review committee compliance should also be reviewed. After the study, the issue of planned versus

Patient databases	
Medstat 801 Crescent Center Drive, Suite 400, Franklin, TN 37067, USA www.medstat.com www.medstat.com/1pharma/ctr.asp	Medstat tracks 8 million lives analysed down to local area levels that can be used to help clinical trial administrators recruit patients and investigators more quickly and effectively. They also have a free white paper (<i>Using data and metrics to select investigators and recruit patients for clinical trials</i>) that is available from their main website
Convergence Clinical Trials 6130 Stoneridge Mall Road, Suite 115, Pleasanton, CA 94588, USA www.convergencect.com	Convergence Clinical Trials have patient recruitment feasibility assessment services that can be used in the rapid identification of patient populations for conducting clinical trials, and to link patient data at healthcare institutions with sponsor's needs for clinical trial planning
i3research www.i3research.com	i3research is part of a global company that includes the UnitedHealth Group (tracking 80 million lives) and Ingenix, which can be used to link costs, planning and analytical requirements to this massive patient database
General information	
Centerwatch www.centerwatch.org	Centerwatch provides information about mainly US clinical trials
EudraCT www.eudract.emea.eu.int/document.html	EudraCT provides information about European clinical trials

Table 7. Sources of information about clinical trials.

actual recruitment and patient retention are an important performance metrics by which to assess the quality of each site in terms of subsequent reuse.

Good investigator-site selection is crucial to successful patient recruitment

Foley emphasised that good investigator-site selection is crucial to successful patient recruitment. Proven good sites must be nurtured and, where a site is unknown, external experts are usually asked for their advice unless the therapeutic area is thoroughly known by the company through a wide portfolio of previous studies.

Sites that have a minimal turnover of investigator staff who are sufficiently well trained and well motivated, that produce clean data and have access to appropriate patient populations and are taking part in no competing studies are to be preferred.

Important considerations in investigator-site selection are accessibility of sites and their individual patient catchment areas. Parking for patients undergoing clinical trials is vital: they often ask very early on during attempts to recruit them whether they will be given convenient, free parking. Not all sites can accommodate this, but this is Maslow in action: it represents a fundamental need that must be addressed before most patients would even consider asking higher hierarchical questions about the trial that the investigators would consider far more important (see pages 7–8).

Similarly, many patients request flexible hours for convenience. Again, this is a low-level Maslow physiological-comfort core question that is often missed by companies, CROs and investigators who wonder why their patient recruitment has been poor. Network and patient advocacy groups are often extremely helpful in some of these areas of investigator-site selection.

The use of patient databases

Several speakers discussed how sponsors have increasingly been turning to large patient databases to source participants for their clinical trials. Three databases are particularly useful for this purpose and details are given in Table 7. Other general information on European and US clinical trials can also be found in this table.

Investigator-site support

In order to gain full investigator-site support for the trial, the importance of paying competitive rates, paying nurses to review for potential patients and providing spreadsheets to record data was widely noted. Equally, it is also important to ensure that retraining on the requirements of the specific clinical trial is adequate. Timelines of studies should be kept as short as possible; if studies are conducted quickly there is less chance of a change of new, incoming investigator staff requiring specific training and consequent study delays. For studies with long recruitment periods the option of holding interim investigator meetings to discuss protocol issues was suggested. Speakers also cited

the placement of country co-ordinators, whether from the sponsor or a CRO, as important. However, poorly recruiting sites must be visited by various members of staff in order to obtain different opinions on what are the issues and how best to address them. It was felt that it is often helpful to get successful recruiting sites to contact those less flourishing to share their tips and skills.

Advertising and referrals

Clearly, recruiting for patients remains a challenge for the industry. One common tool by which to achieve this is advertising. Sometimes this proves useful, other times there is no response at all. In all cases, it is important at the outset to check local requirements regarding advertising. Normally, advertising would be promoted regionally in those media known to give the best results. These could include:

- newspapers
- journals
- noticeboards
- radio
- television
- press releases
- posters in hospital waiting rooms
- the internet.

It is important to understand precisely the pattern of how potential patients typically learn about upcoming clinical trials in each country to be included in the study, since this varies widely across geographies. For example, data from Thomson Centerwatch reveal that whereas 75% of

patients in Europe learn about trials from their physician or from referrals, this percentage falls to 46% in the USA. In addition, 16% of patients in Europe learn about trials from a friend compared with 8% of patients in the USA. In contrast, patients in the USA are more likely to learn about trials through the media (35% versus 5% in Europe) and the internet (11% versus 0%).

Ruane discussed the Novartis PEAK (Patient's Expectations, Attitudes and Knowledge) programme conducted by Dr Mikhail Rojavin (Novartis). The programme found that 34% of patients learnt about the study from their physician, 21% from newspapers and 17% from the radio. Only 10% discovered the study through the internet, with 7% hearing from family or friends and a mere 3% from television. These ratios differ across different countries so it is important to ascertain what works near the chosen study site locations. Rojavin's team have recently published their most recent findings on the factors affecting recruitment (age, ethnicity and educational status, altruism, possibility of receiving professional care).³ Their findings demonstrate how recruitment can be enhanced by targeting these motivations in physician/patient communications, in the informed consent process and when advertising for study participants.

It is also important to understand, on a country-by-country basis, why patients choose not to enter a clinical trial. Ruane said the significant chance of receiving a placebo (and therefore inadequate therapy) was important to some, whereas other reasons were inadequate compensation, risk of side effects and inconvenient locations (see Tables 2 and 3, page 8). Figure 2, which details Quintiles' own research in this area, demonstrates some responses of patients declining to participate in clinical trials.

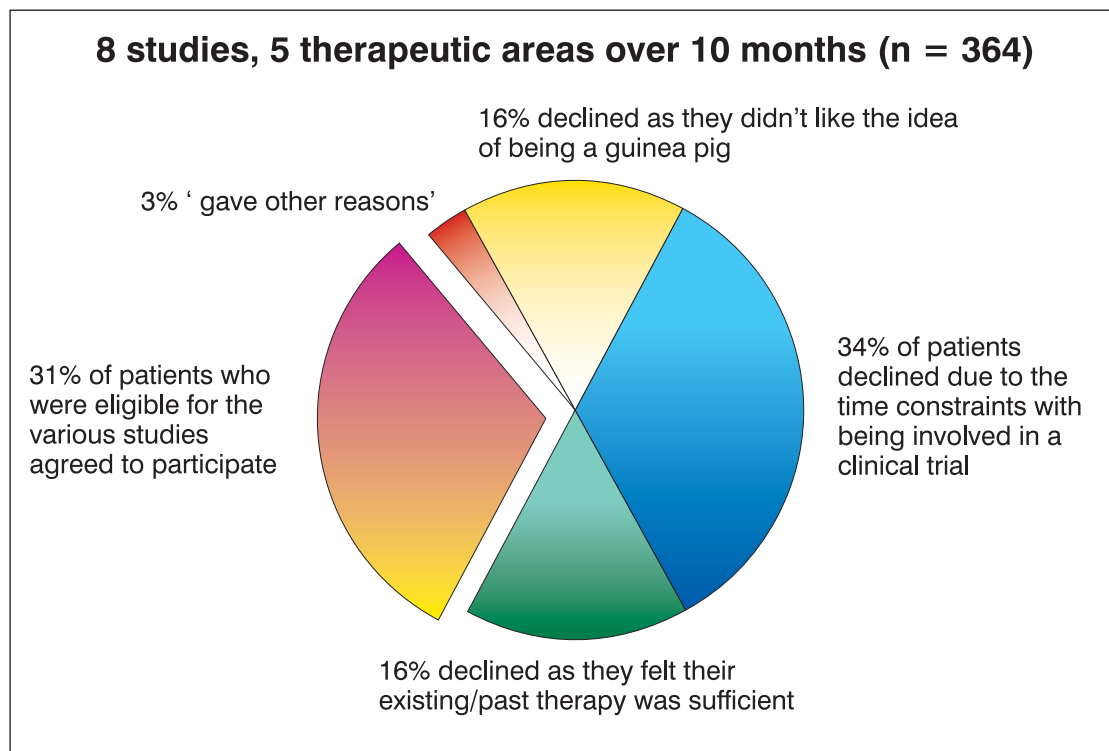


Fig. 2. Reasons patients give for declining participation in a clinical trial. Reproduced with permission from Ruane (Quintiles).

Another concern to address is that when doctors and nurses treat patients this is on a one-way basis. According to Ruane, they actually have limited skills when it comes to picking up the telephone in the opposite situation to invite patients to enrol in a clinical trial. They may meet their 'deliverable' number of telephone calls to their patients, but the recruitment rates can be abysmally poor. For this reason, Quintiles has often been compelled to bring investigator staff into their offices for specific training in this area.

The shorter the response time to a patient enquiry, the higher the recruitment rate

When patients answer media advertisements, Ruane feels it is vital to ensure that sufficient resources are in place to react to these prospective patient enquiries, either at the investigator site, or at the sponsor/CRO. This is because there is a close correlation between the rapidity of the response time to an enquiry by a patient and their subsequent successful recruitment into a clinical trial, with the percentage of patients willing to participate in a trial falling from 98% when recruitment is within 1 day of a patient enquiry to 80% by day 2, and 75% by day 3. No response for 5 days sees recruitment fall to just 51%, and it falls to just 30% when the response time is 9 days.⁴

Many companies are exploring the use of technology to effectively qualify candidates responding to advertising campaigns. One of these strategies is to deliver computerised clinical assessments using automated phone and web solutions: Interactive Voice Response (IVR) and Interactive Web Response (IWR). Dr Bill Byrom (ClinPhone Group Ltd) presented one example where a computerised assessment for depression (Hamilton Depression Rating Scale) was delivered using IVR for candidates responding to advertising and those referred via a clinic. Byrom discussed the use of these technologies, which have, he said, many proven advantages. In particular:

- when using a validated clinical assessment for screening
- for sensitive medical questionnaires
- for consistency of delivery of screening across many languages and countries
- when expecting a high call volume.

They are also useful when screening involves sophisticated branching, or for long screeners (when the use of online dynamic screeners works best). Using IVR/IWR has proved to be extremely cost-effective and, when used in combination with IVR/IWR randomisation and trial supply management, produces extremely clear patient recruitment campaign metrics for the sponsor.

These metrics include:

- number of candidate enquiries
- number of qualified candidates
- number of informed consents
- number of successfully screened candidates
- number of randomised participants
- number of evaluable participants
- number of treatment-completed participants
- cost per successfully screened candidate
- cost per randomised participant
- cost per qualified candidate.

Using IVR/IWR has proved to be extremely cost-effective, and produces extremely clear patient recruitment campaign metrics for the sponsor

Figure 3 shows the candidate response funnel following use of IVR for the recruitment of patients for a depression study. The qualification screener was effective in providing highly qualified patients to site (screening failure rate only 50% [Fig. 3]). ClinPhone find that IVR/IWR can be used with or without a call centre, and that their dynamics and structure actually enhance patient qualification through their multilingual channels. In his presentation looking at response technologies, Chapman (essentiapharm) confirmed that IVR was extremely cost-effective for his company, and that it was inexpensive to get prospective patients to talk to a machine, though the duration of the call should not be too long.

Recruitment tracking, metrics and inclusion/exclusion criteria

Once a study has started, it is important to track recruitment at each site, in each country and overall, and to benchmark against the recruitment plan that was compiled earlier. Typically, the first patient in-date for each of these sites and countries should be recorded, as well as recruitment dynamics, aspects of patient eligibility and numbers of patients identified versus numbers that have consented to participate. If sites are performing poorly then visit the site to identify the reasons for slippage. This could be due to a lack of time or resources, a need for additional training, advertising or referral systems not working, problems getting patients to consent because of aspects of the protocol or local procedures or facilities (such as parking and opening times) at the investigator site. Consider revising site recruitment targets if they now seem unrealistic, since

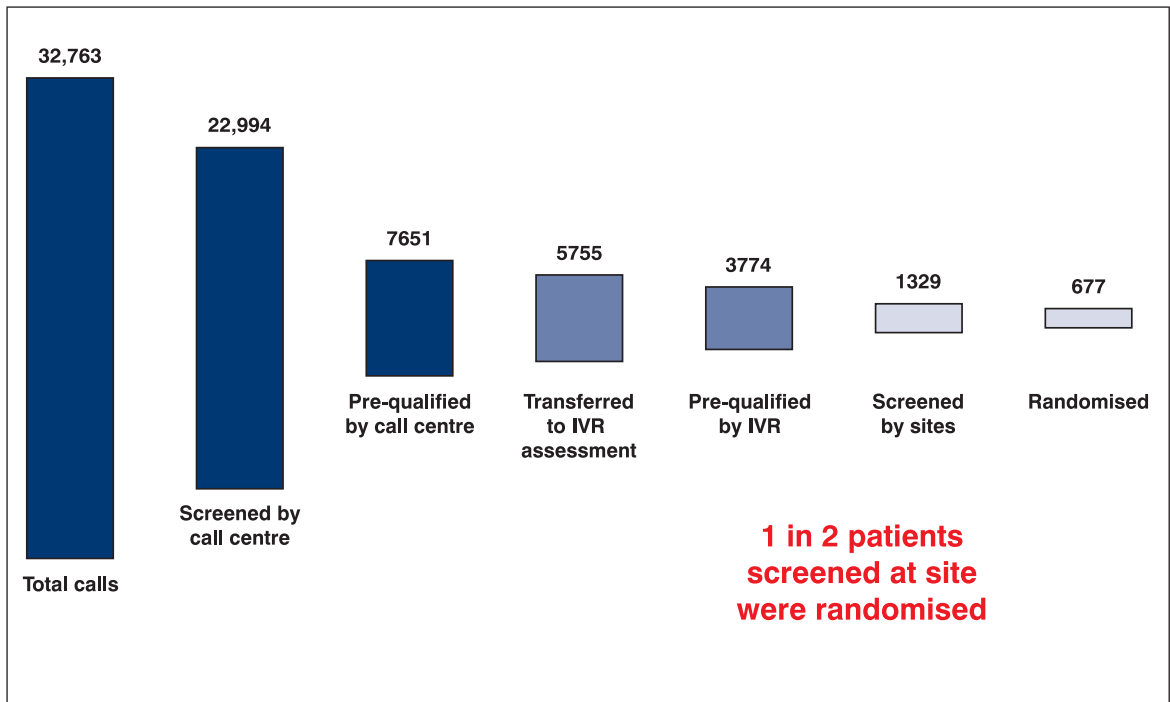


Fig. 3. Candidate response funnel following use of IVR for patient recruitment.⁵ Reproduced with permission from Byrom (ClinPhone).

more realistic targets will motivate staff who may need encouragement if they feel they are underperforming. Targets can be re-expanded later once staff are motivated. In the meantime, use other sites to bolster recruitment. Also, consider implementing revisions to the protocol, whether by adjustment of schedules or by amending the inclusion/exclusion criteria.

Dr Alan Wade (CPS Research) showed that CPS had increased recruitment by 53% and met timelines in an oral hypoglycaemic study simply by increasing the inclusion criterion for patient age; in this case, to above 70 years. Obviously, such transformations depend on the therapeutic area in question, but simple changes such as this may be allowed within the protocol.

Chapman showed that metrics were able to demonstrate precisely the relative benefits, and precise associated costs, of using a variety of response technologies (voice, IVR, webchat, email or SMS text messaging) during patient recruitment initiatives. Particularly effective was when a website took a patient through a self-screening questionnaire and flagged eligible topics (based on disease, geography and other demographics) to the response centre, from where nurses then called to complete the screening.

Performance metrics should be examined at site, country and global levels. This benchmarking allows a company to revisit historical studies and set targets for future studies. Site level metrics include the planned versus actual number of patients screened, the number of protocol violations, costs involved at each stage and the patient retention rate. Country level metrics include the number of enrolled participants per site, the number of sites meeting the targeted enrolment, the average screen failure ratio and the first and last patient screened. Global metrics include the number of patients enrolled in each

country, planned versus actual numbers, global first and last patient screened and the overall study costs.

The subject of electronic Case Record Forms (e-CRFs) was discussed by several speakers, who agreed that they could be good for quality assurance and long-term data storage. However, whereas Wade felt they could be excellent in certain circumstances he also noted that some patients were not always happy with them. He pointed out that a lengthy log-in process, or any other data entry delay either by a nurse or the patient, rapidly caused participants to become uninterested.

Site selection and investigator-site networks

Methods to enhance relationships with investigators, and to form investigator hubs and preferred providers, thereby to attempt to increase quality and efficiency, were also widely discussed at the conference.

Ruane shared Quintiles' 'Partner Site Model'. He said that by partnering with investigator sites the company was now able to share control of the deliverables. Their basic principle of working with a partner site is that these sites are different from conventional GP clinics, hospitals or clinics. It is Quintiles' own experience that it is unreasonable to expect a junior CRA to have the business acumen to partner with these sites and to get the best out of them. Therefore, their CRAs are asked to focus at the site level on monitoring, and to carry out the Good Clinical Practice (GCP) and International Conference on Harmonisation (ICH) procedures. However, for the actual business relationship at a management level, to get the best from both the CRO and the partner site, they find they need a separate dedicated internal team with more mature skills and business acumen.

From Quintiles' experience, partner sites offer them in-depth GP/clinician relationships and physician networks, a detailed knowledge of site capabilities and master contracts, and a long-term relationship based on mutual trust. As examples, Ruane cited partner sites in Germany, the UK, USA and China. For example, one of their partners in Berlin provides about 25,000 patients per year for their clinical trial programmes. The same partners also provide experts in all therapeutic areas, a dedicated study team and a separate recruitment department with a call centre facility. Ruane said that Quintiles are looking for a 20% improvement over conventional sites in terms of numbers of patients, better audit results and reductions in query rates. In fact, they track a variety of metrics: screen failure rates, enrolment per month and patient dropout. Quintiles' Partner Site Model has so far proved better with regard to contract days (44 days for partner versus 50 days for non-partners) and also for processing regulatory documents (72 days for partner versus 98 days for non-partners).

Dr Hans-Detlev Stahl (Clinpharm) discussed the use of investigator hub sites for clinical trials. A unique feature of this initiative is that the investigator hub sites he described are fully owned by Clinpharm, who describe themselves not as a CRO, but as clinical investigators. They do not compete with CROs, rather they partner with both them and pharmaceutical companies in order to conduct clinical trials. It is an interesting concept that is likely to grow in future years as other groups of investigators choose to go down a similar route. Clinpharm find that this approach provides a single point of contact for the sponsor. Moreover, it means that they can provide a large number of individual sites under their central management.

Clinpharm employs full-time clinical investigators and study nurses who do nothing else but clinical trials, and they have full control over which studies to accept. Advantages are that their initiative represents a one-stop shop for CROs and pharmaceutical companies. The centralised system they have developed (13 centres in

five countries) means they have been able to assemble large patient groups (in total, 60,000 by the end of 2006), which they find massively decreases recruitment costs per patient. Centralised documentation management (FDA, EMEA, EC) means that documentation is typically available within days, and contracts with sponsors can usually be signed very rapidly, normally within 2 weeks. They are aiming for 25 sites in 11 European countries by 2008, and believe this will offer sponsors industry best practice in terms of accelerated execution of the highest-quality clinical trials.

Dr Ian Smith (Synexus) said that investigator hub sites that are dedicated to proactive patient recruitment and retention are the only answer for large-scale studies, particularly with quantitative inclusion criteria. Synexus owns its own investigator sites and employs all the staff, including the investigators. Using these hubs, it is able to recruit high volumes of patients at some of the lowest industry costs, underlining the benefits of using a large organisation with high patient throughput. By conducting studies at its own sites it achieves savings by proactively recruiting patients into its clinical trials, and by closely managing patients throughout the total study life.

In terms of proactive recruitment, Synexus has access to 2 million people through its GP network, and 250,000 through its own database. Consequently, using this hub-based approach it has achieved 10–15 times as many patients attending its sites as would be expected over a similar time period in a traditional investigator-site setting. In turn, this high-volume throughput leads to huge savings per patient, and the incremental costs of choosing to add more patients later are exceptionally low (Fig. 4).

Strategies for increasing patient retention

The issue of patient retention remains as important as that of patient recruitment for the industry. The questions

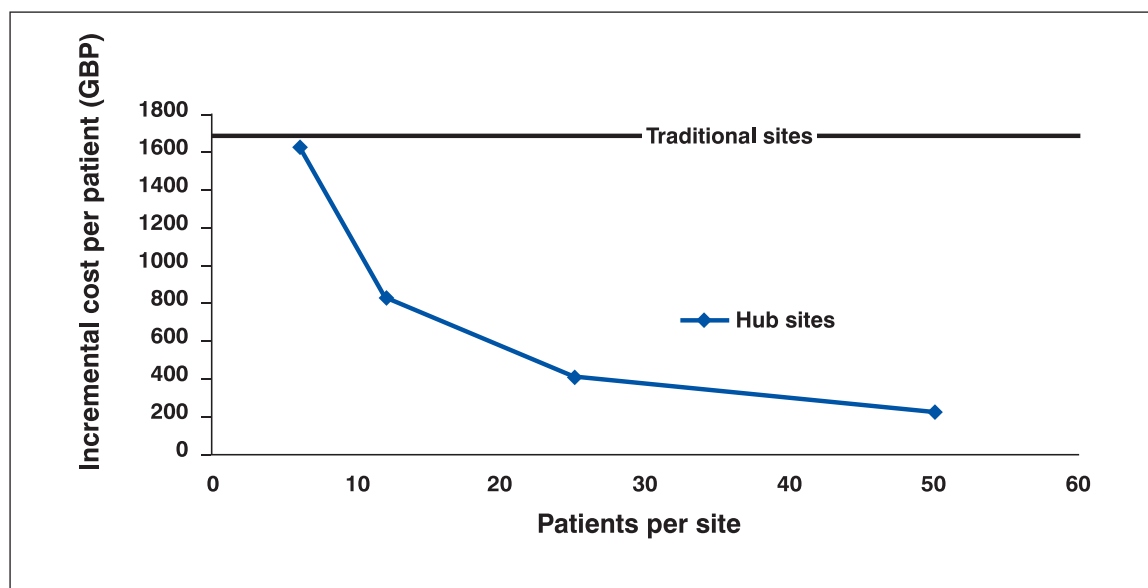


Fig. 4. Incremental cost per patient using an investigator hub site. Reproduced with permission from Smith (Synexus).

are, why do patients drop out of clinical trials, and how can this be minimised? A number of reasons for poor patient retention within trials were highlighted during the conference and are listed in Table 8.

The issue of patient retention remains as important as that of patient recruitment for the industry

Many presenters tackled the challenges of patient retention. Ruane said that retaining patients in most studies was vital. To achieve retention, Quintiles conduct retention campaigns. They use a retention toolbox (Fig. 5), which includes health promotion, lunch and learn meetings, and spa treatments for patients if they reach a certain point in their clinical study (this must always be appropriate to the patient’s disease). They ask investigator sites what is important to their patients. Basically, they use whatever the local ethics committee might allow, including areas of gifts and increased reimbursement.

In trying to improve patient retention, Jim Kremidas (Eli Lilly) took the view that successful patient retention starts with awareness (Fig. 6). He felt that although we are still in the paradigm of the blockbuster, biomarkers and genetics are becoming increasingly more important. Kremidas felt the future demanded a more focused patient recruitment and retention approach with a strong focus on the individual. This, he said, is achieved through better targeting of the messages given to patients. Patients show much better compliance and retention if they feel the messages are targeted precisely to their own patient subgroup since this gives them a far more compelling reason to stay in the study.

Kremidas advocates treating clinical trial patients as customers, not subjects, since they are giving their time to assist the study. To maintain and improve patient

- Perceived lack of efficacy
- Patients believe they are on placebo
- Adverse events
- Study-related factors
- Frequency of visits too intense
- Visits too infrequent
- Specific study procedures
- Bad publicity regarding clinical trials
- Social factors
- They are feeling better
- Wish to become pregnant
- A wish to take disallowed concomitant medications

Table 8. Reasons given by patients for leaving a trial.

retention, Eli Lilly sets up patient healthcare clubs, and sends out appointment reminders, emails and regular newsletters. They also encourage investigator sites to conduct fun celebration events and have face-to-face meetings with enrolled patients.

Byrom confirmed that ClinPhone uses SMS compliance reminders, sometimes combined with outbound IVR/SMS and/or email. They find these technology approaches have been valuable in improving compliance and persistence, and said they feel that integrated IVR/SMS/email systems may offer a practical approach to enhancing patient retention in clinical trials. Crucially, they believe patients find it perfectly acceptable when they use these technologies.

Conclusions

This year’s Accelerating Patient Recruitment in Clinical Trials Conference was an informative review of how companies are finding imaginative and evidence-

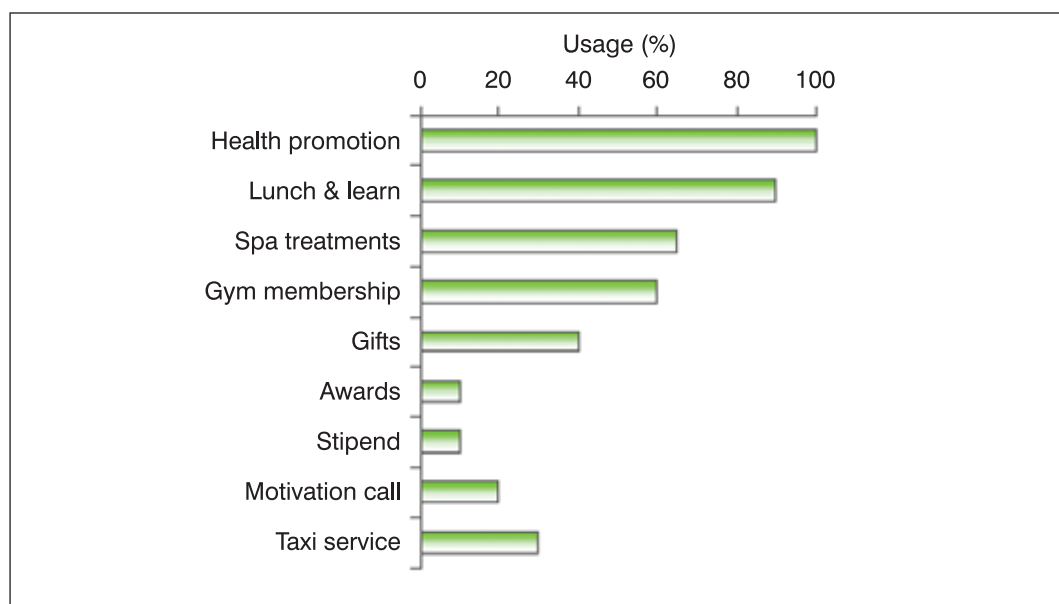


Fig. 5. The Quintiles patient retention toolbox. Adapted with permission from Ruane (Quintiles).

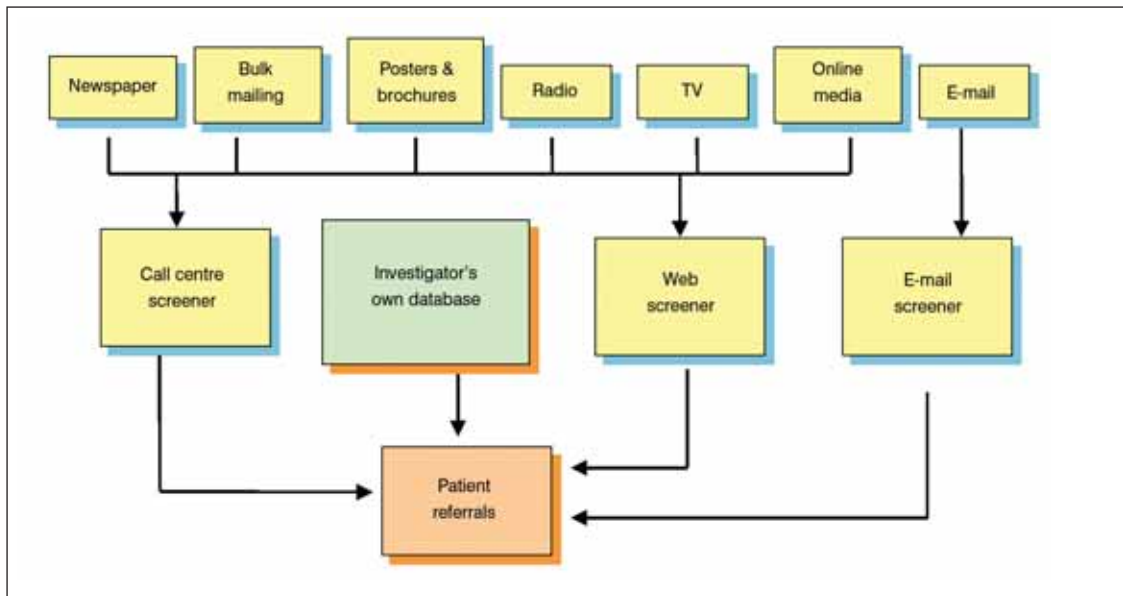


Fig. 6. Patient retention begins with awareness communications (study-specific). Reproduced with permission from Kremidas (Eli Lilly).

based ways to recruit and retain patients in the face of a progressively more difficult competitive and public image environment. Various new themes emerged as companies strive to define how best to conduct all facets of recruitment and retention. Industry best practice has clearly become 'plan well ahead' and 'do feasibility studies early'. A poor feasibility study is often associated with poor recruitment later. They now plan months before site selection and patient recruitment begins. They develop a robust contingency plan that can be rapidly brought into place if recruitment does not meet their expectations. They understand, and are proactive about, what motivates both patients and investigators to agree to be involved with a clinical trial; they realise this is on the critical path to success.

The power of developing centralised investigator hubs and of using technology-based techniques in providing powerful, cost-effective ways of accelerating patient recruitment was well described by the originators of these approaches. Using metrics, such as informative patient databases, benchmarking all main facets of the patient recruitment and retention phases, and integrating good financial and cost-effectiveness controls, the entire process is moving towards a streamlined and effective operation that now represents best industry practice.

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participate, factors influencing the decision to participate, perceived risks and benefits, the informed consent process, and how people prefer to learn about clinical trials.]

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Further reading

Anderson DL. *A Guide to Patient Recruitment and Retention*. Thomson Centerwatch, 2004. ISBN 193062445X. [This manual is designed to help clinical research professionals improve the effectiveness of their patient recruitment efforts. With contributions from 15 industry leaders, it offers real-world, practical recruitment strategies and tactics grounded in facts and experiences. It is an invaluable resource for educating staff on patient recruitment, for managing recruitment initiatives for clinical trials, and for accelerating enrolment and retention efforts. Topics include: trends and issues influencing patient recruitment, retention and ethics, benchmark data on patient volunteer demographics and recruitment costs, effective media strategies and tactics, budget considerations, guidelines on establishing new recruitment and retention practices, and tips on effectively communicating with potential study subjects. It is designed for physicians, study nurses, pharmacists and other health professionals involved in government- and industry-sponsored clinical trials as well as instructors conducting training and educational programmes.]

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