

Clinical Trials: World Market 2009-2024 report extract

Transcript of an interview between Dr Kevin Dykstra, PhD.
Senior Vice President, Worldwide Strategic Consulting Services
for Pharsight, and visiongain publishing.



Clinical Trials: World Market 2009-2024 (extract)

The following is the transcript of an interview between Dr Kevin Dykstra, PhD. Senior Vice President, Worldwide Strategic Consulting Services for Pharsight, and visiongain, a global business information provider. The interview, held on 9 June 2009, also forms a part of visiongain's 2009 report - Clinical Trials: World Market 2009-2024.

Visiongain is a London-based, global business information provider. Visiongain produces market reports and business conferences in the pharmaceutical, defense, and wireless telecoms sectors. Visiongain covers a wide range of healthcare markets in our detailed market- and industry-centred reports. We cover all major therapeutic areas, as well as biotechnology, in-vitro diagnostics and emerging markets. Our reports are highly analytical investigations of contemporary topics, with detailed sales forecasting, thorough interviews, market share analyses, SWOT tables, and pipeline analyses.

The report for which the following interview was conducted - Clinical Trials: World Market 2009-2024 - was published on 9 July 2009.

On the Promises and Problems of Adaptive Trials

Visiongain: What are the promises and problems of adaptive clinical trials?

Dr Dykstra: The promise is that you can learn more from a well-designed trial. Many traditionally designed trials, especially early efficacy trials, are too small to arrive at definitive conclusions; occasionally trials are too large and are therefore wasteful of patient time and sponsor resources. Frequently, trials include ineffective and or non-informative dose arms. Any of these problems are incredibly wasteful. Proper design and sample size means you don't waste patients and resources. You have enough patients to learn what you need to know, and you don't waste their

Clinical Trials: World Market 2009-2024 (extract)

time or your money. Adaption means that you are able, within well-defined limits, to alter the design of a trial on the basis of accumulating information. Effective trials enable appropriate and correct decisions regarding further development of the treatment, eg confirming effective doses, quantifying incidence of side effects, supporting kill decisions for non-viable drug candidates, etc. That's what a trial has to do.

On the Limits of Trials Adaptation

Visiongain: Are there limits to how trials can be adapted?

Dr Dykstra: Yes, of course there are limits. It takes a certain amount of time for a clinical endpoint to develop in a given patient. Many of the conditions under study are chronic, progressive diseases leading to gradually increased disability. One major problem with adaptive trials is that patient outcomes need to be available in time to adapt the trial for future patients. For some disease areas, patients can be enrolled quickly, before the endpoint has time to develop for the patients already in the trial. So for example, in an osteoporosis trial it can take a year to develop an endpoint; in Alzheimer's it can take anywhere between 6-18 months, depending on the goal of the therapy. In these diseases, most of the patients can probably be enrolled before the first patient has completed treatment.

On The Selection of Efficacy Endpoints

Visiongain: What are some of the considerations in selecting an efficacy endpoint?

Dr Dykstra: Efficacy endpoints are determined based on clinical relevance to the condition under study. For example, in diabetes, it's often fasting plasma glucose. Or you can use haemoglobin A1C as a surrogate marker for consistently adequate glucose control.

Visiongain: So endpoints are based on what you expect to happen?

Dr Dykstra: I would stay away from the word "expect". The

Clinical Trials: World Market 2009-2024 (extract)

endpoint should be selected such that an improvement in the endpoint reflects some meaningful improvement in the patient's condition. This is more a reflection of how to study a given disease than what an expected trial outcome is.

These choices are driven by the underlying trial design and the clinical realities of a given disease process, therapeutic area, or the desired product label . For example in Alzheimer's Disease, if the strategy is to show symptomatic relief, there may be ready endpoints that are available in a timely way to permit adaptation. If the strategy is to show a disease-modifying effect, that is to change in the underlying disease process, the endpoints take much longer to detect. And that will then change the length of time each patient will have to be treated in the trial. So for Alzheimer's, symptomatic drugs can show results more quickly, with shorter trials and a few months of patient treatment. But for potentially disease-modifying treatments, you would have to treat patients for longer to see a significant signal.

On Signal Discovery Times and Biomarkers

Dr Dykstra: The rate of progression for Alzheimer's varies significantly from person to person, so signals are difficult to detect, and it's really difficult to tell if your treatment is making a difference. The time, costs and logistics of such multi-year trials are formidable. If it takes two years to confirm that you've modified the course of disease, there will be two fewer years of patent-protected sales once the drug is registered. Unfortunately, patent law imposes its own limits on which therapies can be commercially developed. The disease-modifying agent tarenflurbil (Flurizan) from Myriad, for example, just recently failed in clinical trials.

Biomarkers could represent a significant step forward in addressing many of these issues. Biomarkers are useful because they can provide cheaper or faster signals than the ultimate clinical endpoint. If you have an accepted biomarker, you can run trials faster, possibly using adaptation to change the design and analysis of the trial in mid-stream, where it could not be used before. In Alzheimers, there are not accepted biomarkers at this

Clinical Trials: World Market 2009-2024 (extract)

time, though there may be some interesting candidates on the horizon.

On Trials Adjustments and Endpoints

Visiongain: So do you know beforehand what you're looking for, or do you adjust endpoints as you go?

Dr Dykstra: You generally know the mechanism of action before you get to humans. This is established in preclinical models long before clinical trials begin. The clinical endpoints are likely to change as the overall program progresses. Early, trials are more focused on gathering information on biomarkers, and establishing biological activity based on the MOA. The biomarkers are useful as indicators of clinical efficacy, and it is frequently possible to make predictions of efficacy based on biomarker results through the use of mathematical models.

Visiongain: What aspects of a trial are adaptable? Can you adjust endpoints?

Dr Dykstra: Let's be clear: you rarely get to change endpoints in the middle of the trial, and even then it will involve very serious negotiations with regulators. This would not normally be part of an adaptive trial design. What you can change are the number of patients, or you can get rid of arms that are clearly not producing useful results. You can change the dose, or employ other techniques to maximise signals. You can stop a trial that is clearly destined to fail, or, with better luck, one that shows overwhelming evidence of success.

On Pharsight's "Clinical Utility" Approach to Development Strategies

Dr Dykstra: Pharsight is working on other approaches to support trial strategy and drug development decisions, utilizing an integrated metric of benefit and risk that we call clinical utility. Clinical utility is a way of measuring the relative value of positive and negative effects and using those to decide if a drug is worth pursuing. The decision of whether to continue with a drug or kill it is determined by factors like safety, potential sales, cost-

Clinical Trials: World Market 2009-2024 (extract)

effectiveness, etc. What Pharsight has is a system for evaluating clinical utility during the course of a clinical trial.

Let's say a 2-point drop on the ADAS-cog scale is clinically relevant in Alzheimer's. If we're testing a drug and a higher dose produces that 2-point drop, but that dose also increases the rate of diarrhea, then how do you measure the value of a higher dose? For a condition like Alzheimer's, where there's no disease-modifying drug, a treatment that causes an unpleasant side effect may not be worth the slight benefit in the longer term. But clinicians can disagree on the relative value of benefits and side effects, so we have them put numbers to both the benefits and the toxic effects. Those numbers allow us to assess the overall patient benefit or "clinical utility" of the drug.

With the combination of clinical relevance and disease modelling, we can correlate exposure and response relationships, and tell our clients about usefulness and efficacy. We can tell them what kind of chance the drug has for being as good or better than what is already approved or in a competitor's pipeline and for which some results have already been published. And we can be more certain in our results.

All these techniques make the decision path, and its associated risks and rewards, clearer. The difficult aspect of clinical development is knowing when to proceed with a drug, and when to kill it and invest finite resources elsewhere. The point of our clinical effectiveness system is to make the grounds for that decision much more certain.

On Software Innovations and Trials Efficiency

Visiongain: Are there any innovations in software that will make clinical trials significantly more efficient?

Dr Dykstra: All the things I've been discussing are methods, not software. Of course we produce software - like Phoenix™, Pharsight's new analysis and modelling platform, along with Drug Model Explorer® and Trial Simulator™ - and the software is key to our work. But the core is the consultative process, and the highly

Clinical Trials: World Market 2009-2024 (extract)

quantitative approach to decision making that draws from the disciplines of pharmacology, drug and disease modeling, biostatistics, and decision analysis. It's during the consultation that we collaborate with the sponsor to agree on key questions to be answered, on what we're looking for and how to construct a model that is fit-for-purpose. Software is a tool, but the really important work comes from the consultation.

On Phased Development Becoming or Not Becoming Obsolete

Visiongain: Will the Phase 0-IV system become obsolete within the next 15 years?

Dr Dykstra: Dr Lew Scheiner described the ideal drug development paradigm as "learn and confirm". The early phases are learning about what the drug does in the human body, and the later studies confirm the positive effects.

In Phase 0, you're taking preclinical information, looking for significant biomarkers of positive effects, and possible toxicities. You're also projecting the range of possible human doses, and accumulating other useful information. This is part of the learning mode.

Phase I, you're looking at how long the drug stays in the body, how long the effects last, and so on. You're looking to see if it has the biological effect it should have, and how long the drug keeps working. I would consider Phases 0 and I as building the knowledge infrastructure to enable continuing with development. Some of these tests are done in healthy subjects and some in patients, depending on what you're testing.

Phase II, you're doing studies in the disease population to start understanding safety and efficacy in the target patient population. Here you're looking for clinical endpoints, and looking to define what the dose response will be.

Phase III is confirmation - from the "learn and confirm" model - of what the drug does. You want to confirm that the effects are

Clinical Trials: World Market 2009-2024 (extract)

significant, and seeks to demonstrate that an acceptable benefit/risk profile is achieved in a large and representative patient population.

Phase II is where the system is most broken. Phase II is often divided into IIA and IIB trials. Phase IIA is looking for proof-of-concept, but the trials are often undersized for this purpose. These trials often require the better part of a year to complete, and if they're too small to be reasonably definitive, then you've just wasted that year getting an ambiguous result.

I sometimes call those Phase IIA trials "hope of concept" trials, because they don't prove anything. I say that sponsors should run a sufficiently robust Phase II trial to identify a dose response, and use prior information to quantify what aspects they can - it's worth spending the money for reasonably good information. If you have a clear dose response, then you have, by definition, established the drug effect. Good information will let you know whether you want to proceed, quickly identifying the potential winners, helping to kill a non-performing compound sooner, which saves both money and patient resources.

On Combining Phase II and III Trials

Visiongain: Will Phase II and III be combined in the near future?

Dr Dykstra: Maybe eventually. We do hear of individual programs combining Phases II and III, but I don't believe this will be general practice for awhile. Phase III is run in a different way from Phase II; they're looking for different things. Phase II is still part of the learning process, and that's different from a confirming process. You need a different approach. Phase III trials gather data that is more clinically focused in a large number of patients, as opposed to being scientifically focused. Because the trials are much larger, it is not always feasible to gather the depth and breadth of data on each patient that is frequently gathered in a Phase II study where patients are more intensively monitored.

On the Future and Usefulness of Placebo Models and Datasharing

Clinical Trials: World Market 2009-2024 (extract)

Visiongain: Do you think that datasharing - for genomics information or for trials for similar compounds - will happen and/or be useful?

Dr Dykstra: Models based on public data for standard of care and/or placebo treatment would be indispensable. Existing public data can be worked up into models, and the knowledge encapsulated in these models can materially facilitate clinical trials. The FDA and other organisations, ourselves included, are working up data from publicly available trial results into models, so they can be incorporated into analysis of ongoing clinical trials. If you can add prior information regarding placebo and other, competing treatments into models, you can remove a lot of the noise from trials and really improve the precision of results.

Fields where this is already happening include non-small-cell lung cancer. It's also happening in other types of oncology and some CNS areas, especially Alzheimer's and Parkinson's. In Alzheimer's, data from the Alzheimer's Disease Neural Imaging study are publicly available. That's an enormous resource - people can use the imaging data in conjunction with biomarker and clinical information to help analyze their own studies, and as a general clinical picture of the disease.

On Databases of Drugs' Mechanisms

Visiongain: So what about databases on drugs with similar mechanisms?

Dr Dykstra: There are a lot of drugs with similar mechanism, and those could potentially be put into an open model. We have actually done that for statins. In collaboration with Pfizer, we took data available from the literature - this is all publicly available data - and we constructed drug-disease models for a number of statins. And they're remarkably accurate. We can predict dose- and treatment-response to monotherapy and combination therapies, with surprising accuracy. So just from what's available in the literature, we've built a very useful model. The same could potentially be done for other treatments, e.g. oncology. And as I said before, models for placebo would be indispensable.

[end transcript]

For more information about the associated visiongain report, [Clinical Trials: World Market 2009-2024](#), please contact us at:

Web: www.visiongain.com
info@visiongainglobal.com
gordon.low@visiongainglobal.com

visiongain LTD
BSG House
226-236 City Road
London
EC1V 2QY
United Kingdom

Tel: +44 (0) 20 7336 6100
Fax: +44 (0) 20 7549 9930

source: *visiongain 2009*