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Vol. 1, No. 7, July 2005 "Can You Handle the Truth?"

# What is Killing Off the Investigators? A Clinical Research Mystery

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In 2004, 21,735 unique principal investigators conducted U.S. FDA and NIH clinical trials. Only 65% of these investigators conducted a study in the previous year. Only 10% of them conducted at least one study in each of the five years from 2000 to 2004.1 In other words, there is a core population of at most 2,200 principal investigators, and an annual turn-over of about 40% of the rest.

Despite increasing expenditures on clinical research by pharmaceutical and biotech companies, the number of new principal investigators each year declined by 21% from 2001 to 2004.1 The total number of principal investigators declined by 6% from 2001 to 2004.1 In other words, it is becoming more difficult to attract and keep investigators in the industry. In addition, the rate at which principal investigators permanently left the industry doubled from 1990 to 2000.2 Changing demographics suggest that the trend will continue to accelerate: From 1992 to 2004, the average principal investigator's age rose from 43 years to 50 years.[2] Coincidently, from 1994 to 2004, the percentage of principal investigators in the (low-cost) South rose by 20%.[2]

It is no wonder that sponsors complain of a shortage of qualified investigators:

- Despite decades of practice identifying good investigators, only about one-third of the investigators in a study meet or beat their enrollment targets. About 30% enroll no subjects.[3] As Tables 1 and 2 show, the cost of zero-enrollment is substantial to both parties.[3]
- The high percentage of inexperienced investigators – 84% with fewer than five studies under their belt – mean that most investigators are not in the industry long enough to master their profession.[4]
- The number of complaints by the public to the FDA about investigators has grown dramatically. From an average of 11 in the years 1992 to 1998, it jumped to 106 in 1999 and grew steadily to 158 in 2003.[5]

There are over 700,000 practicing physicians (doctors who see patients) in the United States, yet there is a shortage of qualified investigators.[6] Something must be killing them off.

## The Victims

Investigators exist in a symbiotic relationship with sponsors: sponsors get data and customers; investigators may get a number of advantages, including patient benefits, practice benefits, direct revenue, and publications. As with any symbiotic relationship, both parties have to benefit from working together on a study. The benefit has to be a net positive in an absolute sense, i.e., profitable. It also has to be a net positive relative to other activities, i.e., opportunity cost. In the absence of these two net benefits, one party or the other will lose interest in the relationship. Sponsors, for example, do not want to invest time and money initiating a site that enrolls no subjects. Physicians do not want to invest time and money conducting a study that creates unhappy subjects.

As with any relationship, the outcome is seldom predetermined. There are multiple elements of risk for both parties in a clinical trial. If the relationship is new, the risks are magnified by

uncertainty: What are the other party's expectations? Are they ethical? Will they behave in a reasonable manner? Amplifying the risk for the sponsor are two very unusual features of the relationship:

- Most investigators are also customers, i.e., prescribers.
- Sponsors do not share customer references on investigators.

For the practicing physician, the apparent risk is often amplified because clinical research is out of his/her comfort zone of medical practice. It's a bit like asking a shortstop to pitch an inning of baseball. He/she has a good arm, but it's a different position.

The healthiest relationships are often between similar parties with congruent objectives, balanced contributions, and equivalent power in the relationship. For example, baseball teams without any stars but outstanding teamwork often emerge victorious. In contrast, the relationship between sponsor and investigator is often unbalanced:

**Table 1: Site Cost to Initiate & Close a Study**

| | |
|---|---|
| Site Initiation: | |
| Administrative | $2,000 |
| Qualification Visit | $ 500 |
| Initiation Visit | $1,000 |
| Investigator Meeting (PI+CRC)* | $4,000 |
| Initiation Total | $7,500 |
| Interim Visit | $ 500 |
| Closeout | $1,000 |
| Total | $9,000 |

* Assumes two days lost physician revenue; varies substantially.

- The sponsor is usually a much larger entity than the investigator, with substantially more business resources.
- The sponsor contracts with numerous investigators on the study, under identical protocols and very similar contracts; the investigator contracts with multiple sponsors, each with its own protocol and contract.
- For the sponsor's study team, the study is everything and time is of the essence; for the investigator, the study is just one of many priorities, usually much less important than patient care.
- If the investigator is at an academic site, his/her intellectual property and publication objectives are very different than the sponsor's objectives.

In a healthy relationship, both parties value the relationship. In clinical research, however, each party often looks at the other as just another fish in the sea. When sponsors ask investigators if they have ever done a study for that sponsor, it doesn't take a rocket scientist to figure out that their performance – or non-performance – on a study is unlikely to have any long-term impact. It's like throwing a fish back in the lake; you can always catch it again tomorrow.

**Table 2: Sponsor Cost to Initiate & Close a Site**

| | |
|---|---|
| Site Initiation: | |
| Administrative | $2,000 |
| Qualification Visit | $2,000 |
| Initiation Visit | $2,400 |
| Investigator Meeting (PI+CRC) | $3,000 |
| Initiation Total | $9,400 |
| IRB Fees | $1,500 |
| Interim Visit | $2,000 |
| Closeout Visit | $2,400 |
| Total* | $15,300 |

* Excludes start-up fees, if any.

**The Diagnosis**

Both the pharmaceutical and physician businesses were historically very profitable, but are now undergoing significant challenges. These challenges are stressing the fundamental economics of the sponsor/investigator relationship.

The sponsors' business model, historically based on huge profit margins and rapid growth in protected markets, is severely challenged:

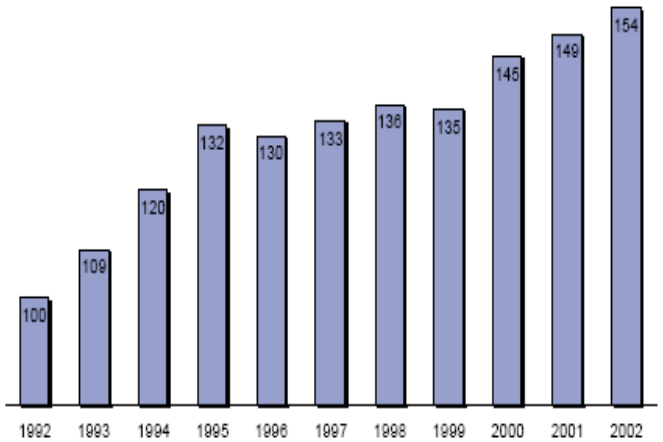
- Declining R&D productivity (fewer new medicines, especially "blockbusters", despite increasing R&D budgets)
- Shorter periods of exclusivity without competitive medications
- Expiring patents and increasing generic market share
- Re-importation (bizarre)
- Consolidation of purchasing power
- Increasing regulation
- Increasing withdrawals of approved drugs from the market
- Lower share prices (higher cost of capital)
- Declining reputation with the public

Sponsors and external forces are putting pressure on the investigators' business model, historically based on lucrative studies with easy enrollment and a lot less paperwork. Margins are tight or negative, and growing tighter:

- Study budgets are flat while procedures per subject are increasing. (Table 3)
- Narrow subject eligibility requirements make subject recruiting difficult.
- New technologies increase costs: Electronic Case Report Forms (eCRFs) move data entry costs from the sponsor to the investigator; eDiaries generate reminder phone calls.
- HIPAA, ICH, etc. are increasing regulatory compliance costs both directly and through more stringent sponsor and IRB requirements. HIPAA, in particular, increases the cost of subject recruitment and informed consent.

The symbiotic relationship between sponsors and investigators is thus dissolving. The diagnosis? Investigators are not profiting from the relationship. *Sititis investigatorum* is killing them off faster than they can be replaced, adding yet another threat to the health of the pharmaceutical industry, and the public at large.

**Table 3: Phase I-III Procedures per Subject**




Source: DataEdge, 2003

**The Prognosis**

If:

- 80% (560,000) of practicing physicians are in specialties that engage in clinical research; and
- 30% of those (168,000) are interested and able to conduct studies at some point in their career; and
- 16% (100%-84%) of those develop the experience (5 or more studies) necessary to become qualified,

then the potential pool of experienced qualified principal investigators is about 27,000.

About 20,000 new physicians obtained licenses in 2003.7 About 79% of licensed physicians practice, i.e., see patients, so about 16,000 new practicing physicians entered the profession in 2003.

About 600 (16,000 new graduates X 80% X 30% X 16%) new physicians join the pool of potential investigators each year. Since about 8,000 will drop out of the industry this year, the pool of potential principal investigators will decline by about 7,000 or 26% (7,000/27,000) this year. With shrinkage of 26% per year, the pool will shrink by 78% to about 6,000 over the next five years. Although the assumptions appear plausible, this number appears to be too low. However, there is no doubt about the trend – the pool of potential U.S. investigators is rapidly shrinking.

The prognosis? Assuming the above calculation is even roughly correct, the 6% decline in principal investigators over the past five years will accelerate dramatically and S. investigatorum will kill off most of the survivors in the next few years. The industry has four alternatives: rely on less-qualified investigators, train them more rapidly, address their needs, or rely on investigators in developing countries. (Increasing globalization of clinical research is inevitable and a positive development, but a healthy clinical research industry in the U.S. (and other developed countries) has numerous advantages to sites, sponsors and the public.)

**The Cure**

There is no pill to cure *S. investigatorum.* Like many modern plagues, successful treatment requires multiple medications. Fortunately, we have a robust pharmacopoeia:

- New investigators need to understand the technical, ethical and business differences between clinical research and their regular medical practice. If they don't enter the business with their eyes open, they are asking for trouble, and will deliver it to sponsors as well. Investigator meetings should include a "clinical research realities" session for new investigators. If an investigator runs for the hills, the study is better off without him/her.
- If investigators want to communicate their true costs to sponsors, first they have to understand and measure them. On average, 75-90% of the time that a site spends on a study is not in the study budget as direct or even overhead costs; it is spent on dozens of hidden costs.[3] These hidden costs need to be brought out into the light. Sponsors need to understand that study-related hidden costs are not just the "cost of doing business." As a side benefit, legal prohibitions against overpaying investigators largely become a non-issue.
- Upgrade contracts, budgets and payment schedules. Over 50% of investigators say that the terms and structure of clinical trial agreements are not fair or equitable.[8] Almost half associate the feeling of "fear" or "suspicion" with budget

negotiations.[8] Many sites report average collection periods from sponsors more than 100 days longer than their own average payment periods to site employees and vendors.[3] 52% of sites say contract and budget negotiation is the factor most likely to cause clinical trial delays, more than any other cause.[9]

- When sponsors treat investigators like partners, investigators will treat sponsors like partners. Ask for investigator input on new protocols. Remember their answers in the site questionnaire and hold them accountable. Share study results with them. Ask for their feedback. Sponsors are beginning to understand the value of preferred provider relationships with CROs; extend these relationships to sites.
- By *reducing* their stable of investigators, sponsors can develop real partners. Partners can work together to streamline processes, eliminate hidden costs, and relieve the pressure on study budgets. Get off the site recruitment merry-go-round; don't keep trying to fix the process; eliminate it and invest the savings in investigator partnerships.
- 81% of the general population says that they have never had the opportunity to participate in a clinical study. Of those that have had the opportunity, 58% have enrolled.[10] Most physicians would be excellent sources of subject referrals. Nevertheless, subject recruiting is THE major problem for most investigative sites. 78% of patients trust their physicians to give them accurate health information, so perhaps it is time to re-energize physician referrals and leverage the physician-patient relationship.[11]
- Sponsors and sites should collaborate to counter negative press reports about clinical research. We have a good, objective story to tell; we just need to tell it.
- If sponsors consider the impact of new technologies on investigators, they may avoid increasing investigator costs. eCRFs move data entry costs to sites. eSource Documents will reduce them by eliminating a mostly redundant step. Source documents play an indispensable role, but it makes no sense to create a new source document just so it can be compared to a CRF that has been copied from it.
- Sites can be better partners by investing in their business, for example, in training and certification. Sponsors can reimburse these costs with a small extra fee for studies conducted by certified personnel. Sites that invest in infrastructure to improve quality should be able to charge premium prices.
- By choosing their competitive battles, sponsors can cooperate to solve common problems. For example, MAGI, the Model Agreement Group Initiative, will take weeks out of the process of initiating investigative sites.[12]

The mystery is solved. By working together, we can cure *S. investigatorum* and stop this tragic epidemic in its tracks. The U.S. automobile industry slashed its cost, quality and delivery problems decades ago with a similar treatment; we can do it too.

**Notes**


1. Acurian analysis of Form FDA 1572 filings, 2005
2. "Numbers of active investigators in FDA-regulated clinical trials drop", Tufts Center for the Study of Drug Development Impact Report, May/June 2005
3. Analysis by large CRO
4. "A Bright Future for ACRP and R&D", ACRP White Paper, 1999
5. FDA Office of Compliance
6. American Medical Association (last accessed on June 30, 2005 at http://dbapps.ama-assn.org/aps/amahg.htm)

7. American Medical Association, personal communication
8. RapidTrials industry survey, 2003
9. "2005 Thomson CenterWatch U.S. Report Card Survey"
10. "Public Awareness of Clinical Trials Increases", Harris Interactive, June 11, 2004
11. Thomson CenterWatch Volunteer Survey, 2004
12. Model Agreement Group Initiative (last accessed on June 30, 2005 at http://www.firstclinical.com/magi)

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